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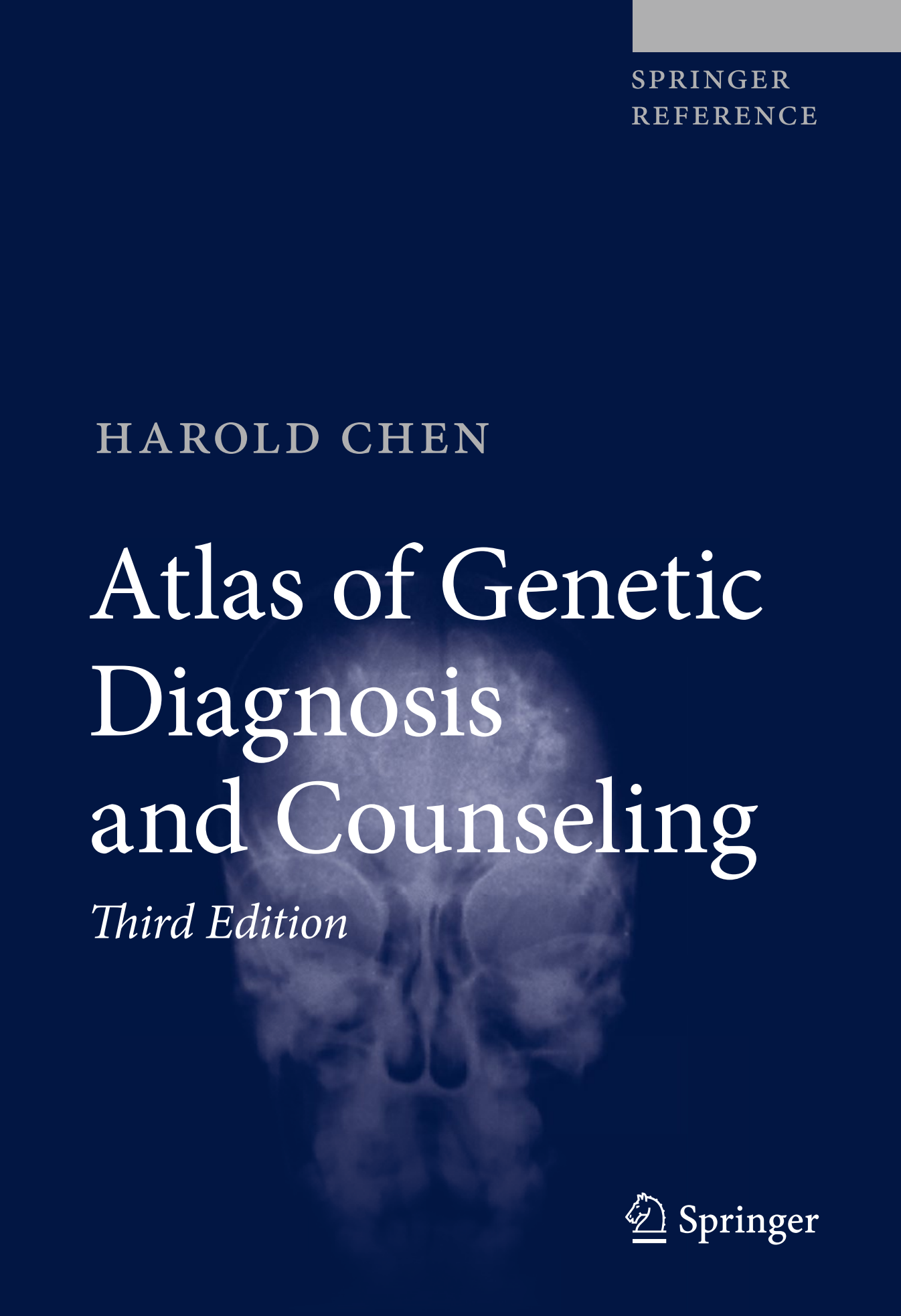
HAROLD CHEN

Atlas of Genetic Diagnosis and Counseling

Third Edition



Springer

Atlas of Genetic Diagnosis and Counseling

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Third Edition

With 1242 Figures and 1 Table

Springer

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I would like to dedicate this atlas to Children's Hospital, Louisiana State University School of Medicine in Shreveport and Shriners Hospitals for Children, Shreveport, Louisiana, USA

Preface to the Third Edition

It has been 5 years since the publication of the second edition of this atlas in 2012. Since then, significant progress has been made in the field of genetic diagnosis and counseling, especially in genomic medicine. The third edition covers 284 chapters with the addition of the following 30 new chapters: Congenital Infiltrating Lipomatosis of the Face, Congenital Radioulnar Synostosis, Cutaneous Vasculitis, Emanuel Syndrome, Feingold Syndrome, Fibular Hemimelia, Gilbert Syndrome, Hemangiomas of Infancy, Hereditary Sensory and Autonomic Neuropathies, Hereditary Spastic Paraplegia, Hydranencephaly, Hypertrophic Cardiomyopathy, Isolated Growth Hormone Deficiency in Children, Lymphangiomas and Lymphangiomatosis, Macrodactyly, Mitochondrial Myopathies, Mőbius Syndrome, Nager Acrofacial Dysostosis, Nasal Obstruction in Neonates and Children, Niemann-Pick Disease, Opitz Trigonocephaly Syndrome, Osteogenesis Imperfecta/Ehlers-Danlos Syndrome Overlap Syndrome, Patellar Instability, Peutz-Jeghers Syndrome, Primary Microcephaly, Schwartz-Jampel Syndrome, Symphalangism, Tibial Hemimelia, Tyrosinemias, and Winchester Syndrome.

As with the previous edition, a detailed outline of each chapter is provided, describing the genetics/basic defects, clinical features, diagnostic investigations, and genetic counseling including recurrence risk, prenatal diagnosis, and management. The illustrative cases are supplemented by case history and diagnostic confirmations through imaging, cytogenetic, biochemical, and/or molecular genetic studies. In this edition, it was a formidable task trying to cite the relevant references in the text, which was not done in the previous editions.

In addition to the individual contributions mentioned in the acknowledgments in previous editions, I thank the following individuals for their contribution and support to this edition: Richard A. Hruska, Springer Publishing Editor, for inviting me to write this third edition of the atlas and Neha Thapa, Springer Editor, and K. Arun Kumar, Springer Project Manager, for editing and production of this atlas. Individual contributors have been acknowledged in the case illustrations. I am especially thankful to the staff at the Shreveport Shriners Hospitals for Children (Kim Green, administrator; Dee Chambers, Medical Staff Coordinator; Kim Blankenship, Director of Outpatient Clinic; Dr. John Fox, Chief of Staff; Dr. Anne Hollister, hand surgeon; Dr. Don Holton, radiologist; Sheila Barritt, Director of Radiology) and staff at LSU School of Medicine (Dr. Susonne Ursin, clinical geneticist; Mary Moore, BBA, Administrative Assistant; Dr. Joseph Bocchini, Chairman of the

Department of Pediatrics; Dr. Jennifer Woerner, Program Director of Craniofacial Fellowship and Oralmaxillofacial Residency Program; Diane DunkiJacobsNolten, RN, Clinical Coordinator; and Dr. Ghali Ghali, Chancellor and Dean of School of Medicine and Chairman of the Department of Oral and Maxillofacial Surgery). Special thanks are due to Dr. Grace Guo, a pediatric radiologist at Nemours/Alfred I. duPont Hospital for Children, for her contributions to cases with excellent imagings provided throughout this atlas.

As previously, I would welcome comments, corrections, and criticism from readers.

Shreveport, LA, USA Harold Chen
February 2017

Preface to the Second Edition

It has been 5 years since the publication of the first edition of this atlas in 2006. Since then, significant progress has been made in the field of genetic diagnosis and counseling. The first edition of the atlas covered 203 chapters which were revised with current literature and addition of many illustrations, mostly in color. Fifty-two new chapters have been added to this edition. Selected references have also been added to the text for the sources of the information.

As with the previous edition, a detailed outline of each disorder is provided, describing the genetics, basic defects, clinical features, diagnostic investigations, and genetic counseling, including recurrence risk, prenatal diagnosis, and management. Relevant references are added in the second edition. The cases are supplemented by case history and diagnostic confirmations by imaging, cytogenetic, biochemical, and/or molecular studies.

I am grateful to the following individuals for their contribution and support of this edition: Dr. Susonne Ursin, my genetic colleague and Chief of Perinatal Genetics, for case studies (Joubert syndrome, Mowatt-Wilson syndrome, otopalatodigital syndrome, rigid spine syndrome, Saethre-Chotzen syndrome, Silver-Russell syndrome); Dr. RMS Riel-Romero for megalencephalic leukoencephalopathy with subcortical cysts; Dr. Amal Anga for Duncan syndrome; Drs. Richard McCall, Phillip Gates, and Anne Hollister, Shreveport Shriners Hospital for Children; Dr. Ghali Ghali, Chairman of Oral and Maxillofacial Surgery; and Dr. Renata Pilatova, Pinecrest Development Center, for providing patients for studies and inclusion into this edition; Dr. Leonard Prouty, Ms. Rhonda Lee Young, and Mr. Jozo Ivancic, LSU Cytogenetics Laboratory for part of the karyotypes used in this edition; Mrs. Lynn Martin, Beverely Gildon, and Diane DunkiJacobsNolten for nursing care; and Ms. Ashli Daigle and Mrs. Barbara McHenry for their excellent clerical and secretarial help. My apologies in the event that I failed to mention others who have contributed to this edition. Without the patience and encouragement of my dear wife, Cheryl, this edition of the atlas would not have been possible. I would like to express my sincere appreciation to Dr. Joseph Bocchini, Chairman of the Department of Pediatrics, for his encouragement and support. I would like to dedicate this edition of the atlas to the Children's Hospital,

Louisiana State University Health Sciences Center in Shreveport, for its excellence in pediatric care and education.

As previously, I would welcome comments, corrections, and criticism from readers.

Shreveport, LA, USA Harold Chen
October 2011

Preface to the First Edition

This book, *Atlas of Genetic Diagnosis and Counseling*, reflects my experience in 38 years of clinical genetics practice. During this time, I have cared for many patients and their families and taught innumerable medical students, residents, and practicing physicians. As an academic physician, I have found that a picture is truly "worth a thousand words," especially in the field of dysmorphology. Over the years, I have compiled photographs of my patients, which are incorporated into this book to illustrate selected genetic disorders, malformations, and malformation syndromes. A detailed outline of each disorder is provided, describing the genetics, basic defects, clinical features, diagnostic investigations, and genetic counseling, including recurrence risk, prenatal diagnosis, and management. Color photographs are used to illustrate the clinical features of patients of different ages and ethnicities. Photographs of prenatal ultrasounds, imaging, cytogenetics, and postmortem findings are included to help illustrate diagnostic strategies. The cases are supplemented by case history and diagnostic confirmation by cytogenetic, biochemical, and molecular studies, if available. An extensive literature review was done to ensure up-to-date information and to provide a relevant bibliography for each disorder.

This book was written in the hope that it will help physicians improve their recognition and understanding of these conditions and their care of affected individuals and their families. It is also my intention to bring the basic science and clinical medicine together for the readers. *Atlas of Genetic Diagnosis and Counseling* is designed for physicians involved in the evaluation and counseling of patients with genetic diseases, malformations, and malformation syndromes, including medical geneticists, genetic counselors, pediatricians, neonatologists, developmental pediatricians, perinatologists, obstetricians, neurologists, pathologists, and any physicians and health care professionals caring for handicapped children such as craniofacial surgeons, plastic surgeons, otolaryngologists, and orthopedics.

I am grateful to many individuals for their invaluable help in reading and providing cases for illustration. The acknowledgments are provided on a separate page. Without the patience and encouragement of my dear wife, Cheryl, this atlas would not have been possible. I would like to dedicate this book to the Children's Hospital, Louisiana State University Health Sciences

Center in Shreveport, for its continued excellence in pediatric care and education.

I would welcome comments, corrections, and criticism from readers.

Harold Chen, M.D., FAAP, FACMG

Contents

Volume 1

Volume 2

Volume 3

Biography

Harold Chen was born in I-Lan, Taiwan, and was a graduate from the National Taiwan University School of Medicine (M.D. degree) in Taipei, Taiwan. He received M.S. degree in Human Genetics from the University of Michigan Graduate School in Ann Arbor, Michigan. He finished pediatric residency and fellowship training from Wayne State University School of Medicine in Detroit, Michigan. He had been faculty at Wayne State University (Detroit), Wright State University (Dayton, Ohio), and University of South Alabama (Mobile, Alabama). Currently, he is Professor of Pediatrics, Obstetrics and Gynecology, Pathology, and Oral and Maxillofacial Surgery at the Louisiana State University Health Sciences Center. He is also Chief of Medical Genetics at the Shriners Hospitals for Children, Shreveport, LA. Dr. Chen is board-certified in American Board of Pediatrics and American Board of Medical Genetics in Clinical Genetics and Clinical Cytogenetics.

Acardia

Contents

Acardia is a bizarre fetal malformation occurring only in twins or triplets. It is also called acardius acephalus, acardiac twinning, or twin reversed arterial perfusion (TRAP) syndrome or sequence. This condition is very rare and occurs in 1 in 34,600 births or 1 in 100 monozygotic twins (Gillim and Hendricks 1953) and 1 in 30 monozygotic triplets (Van Allen et al. 1983; Napolitani and Schreiber 1960; Moore et al. 1990; Sanjaghsaz et al. 1998; Blenc et al. 1999) and even in quintuplets. Almost all cases reported are monozygotic twins. However, there are reports of dichorionic monozygotic twin gestations with TRAP sequence (French et al. 1998; Gewolb et al. 1983).

Acardia requires the presence of arterial-arterial anastomosis in the placenta, with retrograde perfusion of poorly oxygenated blood from the normal twin (also called donor or pump twin) to the acardiac twin, venous-venous anastomosis carrying blood back from the acardiac to the donor twin, and circulatory failure of the acardiac twin (Steffensen et al. 2008).

Synonyms and Related Disorders

Acardiac twinning; Acardius acephalus; Twin reversed arterial perfusion sequence

Genetics/Basic Defects

1. Etiology
    1. Rare complication of monochorionic twinning, presumably resulting from the fused placentation of monochorionic twins.
    2. Represents manifestation of abnormal embryonic and fetal blood flow rather than a primary defect of cardiac formation.
    3. Heterogeneous chromosomal abnormalities are present in nearly 50% of the cases, although chromosome errors are not underlying pathogenesis of the acardiac anomaly. Rather, the placental vascular anastomoses are the principal pathogenetic event (Benirschke and des Roches Harper 1977).
        1. 45,XX,t(4;21)del(4p)
        2. 46,X,i(Xp)
        3. 47,XX,+2 (Blaicher et al. 2000)
        4. 47,XX,+11
        5. 47,XY,+G
        6. 47,XXY (Rehder et al. 2012)
        7. 69,XXX
        8. 70,XXX,+15
        9. 94,XXXXYY

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_1

2. Pathogenesis: reversal of fetal arterial perfusion
    1. First hypothesis
        1. A primary defect in the development of the heart
        2. Survival of the acardiac twin as a result of the compensatory anastomoses that develop
    2. Second hypothesis
        1. The acardiac twin begins life as a normal fetus.
        2. The reversal of the arterial blood flow results in atrophy of the heart and the tributary organs.
3. Classification of TRAP sequence (syndrome)
    1. Classification according to the status of the heart of the acardiac twin
        1. Hemiacardius (with incompletely formed heart)
        2. Holoacardius (with completely absent heart)
    2. Morphologic classification of the acardiac twin (Gillim and Hendricks 1953; Napolitani and Schreiber 1960; Nicolaidis et al. 1990; Alderman 1973; Thelmo et al. 2007; Obladen 2010; Buyukkaya et al. 2015)
        1. Acardius amorphous
            1. The least differentiated form
            2. Little more than a lump of connective tissue, covered by edematous skin
            3. No identifiable organs
            4. No resemblance to classical human form
            5. Anatomical features: presence of only bones, cartilage, muscles, fat, blood vessels, and stroma
        2. Acardius myelacephalus
            1. Resembles the amorphous type except presence of rudimentary limb formation
            2. Presence of rudimentary nerve tissue in addition to anatomical features in acardius amorphous
        3. Acardius acephalus
            1. The most common type (60–75%)
            2. Missing head, part of the thorax, and upper extremities
            3. May have additional malformations in the remaining organs
        4. Acardius anceps (~20%)
            1. The least atrophied form
            2. Presence of a partially developed fetal head, a thorax, abdominal organs, and extremities
            3. Lacks even a rudimentary heart
        5. Acardius acormus
            1. The rarest type (10%).
            2. Presence of a rudimentary head only.
            3. Lacks thorax.
            4. The umbilical cord inserts in the head and connects directly to the placenta.
4. The acardia
    1. Characterized by the absence of a normally functioning heart.
    2. Acardia as a recipient of twin transfusion sequence.
        1. Reversal of blood flow in all various types of acardia, hence the term “twin reversed arterial perfusion (TRAP) sequence” has been proposed.
        2. Receiving the deoxygenated blood from an umbilical artery of its co-twin through the single umbilical artery of the acardiac twin and returns to its umbilical vein. Therefore, the circulation is entirely opposite to the normal direction.
    3. Usually, the severe reduction anomalies occur in the upper part of the body.
    4. May develop various structural malformations.
        1. Growth retardation
        2. Anencephaly
        3. Holoprosencephaly
        4. Facial defects
        5. Absent or malformed limbs
        6. Gastrointestinal atresias
        7. Other abnormalities of abdominal organs
5. The co-twin
    1. Also known as the “pump twin or donor twin.”
    2. The donor “pump” twin perfuses itself and its recipient acardiac twin through abnormal arterial anastomosis in the fused placenta.

3. Increased cardiac workload often leading to cardiac failure and causing further poor perfusion and oxygenation of the acardiac co-twin.
4. May develop various malformations (about 10%).

Clinical Features

1. Perinatal problems associated with acardiac twinning.
    1. Pump-twin congestive heart failure
    2. In utero fetal death of the pump fetus
    3. Maternal polyhydramnios
    4. Premature rupture of the membrane
    5. Preterm delivery
    6. Spontaneous abortions
    7. Soft tissue dystocia
    8. Uterine rupture
    9. Postpartum hemorrhage
    10. Increased rate of cesarean section, up to 50%
2. Majority of acardiac twins and their normal twin counterparts are females.
3. Nonviable.
4. Gross features.
    1. Severe reduction anomalies, particularly of the upper body
    2. Characteristic subcutaneous edema
    3. Internal organs: invariably missing
    4. Absent or rudimentary cardiac development: the key diagnostic feature
        1. Pseudoacardia (rudimentary heart tissue)
        2. Holoacardia (completely lacking a heart)
5. Growth abnormality.
6. Cranial vault.
    1. Absent
    2. Partial
    3. Intact
7. Brain.
    1. Absent
    2. Necrotic
    3. Open cranial vault
    4. Holoprosencephaly
8. Facial features.
    1. Absent facial features
    2. Rudimentary facial features
    3. Present with defects
    4. Anophthalmia/microphthalmia
    5. Cleft lip/palate
9. Upper limbs.
    1. Absent
    2. Rudimentary
    3. Radial aplasia
    4. Syndactyly/oligodactyly
10. Lower limbs.
    1. Absent
    2. Rudimentary/reduced
    3. Syndactyly/oligodactyly
    4. Talipes equinovarus
11. Thorax.
    1. Absent
    2. Reduced
    3. Diaphragmatic defect
12. Lungs.
    1. Absent
    2. Necrotic or rudimentary
    3. Single midline lobe
13. Cardiac.
    1. Absent heart tissue
    2. Unfolded heart tube
    3. Folded heart with common chamber
14. Gastrointestinal
    1. Esophageal atresia
    2. Short intestine
    3. Interrupted intestine
    4. Omphalocele
    5. Incomplete rotation of the gut
    6. Imperforated anus
    7. Ascites
15. Liver.
    1. Absent
    2. Reduced
16. Kidney.
    1. Absent (bilateral)
    2. Hypoplastic and/or lobulated
17. Other viscera.
    1. Absent gallbladder
    2. Absent spleen
    3. Absent to reduced pancreas

4. Absent adrenal
5. Absent to hypoplastic gonads
6. Exstrophy of the cloaca
7. Skin with myxedematous thickening

18. Umbilical cord vessels.
    1. Two vessels
    2. Three vessels
19. Severe obstetrical complications.
    1. Maternal polyhydramnios
    2. Preterm labor
    3. Cord accidents
    4. Dystocia
    5. Uterine rupture
20. Severe neonatal complications.
    1. Hydrops
    2. Intrauterine demise
    3. Prematurity
    4. Heart failure
    5. Anemia
    6. Twin-to-twin transfusion syndrome
21. Outcome for the normal sib in an acardiac twin pregnancy (Healey 1994).
    1. Unsatisfactory
        1. Adapting to the increasing circulatory load, resulting in the following situations:
            1. Intrauterine growth retardation
            2. Polyhydramnios
            3. Preterm delivery
            4. Hydrops
            5. Ascites
            6. Pleural effusion
            7. Hypertrophy of the right ventricle
            8. Hepatosplenomegaly
            9. Severe heart failure resulting in pericardial effusion and/or tricuspid insufficiency
        2. Stillbirth
        3. Prematurity
        4. Neonatal death
    2. Mortality for the normal twin reported as high as 50–70% without intervention (Aggarwal et al. 2002; Ibne et al. 2013)

Diagnostic Investigations

1. Radiography
    1. Absent or rudimentary skull
    2. Absent or rudimentary thorax
    3. Absent or rudimentary heart
    4. Vertebral anomalies
    5. Rib anomalies
    6. Limb defects, especially upper limbs
2. Pathology
    1. Microcephaly
    2. Severely rudimentary brain
    3. Developmental arrest of the brain at the prosencephalic stage (holoprosencephaly)
    4. Hypoxic damage to the holospheric brain mantle with cystic change (hydranencephaly)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: overall recurrence risk of about 1 in 10,000. (The recurrence risk is for monoamniotic twinning (1% for couples who have had one set of monozygotic twins) times the frequency of the occurrence of TRAP sequence with near-term survival (about 1% of monozygotic twin sets).)
    2. Patient's offspring: not applicable (a lethal condition)
2. Prenatal ultrasonography (Sherer et al. 1989; Stiller et al. 1989; Langlotz et al. 1991; Donnenfeld et al. 1991; Shalev et al. 1992; Zucchini et al. 1993; Coulam 1996; Schwarzler et al. 1999; Bonilla-Musoles et al. 2001; Martins et al. 2014)
    1. Prenatal diagnosis is suspected on the first trimester ultrasound, when one fetus appears anatomically normal and the other lacks apparent cardiac structures.
    2. Definitive flow is seen in the umbilical artery going toward the acardius (Bornstein et al. 2008).
    3. Fetuses with signs of high-output cardiac failure have poor prognosis and are candidates for intervention such as target occlusion of the umbilical cord of the acardiac twin, including laser ablation, bipolar cord

coagulation, or radiofrequency ablation (Ville et al. 1994).
4. Monochorionic placenta with a single umbilical artery in two-thirds of cases.
5. Acardiac fetus.
    1. Unrecognizable head or upper trunk.
    2. Without a recognizable heart or a partially formed heart.
    3. A variety of other malformations.
    4. Reversal of blood flow in the umbilical artery with flow going from the placenta toward the acardiac fetus (reversed arterial perfusion). Such a reversal of the blood flow in the recipient twin can be demonstrated in utero by transvaginal Doppler ultrasound as early as 12 weeks of gestation.
    5. Early diagnosis by transvaginal sonography on the following signs:
        1. Monozygotic twin gestation (absence of the lambda sign)
        2. Biometric discordance between the twins
        3. Diffuse subcutaneous edema or morphologic anomalies of one of the twins or both
        4. Detection of reversed umbilical cord flow, cardiac activity likely to disappear as the pregnancy progresses
        5. Absence of cardiac activity, although hemicardia or pseudocardia may be present
6. The donor fetus.
    1. Hydrops
    2. Cardiac failure (cardiomegaly, pericardial effusion, tricuspid regurgitation)

3. Amniocentesis to diagnose associated chromosome abnormalities (about 10% of pump twins)
4. Management of pregnancies complicated by an acardiac fetus (Donnenfeld et al. 1991; Hanafy and Peterson 1997; Søgaard et al. 1999)
    1. Conservative treatment
        1. Monitor pregnancy by serial ultrasonography
        2. Conservative approach as long as there is no evidence of cardiac circulatory decompensation in the donor twin
    2. Termination of pregnancies
    3. Treatment and prevention of preterm labor by tocolytics
        1. Magnesium sulfate
        2. Beta sympathomimetics
        3. Indomethacin
    4. Treatment of pump fetus heart failure involving maternal digitalization
    5. Treatment of polyhydramnios by therapeutic repeated amniocentesis
    6. Selective termination of the acardiac twin
        1. To occlude the umbilical artery of the acardiac twin in order to stop umbilical flow through the anastomosis
            1. Intrafunicular injection and mechanical occlusion of the umbilical artery
            2. Embolization by steel or platinum coil, alcohol-soaked suture material, or ethanol
            3. Hysterotomy and delivery of acardiac twin
            4. Ligation of the umbilical cord
            5. Hysterotomy and umbilical cord ligation
        2. Fetal surgery: best available treatment for acardiac twinning (Arias et al. 1998)
        3. Invasive treatment of TRAP sequence
            1. Endoscopic laser coagulation of the umbilical vessels at or before 24 weeks of gestation
            2. Endoscopic- or sonographic-guided umbilical cord ligation at 24 weeks of gestation
            3. Radiofrequency ablation (Tsao et al. 2002; Bebbington et al. 2012)
            4. Fetoscopic laser coagulation of placental communicating vessels or the umbilical cord (Hecher et al. 2006; Nakata et al. 2008)
        4. Summary of acardiac twins treated with invasive procedures reported in the literature
            1. Mortality of the pump twin (13.6%).
            2. Preterm delivery (50.3%).

3. Delivery before 30 weeks gestation (27.2%).
4. Perinatal mortality if untreated is at least 50%.

5. Successful non-invasive blood flow occlusion of TRAP sequence in the acardiac fetus by high-intensity focused ultrasound (HIFU) exposure from outside the maternal abdomen (Okai et al. 2013)
   1. HIFU was applied to blood vessels of the acardiac fetus at the point at which the umbilical cord entered the body in a series of four procedures at 3-day intervals starting at 13 weeks of gestation and in a final procedure with higher power at 17 weeks.
   2. As color Doppler examination revealed absence of blood flow to the acardiac fetus after the second round of HIFU exposure, complete occlusion of target vessels had been achieved.
   3. After delivery by Cesarean section at 37 weeks of gestation, the baby was healthy and growing normally, with exception of congenital pseudarthrosis.

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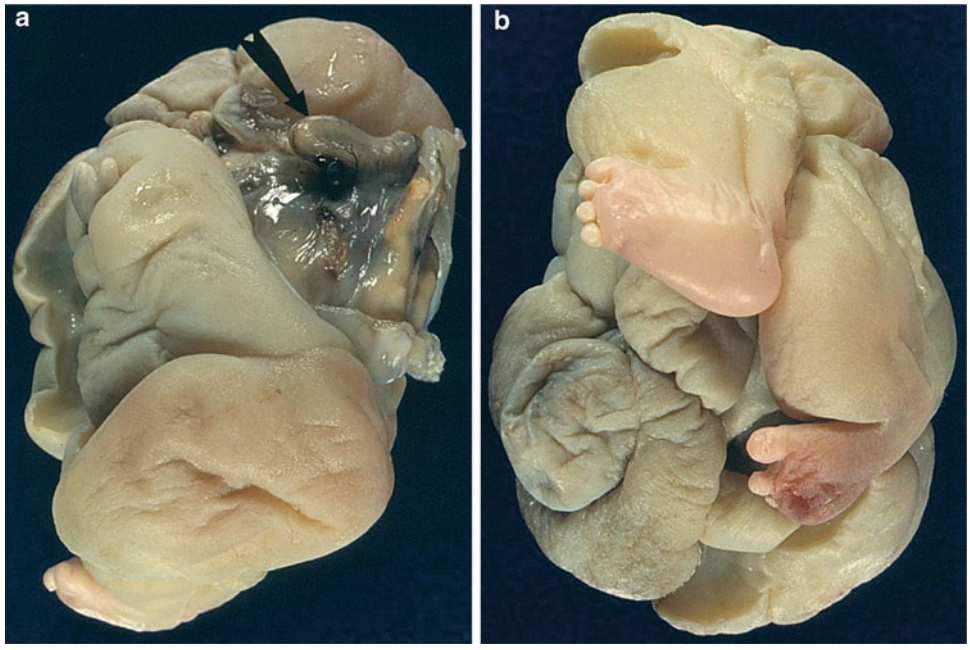

Fig. 1 (**a**, **b**) Ventral view of an acardiac acephalus fetus (**a**) showed a large abdominal defect, gastroschisis (*arrow*), through which small rudiments of gastrointestinal tract were seen. Dorsal view (**b**) shows a very underdeveloped cephalic end and relatively well-developed lower limbs. The co-twin had major malformations consisting of a large omphalocele, ectopia cordis, and absent pericardium, incompatible with life (Chen et al. 1983)

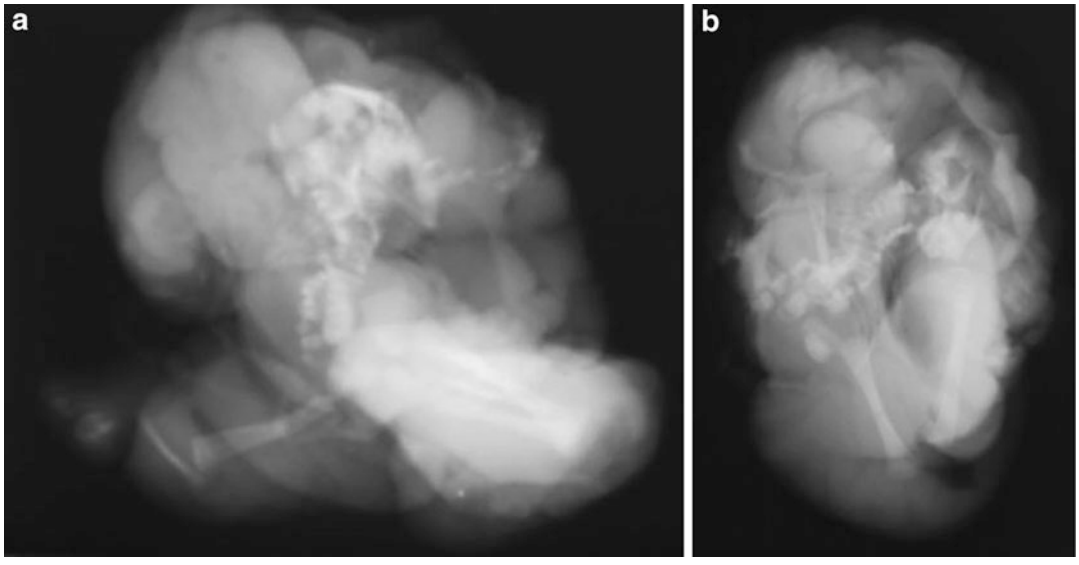

Fig. 2 (**a**, **b**) Radiographs of the above acardiac fetus showing a missing head, cervical vertebrae and part of upper thoracic vertebrae, rudimental lower ribs, malformed lower thoracic and lumbar vertebrae, and relatively well-formed lower limbs (**a**, **b**)

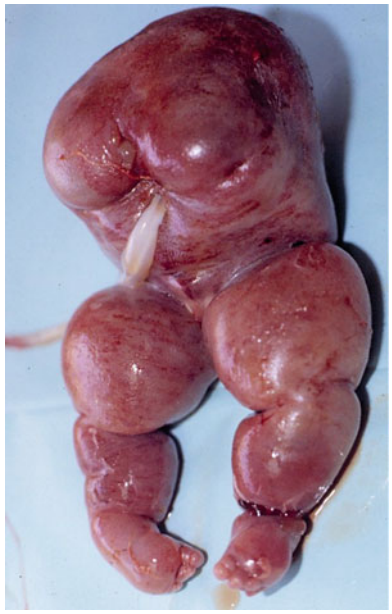

Fig. 3 The head and part of the thorax of this acardiac fetus were completely missing with relatively well-formed lower limbs

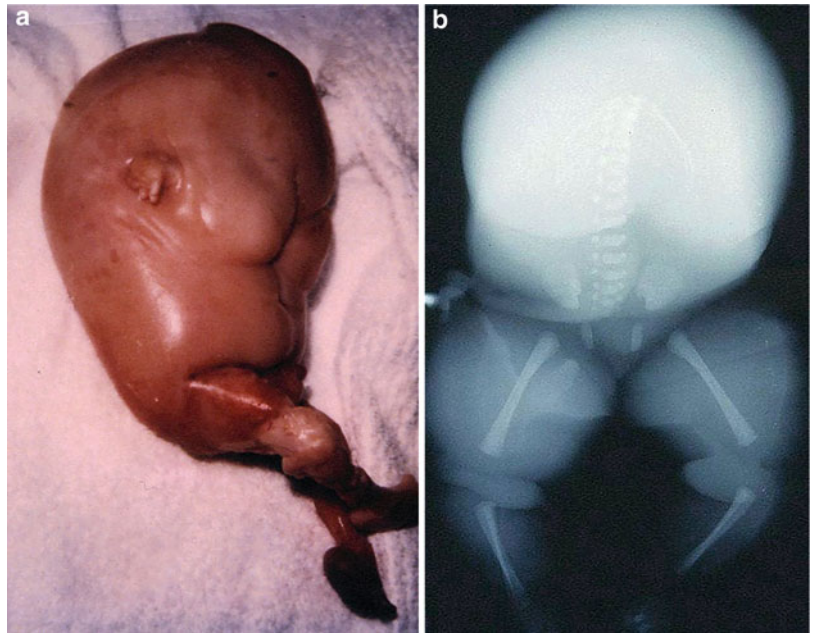

Fig. 4 (**a**, **b**) Another acardiac fetus with a missing head and part of the upper thorax (**a**). Radiograph (**b**) showed missing head, cervical and part of thoracic vertebrae, and ribs. Pelvis and lower limbs are well formed

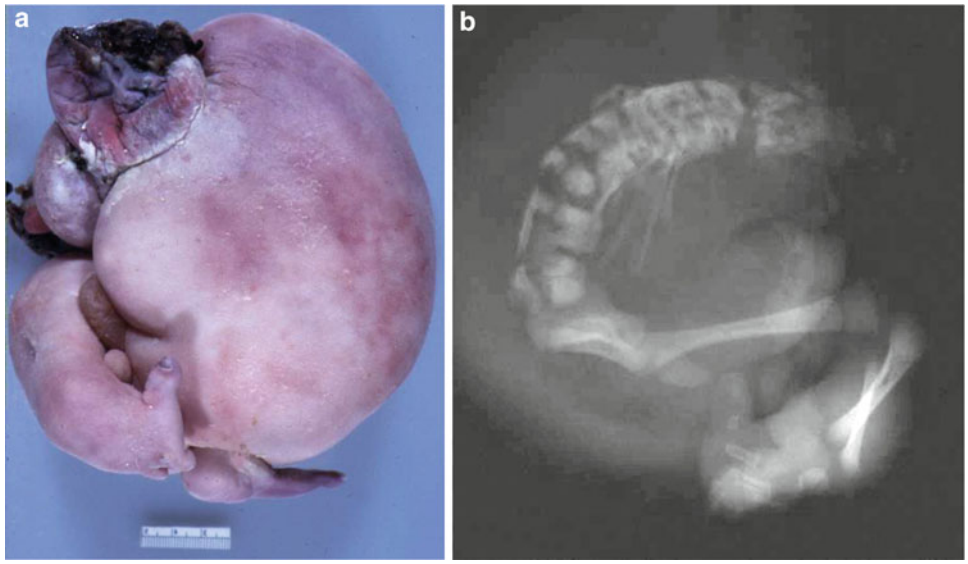

Fig. 5 (**a**, **b**) Acardius (second twin, 36 weeks gestation) showing spherical body with a small amorphous mass of leptomeningeal and glial tissue at the cephalic end (**a**). There were one deformed lower extremity and a small arm appendage. Small intestinal loops, nodules of adrenal glands, and testicles were present in the body. There was no heart or lungs. The placenta was monoamniotic monochorionic with velamentous insertion of the umbilical cord. The other identical twin was free of birth defects. Radiograph of acardius twin (**b**) showed a short segment of the spine, a femur, a tibia, and a fibula

Achondrogenesis

Contents

Marco Fraccaro first described achondrogenesis in 1952 (Fraccardo 1952). He used the term to describe a stillborn female with severe micromelia and marked histological cartilage changes. The term was later used to characterize the most severe forms of chondrodysplasia in humans, which were invariably lethal before or shortly after birth. By the 1970s, researchers concluded that achondrogenesis was a heterogeneous group of chondrodysplasias lethal to neonates; achondrogeneses type I (Fraccaro-Houston-Harris type) and type II (Langer-Saldino type) were distinguished on the basis of radiological and histological criteria.

Achondrogenesis type I was further subdivided, on the basis of convincing histological criteria, into type IA, which has apparently normal cartilage matrix but inclusions in chondrocytes, and type IB (Borochowitz et al. 1988), which has an abnormal cartilage matrix. Classification of type IB as a separate group has been confirmed recently by the discovery of its association with mutations in the diastrophic dysplasia sulfate transporter (*DTDST*) gene, making it allelic with diastrophic dysplasia.

Synonyms and Related Disorders

Achondrogenesis type IA (Houston-Harris type); Achondrogenesis type IB (Fraccaro type); Achondrogenesis type II (Langer-Saldino type); Type II achondrogenesis-hypochondrogenesis

Genetics/Basic Defects

1. Type IA: an autosomal recessive disorder, caused by mutation in the thyroid hormone receptor interactor 11 (TRIP 11) gene which is mapped on 14q32.12 (Smits et al. 2010)
2. Type IB
   1. An autosomal recessive disorder
   2. Resulting from mutations of the *DTDST* gene, which encodes the SLC26A2 sulfate transporter, which is located at 5q32–q33 (Superti-Furga et al. 1996a)
3. Type II
   1. Autosomal dominant type II collagenopathy.
   2. Resulting from mutations in the *COL2A1* gene, which is located at 12q13.1–q13.3.

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3. Report of a familial case of achondrogenesis type II caused by a dominant *COL2A1* mutation and "patchy" expression in the mosaic father (Forzano et al. 2007) suggests that somatic mosaicism can lead to a milder but generalized clinical phenotype.
4. Type II achondrogenesis-hypochondrogenesis (Borochowitz et al. 1986): identification of abnormal type II collagen (COL2A1 gene mutations) (Godfrey and Hollister 1988; Körkkö et al. 2000).

4. Mutations within the *COL2A1* gene also cause the following skeletal dysplasias (Forzano et al. 2007):
   1. Hypochondrogenesis
   2. Spondyloepiphyseal dysplasia (SED) congenita
   3. SED Namaqualand type
   4. Mild SED with precocious osteoarthritis
   5. Spondyloepimetaphyseal dysplasia, Strudwick type
   6. Kniest dysplasia
   7. Multiple epiphyseal dysplasia with myopia and conductive deafness
   8. Spondyloperipheral dysplasia
   9. Stickler dysplasia type I
5. Genetically related (allelic) disorders: three other phenotypes (all with an autosomal recessive inheritance) associated with SLC26A2 (DTDST) mutation (Bonafé et al. 2013)
   1. Atelosteogenesis type 2: a neonatal-lethal chondrodysplasia with clinical and histological characteristics that resemble those of diastrophic dysplasia (Hastbacka et al. 1996).
   2. Diastrophic dysplasia: a skeletal dysplasia characterized by short stature, joint contractures, cleft palate, and characteristic clinical signs such as the "hitchhiker" thumb and cystic swelling of external ears. The first mutations in *SLC26A2* were found in individuals with DTD (Hastbacka et al. 1994).
   3. Recessive multiple epiphyseal dysplasia (EDM4): characterized by joint pain (usually in the hips and knees); deformities of the hands, feet, and knees; and scoliosis. Approximately 50% of affected individuals have an abnormal finding at birth (e.g., clubfoot, cleft palate, or cystic ear swelling) (Superti-Furga et al. 1996b, 1999, 2001).

Clinical Features

1. Prenatal/perinatal history (Chen 2013, 2015)
   1. Polyhydramnios
   2. Hydrops
   3. Breech presentation
   4. Perinatal death
2. Achondrogenesis type I
   1. Growth
      1. Lethal neonatal dwarfism
      2. Mean birth weight of 1,200 g
   2. Craniofacial features
      1. Disproportionately large head
      2. Soft skull
      3. Sloping forehead
      4. Convex facial plane
      5. Flat nasal bridge, occasionally associated with a deep horizontal groove
      6. Small nose, often with anteverted nostrils
      7. Long philtrum
      8. Retrognathia
      9. Increased distance between lower lip and lower edge of chin
      10. Double chin appearance
   3. Extremely short neck
   4. Thorax
      1. Short and barrel-shaped thorax
      2. Lung hypoplasia
   5. Heart
      1. Patent ductus arteriosus
      2. Atrial septal defect
      3. Ventricular septal defect
   6. Protuberant abdomen
   7. Limbs
      1. Extremely short (micromelia), shorter than type II

2. Flipper-like appendages
3. Achondrogenesis type II (Langer-Saldino type) (Chen et al. 1981)
   1. Growth
      1. Lethal neonatal dwarfism
      2. Mean birth weight of 2,100 g
   2. Craniofacial features
      1. Disproportionately large head
      2. Large and prominent forehead
      3. Midfacial hypoplasia
         1. Flat facial plane
         2. Flat nasal bridge
         3. Small nose with severely anteverted nostrils
      4. Normal philtrum
      5. Micrognathia
      6. Cleft palate
   3. Extremely short neck
   4. Thorax
      1. Short and flared thorax
      2. Bell-shaped cage
      3. Lung hypoplasia
   5. Protuberant abdomen
   6. Extremely short limbs (micromelia)

Diagnostic Investigations

1. Radiological features (Chen 2013)
   1. Variable features
   2. No single obligatory feature
   3. Distinction between type IA and type IB on radiographs not always possible
   4. Degree of ossification: age dependent and caution is needed when comparing radiographs at different gestational ages
   5. Achondrogenesis type I
      1. Skull: varying degrees of deficient cranial ossification consisting of small islands of bone in membranous calvaria
      2. Thorax and ribs
         1. Short and barrel-shaped thorax
         2. Thin ribs with marked expansion at costochondral junction, frequently with multiple fractures
      3. Spine and pelvis
         1. Poorly ossified spine, ischium, and pubis
         2. Poorly ossified iliac bones with short medial margins
      4. Limbs and tubular bones
         1. Extreme micromelia, with limbs much shorter than in type II
         2. Prominent spikelike metaphyseal spurs
         3. Femur and tibia frequently presenting as short bone segments
      5. Subtype IA (Houston-Harris type)
         1. Poorly ossified skull
         2. Thin ribs with multiple fractures
         3. Unossified vertebral pedicles
         4. Arched ilium
         5. Hypoplastic but ossified ischium
         6. Wedged femur with metaphyseal spikes
         7. Short tibia and fibula with metaphyseal flare
      6. Subtype IB (Fraccaro type)
         1. Adequately ossified skull
         2. Absence of rib fractures
         3. Total lack of ossification or only rudimentary calcification of the center of the vertebral bodies
         4. Ossified vertebral pedicles
         5. Iliac bones with ossification only in their upper part, giving a crescent-shaped, “paraglider-like” appearance on X-ray
         6. Unossified ischium
         7. Shortened tubular bones without recognized axis
         8. Metaphyseal spurring giving the appearance of a “thorn apple” or “acanthocyte” (a descriptive term in hematology)
         9. Trapezoid femur
         10. Stellate tibia
         11. Unossified fibula
         12. Poorly ossified phalanges
   6. Achondrogenesis type II
      1. Skull

1. Normal cranial ossification
2. Relatively large calvaria

2. Thorax and ribs
1. Short and flared thorax
2. Bell-shaped cage
3. Shorter ribs without fractures

3. Spine and pelvis: relatively well-ossified iliac bones with long, crescent-shaped medial and inferior margins
4. Limbs and tubular bones
1. Short, broad bones, usually with some diaphyseal constriction and flared, cupped metaphyseal ends
2. Metaphyseal spurs, usually smaller than type I

2. Histological features (Yang and Bernstein 1975, 1977; Yang et al. 1974, 1976a, b; Molz and Spycher 1980; Horton et al. 1987; Yang and Gilbert-Barnes 1997)
1. Achondrogenesis type IA
1. Normal cartilage matrix
2. Absent collagen rings around the chondrocytes
3. Vacuolated chondrocytes
4. Presence of intrachondrocytic inclusion bodies (periodic acid-Schiff [PAS] stain positive, diastase resistant)
5. Extraskeletal cartilage involvement
6. Enlarged lacunas
7. Woven bone

2. Achondrogenesis type IB
1. Abnormal cartilage matrix: presence of "demasked" coarsened collagen fibers, particularly dense around the chondrocytes, forming collagen rings
2. Abnormal staining properties of cartilage
1. Reduced staining with cationic dyes, such as toluidine blue or Alcian Blue, probably because of a deficiency in sulfated proteoglycans.
2. This distinguishes type IB from type IA, in which the matrix is close to normal and inclusions can be seen in chondrocytes, and from achondrogenesis type II, in which cationic dyes give a normal staining pattern.

3. Achondrogenesis type II
1. Cartilage
1. Slightly larger than normal
2. Grossly distorted (lobulated and mushroomed)

2. Markedly deficient cartilaginous matrix
3. Severe disturbance in endochondral ossification
4. Hypercellular and hypervascular reserve cartilage with large, primitive mesenchymal (ballooned) chondrocytes with abundant clear cytoplasm (vacuoles) ("Swiss cheese-like")
5. Overgrowth of membranous bones resulting in cupping of the epiphyseal cartilages
6. Decreased amount and altered structure of proteoglycans
7. Relatively lower content of chondroitin 4-sulfate
8. Lower molecular weight and decreased total chondroitin sulfation
9. Absence of type II collagen
10. Increased amounts of type I and type III collagen

3. Scanning and transmission electron microscopy (Ornoy et al. 1976)
1. Metaphysis: deficient intercartilaginous septa with abnormally large calcifying globules
2. Diaphysis: disturbed orientation of bone trabeculae and collagen fibers within trabeculae
3. Osteocytic lacunae: numerous, wide, and irregular arrangement and shape

4. Biochemical testing
1. Lack of sulfate incorporation: cumbersome and not used for diagnostic purposes
2. Sulfate incorporation assay in cultured skin fibroblasts or chondrocytes: recommended in the rare instances in which the diagnosis of achondrogenesis type IB is strongly suspected but

molecular genetic testing fails to detect *SLC26A2* (*DTDST*) mutations

5. Molecular genetic studies
    1. Mutation analysis of the *DTDST* gene, reported in:
        1. Achondrogenesis type IB (the most severe form)
        2. Atelosteogenesis type II (an intermediate form)
        3. Diastophic dysplasia (the mildest form)
        4. Recessive multiple epiphyseal dysplasia
    2. Achondrogenesis type IB
        1. Mutation analysis: testing of the following four most common *SLC26A2* (*DTDST*) gene mutations (mutation detection rate about 60%)
            1. R279W
            2. IVS1 + 2 > C ("Finnish" mutation)
            3. delV340
            4. R178X
        2. Sequence analysis of the *SLC26A2* (*DTDST*) coding region (mutation detection rate over 90%)
            1. Private mutations
            2. Common mutations
    3. Achondrogenesis type II: mutation analysis of the *COL2A1* gene

Genetic Counseling

1. Recurrence risk (Superti-Furga 1996; Bonafé et al. 2013)
    1. Patient's sib
        1. Achondrogenesis type IA and type IB (autosomal recessive disorders)
            1. Recurrence risk: 25%
            2. Unaffected sibs of a proband: two-third chance of being heterozygotes
        2. Achondrogenesis type II
            1. Usually caused by a new dominant mutation, in which case recurrence risk is not significantly increased.
            2. Asymptomatic carrier parent (germline mutation for a dominant mutation) (Faivre et al. 2004) may be present in the families of affected patients, in which case recurrence risk can be up to 50%.
    2. Patient's offspring: lethal entities not surviving to reproduction
2. Prenatal diagnosis (Soothill et al. 1993; Maizner and Barnhard 1995; Tongsong et al. 1995; Taner et al. 2008)
    1. Ultrasonography
        1. Polyhydramnios
        2. Fetal hydrops
        3. Disproportionally big head
        4. Nuchal edema
        5. Cystic hygroma
        6. A narrow thorax
        7. Short limbs
        8. Poor ossification of vertebral bodies and limb tubular bones (leading to difficulties in determining their length)
        9. Suspect achondrogenesis type I
            1. An extremely echo-poor appearance of the skeleton
            2. A poorly mineralized skull
            3. Short limbs
            4. Rib fractures
    2. Molecular genetic studies: require prior identification of the disease-causing mutations in the family
        1. Prenatal diagnosis of achondrogenesis type IB and type II by mutation analysis of chorionic villus DNA or amniocyte DNA in the first or second trimester
        2. Achondrogenesis type IB
            1. Characterize both alleles of *SLC26A2* (*DTDST*) beforehand.
            2. Identify the source parent of each allele.
            3. Theoretically, analysis of sulfate incorporation in chorionic villi might be used for prenatal diagnosis, but experience is lacking.

3. Achondrogenesis type II
    1. The affected fetus usually with a new dominant mutation of the *COL2A1* gene
    2. Possible presence of asymptomatic carriers in families of an affected patient
    3. Prenatal diagnosis possible if the mutation has been characterized in the affected family
3. Preimplantation genetic diagnosis (PGD) for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.
4. Management
    1. Supportive care
    2. No treatment available for the underlying lethal disorder

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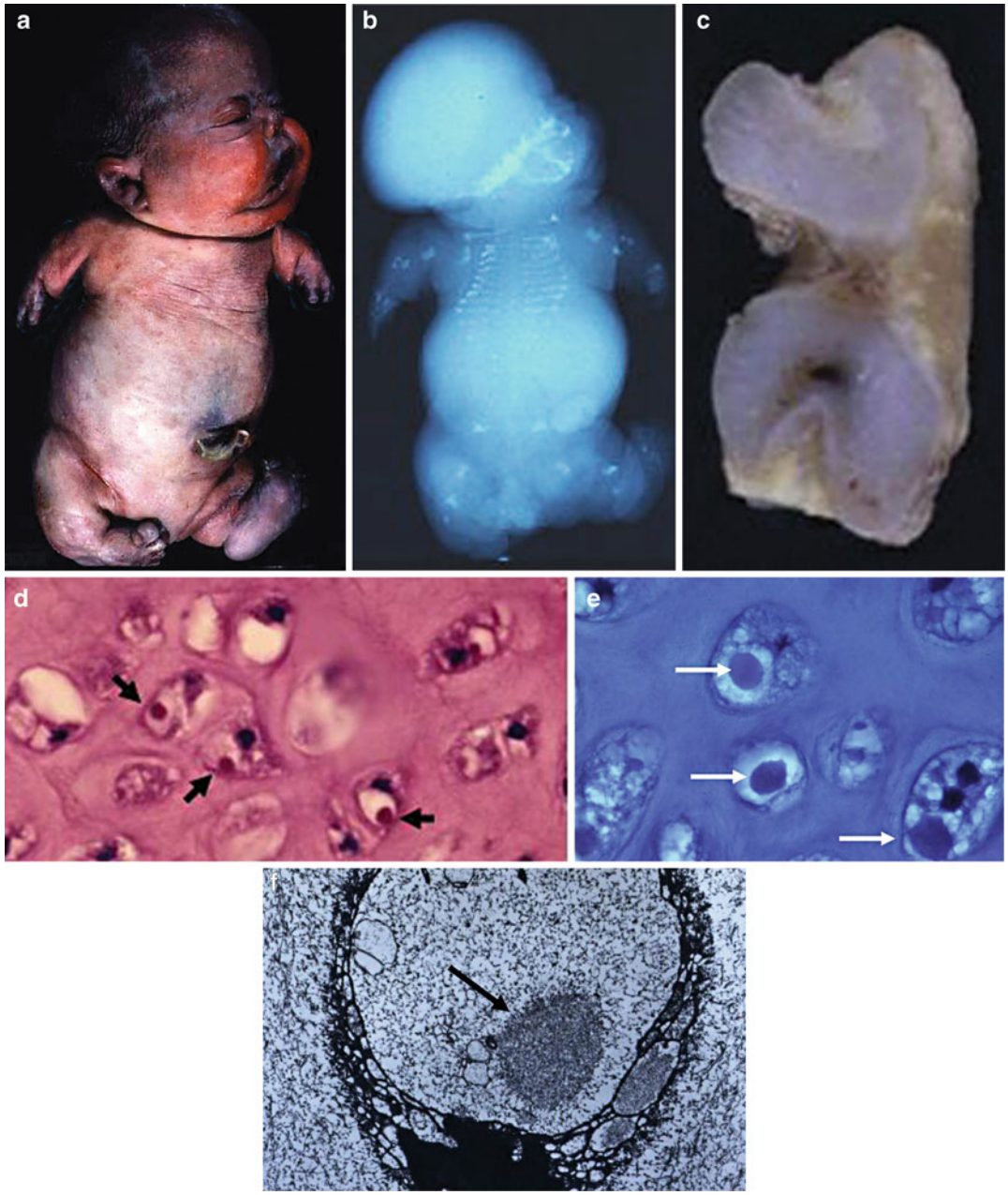

Fig. 1 A neonate with achondrogenesis type I showing large head, short trunk, and extreme micromelia (**a**). Radiographs (**b**) show unossified calvarium, vertebral bodies, and some pelvic bones. The remaining bones are extremely small. There are multiple rib fractures. The sagittal section of the femora and the humeri is similar. An extremely small ossified shaft is capped by a relatively large epiphyseal cartilage at both ends (**c**). Photomicrographs of resting cartilage with high magnification (**d**, **e**) show many chondrocytes that contain large cytoplasmic inclusions which are within clear vacuoles (*arrows*) (diastase PAS stain). Electron micrograph (**f**) shows inclusion as a globular mass of electron-dense material (*arrow*). It is within a distended cistern of rough endoplasmic reticulum (Yang and Bernstein 1977; Yang et al. 1976a) (Courtesy of Dr. Samuel Yang)

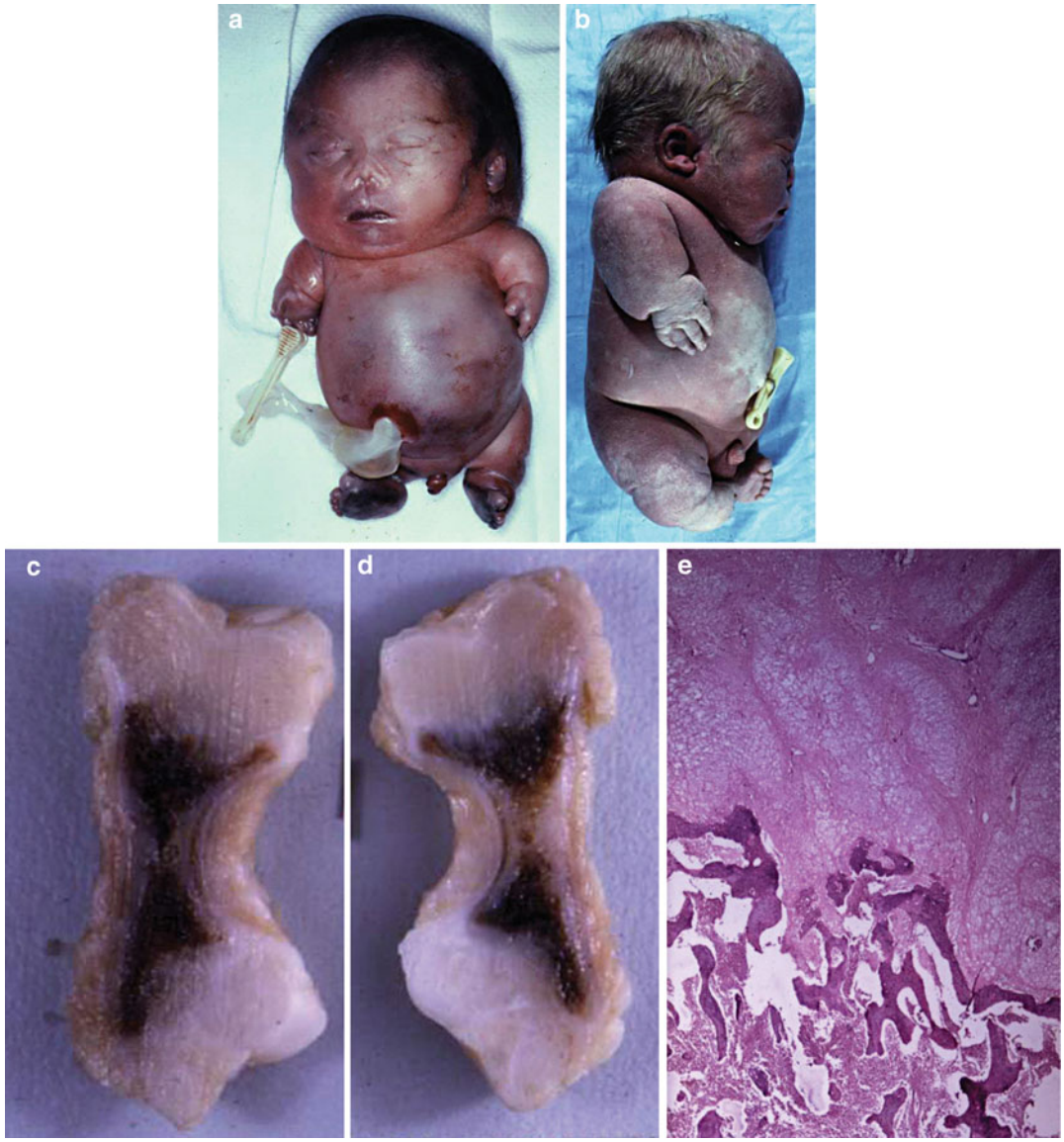

Fig. 2 (**a**–**e**) Achondrogenesis type II. As in type I, this neonate shows large head, short trunk, and micromelia (Yang and Gilbert-Barnes 1997). Sagittal section of the femur shows much better ossification of the shaft than type I. The cartilage lacks glistering appearance due to cartilage matrix deficiency. Photomicrograph of the entire cartilage shows severe deficiency of cartilage matrix. The cartilage canals are large, fibrotic, and stellate in shape. Physeal growth zone is severely retarded (Courtesy of Dr. Samuel Yang)

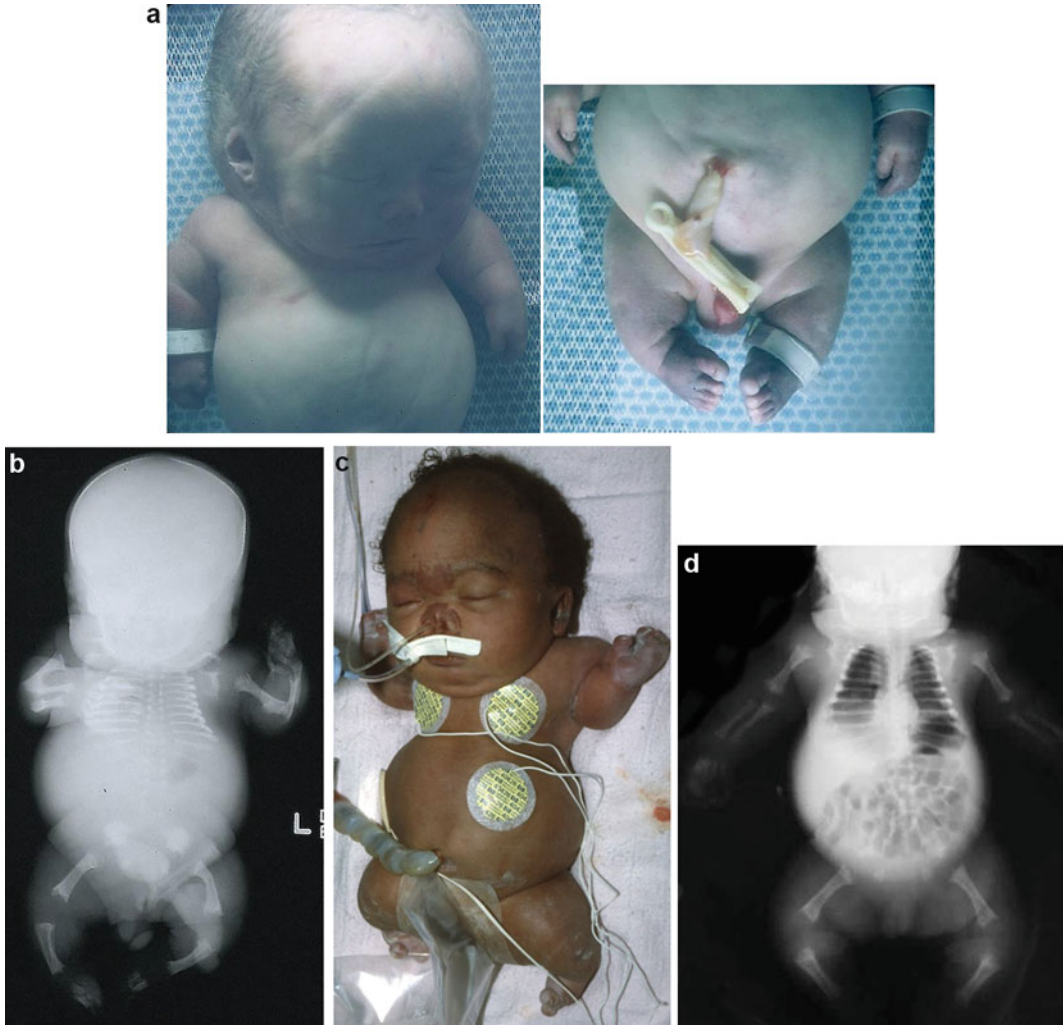

Fig. 3 Two infants (**a**, **c**) with achondrogenesis type II showing milder spectrum of manifestations, bordering the type II and spondyloepiphyseal dysplasia congenita (**b**, **d**)

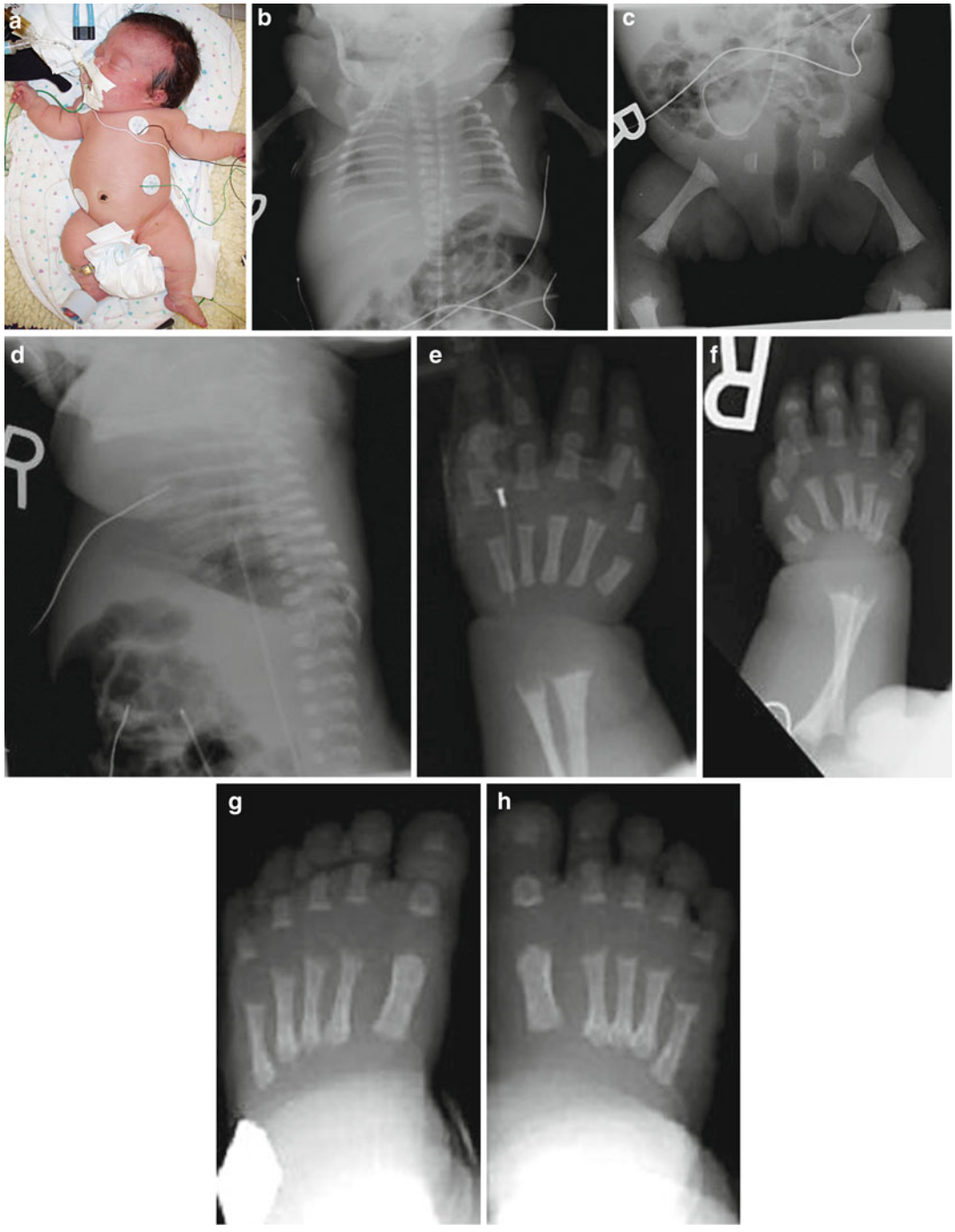

Fig. 4 A newborn girl with achondrogenesis type II showing large head, midfacial hypoplasia, short neck, small chest, and short limbs (**a**). The radiographs show generalized shortening of the long bones of the upper and lower extremities with marked cupping (metaphyseal spurs) at the metaphyseal ends of the bones. This is most evident at the distal ends of the tibia, fibular, radius, and ulna and distal ends of the digits (**c**, **e**–**h**). Radiographs also show short ribs without fractures and hemivertebrae involving thoracic vertebrae as well as the sacrum (**b**, **d**). Conformation-sensitive gel electrophoresis analysis indicated a sequence variation in the fragment containing exon 19 and the flanking sequences of the *COL2A1* gene (Gly244Asp). Similar mutations in this area have been seen in patients diagnosed with hypochondroplasia and achondrogenesis type II

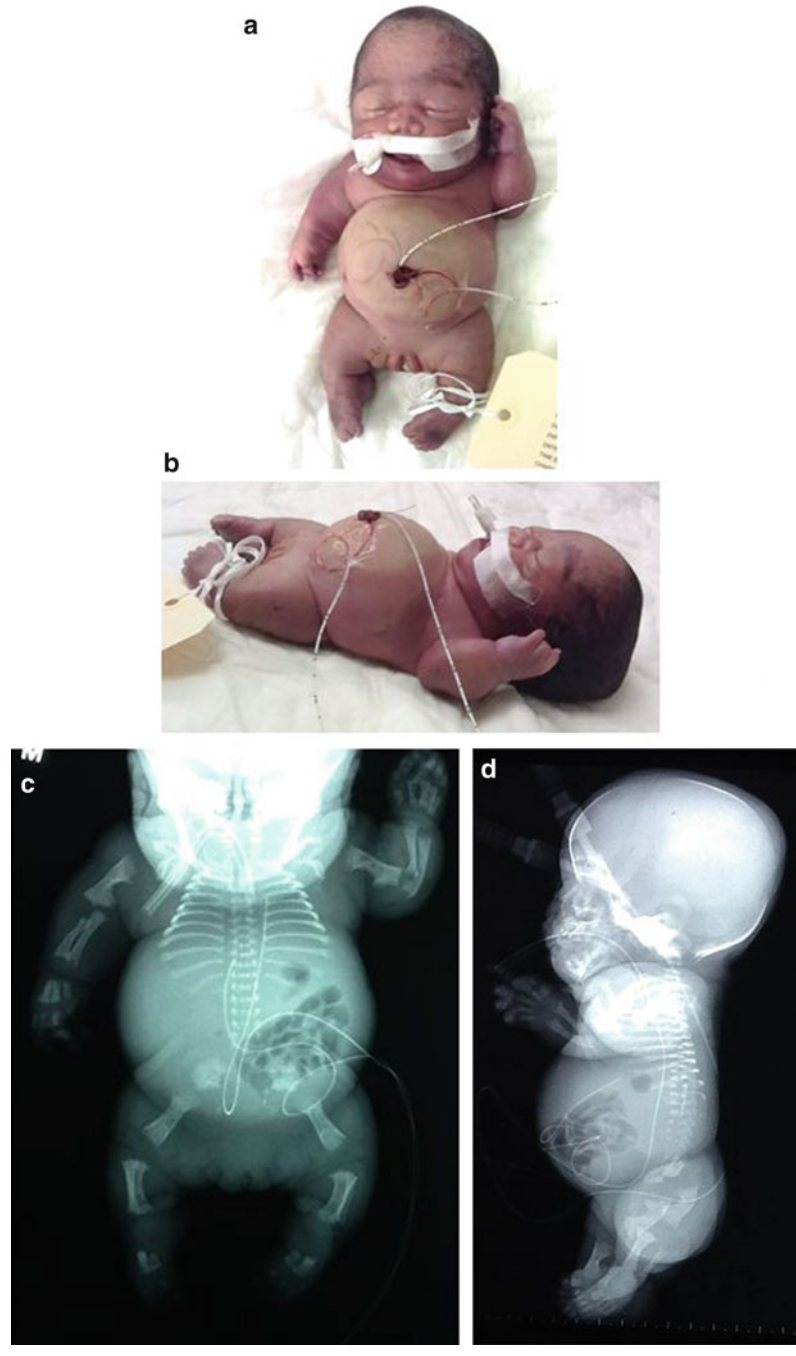

Fig. 5 A neonate (twin A) (**a**, **b**) with achondrogenesis II showing large head, midfacial hypoplasia, short neck, small chest, protuberant abdomen, and short limbs. The radiographs (**b**, **c**) showed generalized shortening of the long bones of the upper and lower extremities with marked cupping (metaphyseal spurs) at the metaphyseal ends of the bones, most evident at the distal ends of the tibia, fibular, radius, and ulna and distal ends of the digits. The infant was delivered at 29 weeks via cesarean section secondary to breech presentation of twin A. Twin B weighed 780 g and had APGARS of 1, 2, and 2 at 1, 5, and 10 min, respectively. The fetus expired shortly after birth due to respiratory failure despite ventilator support. *COL2A1* gene analysis from cultured fibroblasts showed a variation in the fragment containing exon 22 and the flanking sequences of the *COL2A1* gene. Sequencing revealed a nucleotide G to A substitution that converted a codon for glycine-316 (GGT) to a codon for aspartic acid (GAT) at cDNA position c.1340 (position from +1Met gly516asp c.1547). This exact mutation has been previously reported in patients diagnosed with achondrogenesis type II. The fetus is heterozygous for the mutation (c.1340G>A)

Achondroplasia

Contents

Genetics/Basic Defects

1. Inheritance.
    1. Autosomal dominant disorder with complete penetrance
    2. Sporadic in about 80% of the cases, the result of a de novo mutation
    3. Presence of paternal age effect (advanced paternal age in sporadic cases)
    4. Gonadal (germinal) mosaicism (two or more children with classic achondroplasia born to normal parents) (Fryns et al. 1983)
2. Caused by mutations in the gene of the fibroblast growth factor receptor 3 (*FGFR3*) on chromosome 4p16.3 (Velinov et al. 1994; Shiang et al. 1994).
    1. About 98% of achondroplasia with G-to-A transition and about 1% G-to-C transversion at nucleotide 1138. Both mutations resulted in the substitution of an arginine residue for a glycine at position 380 (G380A) of the mature protein in the transmembrane domain of *FGFR3*.
    2. A rare mutation causing substitution of a nearby glycine 375 with a cysteine (G375C).
    3. Another rare mutation causing substitution of glycine346 with glutamic acid (G346E).
    4. The specific mechanisms by which *FGFR3* mutations disrupt skeletal development in achondroplasia remain elusive.
3. Different mutations in *FGFR3* can cause the following spectrum of disorders (Spranger 1988; Spranger et al. 1994; Lemyre et al. 1999; Vajo et al. 2000; Superti-Furga and Unger 2007):
    1. Hypochondroplasia
    2. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDN) (Bellus et al. 1999)
    3. Thanatophoric dysplasia
    4. Muenke coronal craniosynostosis
    5. Crouzon syndrome with acanthosis nigricans
4. *FGFR3* mutations affect the cartilaginous growth plate in the growing skeleton, therefore disturbing cartilage function during linear bone growth (Richette et al. 2008).
5. Basic defect: zone of chondroblast proliferation in the physeal growth plates.
    1. Abnormally retarded endochondral ossification with resultant shortening of tubular bones and flat vertebral bodies, while membranous ossification (skull, facial bones) is not affected.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Physeal growth zones show normal columnization, hypertrophy, degeneration, calcification, and ossification. However, the growth is quantitatively reduced significantly.
3. Achondroplasia as the result of a quantitative loss of endochondral ossification rather than the formation of abnormal tissue.
4. Normal diameter of the bones secondary to normal subperiosteal membranous ossification of tubular bones, the results being production of short, thick tubular bones, leading to short stature with disproportionately shortened limbs.

Clinical Features

1. Major clinical symptoms (Spranger et al. 1974; Horton et al. 2007; Baujat et al. 2008; Shirley and Ain 2009)
    1. Delayed motor milestones during infancy and early childhood
    2. Sleep disturbances secondary to both neurological and respiratory complications
    3. Breathing disorders
        1. A high prevalence (75%) of breathing disorders during sleep.
        2. Snoring is the commonest observed abnormality, but the reported incidence of obstructive sleep apnea shows wide variation (10–75%) (Afsharpaiman et al. 2013).
        3. Obstructive apnea caused by upper airway obstruction.
        4. The majority of respiratory complaints due to restrictive lung disease secondary to diminished chest size or upper airway obstruction and rarely due to spinal cord compression.
    4. Symptomatic spinal stenosis in more than 50% of patients as a consequence of a congenitally small spinal canal
        1. Back pain
        2. Lower extremity sensory changes
        3. Incontinence
        4. Paraplegia
        5. Onset of symptoms: usually after 20 s or 30 s
    5. Neurologic symptoms classified based on neurologic severity and presentation of spinal stenosis (Lutter and Langer 1977)
        1. Type I (back pain with sensory and motor change of an insidious nature)
        2. Type II (intermittent claudication limiting ambulation)
        3. Type III (nerve root compression)
        4. Type IV (acute onset paraplegia)
    6. Symptoms secondary to foramen magnum stenosis
        1. Respiratory difficulty
        2. Feeding problems
        3. Cyanosis, quadriparesis
        4. Poor head control
    7. Symptoms secondary to cervicomedullary compression
        1. Pain
        2. Ataxia
        3. Incontinence
        4. Apnea
        5. Progressive quadriparesis
        6. Respiratory arrest
2. Major clinical signs
    1. Disproportionate short stature (dwarfism)
    2. Hypotonia during infancy and early childhood
    3. Relative stenosis of the foramen magnum in all patients, documented by CT
    4. Foramen magnum stenosis considered as the cause of increased incidence of:
        1. Hypotonia
        2. Sleep apnea
        3. Sudden infant death syndrome
    5. Symptomatic hydrocephalus in infancy and early childhood rarely due to narrowing of the foramen magnum
    6. Characteristic craniofacial appearance
        1. Disproportionately large head
        2. Frontal bossing
        3. Depressed nasal bridge
        4. Midfacial hypoplasia
        5. Narrow nasal passages

6. Prognathism
7. Dental malocclusion

7. A normal trunk length
8. A thoracolumbar kyphosis or gibbus usually present at birth or early infancy
9. Exaggerated lumbar lordosis when the child begins to ambulate
10. Prominent buttocks and protuberant abdomen secondary to increased pelvic tilt in children and adults
11. Generalized joint hypermobility, especially the knees
12. Rhizomelic micromelia (relatively shorter proximal segment of the limbs compared to the middle and the distal segments)
13. Limited elbow and hip extension
14. Trident hands (inability to approximate the third and fourth fingers in extension produces a "trident" configuration of the hand)
15. Short fingers (brachydactyly)
16. Bowing of the legs (genu varum) due to lax knee ligaments
17. Excess skin folds about thighs

3. Complications/risks (Hunter et al. 1998)
    1. Recurrent otitis media during infancy and childhood
        1. Conductive hearing loss
        2. Delayed language development
    2. Thoracolumbar gibbus
    3. Osteoarthropathy of the knee joints
    4. Neurological complications (Hecht et al. 1987; Hecht and Butler 1990; King et al. 2009)
        1. Small foramen magnum
        2. Cervicomedullary junction compression causing sudden unexpected death in infants with achondroplasia
        3. Apnea
        4. Communicating hydrocephalus
        5. Spinal stenosis
        6. Paraparesis
        7. Quadriparesis
        8. Infantile hypotonia
    5. Obesity
        1. Aggravating the morbidity associated with lumbar stenosis
        2. Contributing to the nonspecific joint problems and to the possible early cardiovascular mortality in this condition
    6. Obstetric complications
        1. Large head of the affected infant
        2. An increased risk of intracranial bleeding during delivery
        3. Marked obstetrical difficulties secondary to very narrow pelvis of achondroplastic women
4. Prognosis
    1. Normal intelligence and healthy, independent, and productive lives in vast majority of patients. Rarely, intelligence may be affected because of hydrocephalus or other CNS complications.
    2. Mean adult height.
        1. Approximately 131 cm $\pm$ 5.6 for males
        2. Approximately 124 cm $\pm$ 5.9 for females
    3. Weight for age charts: available for children with achondroplasia (Hoover-Fong et al. 2007).
    4. Standard growth curves: available for achondroplasia (Horton et al. 1978).
    5. Standard weight for height curves: available for achondroplasia (Hunter et al. 1996).
    6. Psychosocial problems related to body image because of severe disproportionate short stature.
    7. Life span for heterozygous achondroplasia.
        1. Usually normal unless there are serious complications
        2. Mean life expectancy approximately 10 years less than the general population (Wynn et al. 2007)
    8. Homozygous achondroplasia (Hall et al. 1969).
        1. A lethal condition with severe respiratory distress caused by rib cage deformity and upper cervical cord damage caused by small foramen magnum. The patients die soon after birth.
        2. Radiographic changes much more severe than the heterozygous achondroplasia.
    9. Normal fertility in achondroplasia.
        1. Pregnancy at high risk for achondroplastic women

2. Respiratory compromise common during the third trimester
3. Advise baseline pulmonary function studies before pregnancy to aid in evaluation and management
4. A small pelvic outlet usually requiring cesarean section under general anesthesia since the spinal or epidural approach is contraindicated because of spinal stenosis

10. Anticipatory guidance: Patients and their families can benefit greatly from anticipatory guidance published by the American Academy of Pediatrics Committee on Genetics (1995) and Clinical Report (2005).
11. Adaptations of patients to the environment to foster independence.
    1. Lowering faucets and light switches
    2. Using a step stool to keep feet from dangling when sitting
    3. An extended wand for toileting
    4. Adaptations of toys for short limbs
12. Support groups: Many families find it beneficial to interact with other families and children with achondroplasia through local and national support groups.

Diagnostic Investigations

1. Diagnosis of achondroplasia made by clinical findings, radiographic features, and/or *FGFR3* mutation analysis
2. Radiologic features (Langer et al. 1967; Horton et al. 2007)
    1. The skull
        1. Relatively large calvarium
        2. Prominent forehead
        3. Depressed nasal bridge
        4. Small skull base
        5. Small foramen magnum
        6. Dental malocclusion
    2. The spine
        1. Caudal narrowing of interpedicular distances in the lower lumbar spine
        2. Short vertebral pedicles
        3. Wide disk spaces
        4. Dorsal scalloping of the vertebral bodies in the newborn
        5. Concave posterior aspect of the vertebral bodies in childhood and adulthood
        6. Different degrees of anterior wedging of the vertebral bodies causing gibbus
    3. Th pelvis
        1. Lack of iliac flaring
        2. Narrow sacroiliac notch
        3. Horizontal acetabular portions of the iliac bones
    4. The limbs
        1. Rhizomelic micromelia
        2. Square or oval radiolucent areas in the proximal humerus and femur during infancy
        3. Tubular bones with widened diaphyses and flared metaphyses during childhood and adulthood
        4. Markedly shortened humeri
        5. Short femoral neck
        6. Disproportionately long fibulae in relation to tibiae
3. Craniocervical MRI
    1. Narrowing of the foramen magnum
    2. Effacement of the subarachnoid spaces at the cervicomedullary junction
    3. Abnormal intrinsic cord signal intensity
    4. Mild to moderate ventriculomegaly
4. Histology
    1. Normal histologic appearance of epiphyseal and growth plate cartilages.
    2. Shorter than normal growth plate: the shortening is greater in homozygous than in heterozygous achondroplasia, suggesting a gene dosage effect.
5. Mutation analysis (Bellus et al. 1995)
    1. G1138A substitution in *FGFR3* (about 98% of cases)
    2. G1138C substitution in *FGFR3* (about 1% of cases)

Genetic Counseling

1. Recurrence risk (Carter et al. 2007; Pauli 2012)

1. Patient's sib
    1. Recurrence risk after the conception of an affected child has always been considered very low, and less than 30 cases of recurrences among sibs have been reported so far (Natacci et al. 2008). It was possible to demonstrate somatic and germinal mosaicism in the mother (Henderson et al. 2000) and germinal mosaicism in the father (Natacci et al. 2008).
    2. Recurrence risk of achondroplasia in the sibs of achondroplastic children with unaffected parents: presumably higher than twice the mutation rate because of gonadal mosaicism. Currently, the risk is estimated as 1 in 443 (0.02%) (Mettler and Fraser 2000).
    3. Fifty percent affected if one of the parents is affected.
    4. Twenty-five percent affected with homozygous achondroplasia (resulting in a much more severe phenotype that is usually lethal early in infancy) and 50% affected with heterozygous achondroplasia if both parents are affected with achondroplasia.
2. Patient's offspring
    1. Fifty percent affected (with heterozygous achondroplasia) if the spouse is normal.
    2. Twenty-five percent affected with homozygous achondroplasia and 50% affected with heterozygous achondroplasia if the spouse is also affected with achondroplasia. There is still a 25% chance that the offspring will be normal.

2. Prenatal diagnosis
    1. Prenatal ultrasonography.
        1. Suspect achondroplasia on routine ultrasound findings of a falloff in limb growth (<3rd percentile), increased biparietal diameter (>95th percentile), and low nasal bridge (Cordone et al. 1993; Mesoraca et al. 1996), usually during the third trimester of pregnancy, in case of parents with normal heights. About one third of cases are suspected this way. However, one must be cautious because disproportionately short limbs are observed in a variety of conditions.
        2. Inability to make specific diagnosis of achondroplasia with certainty by ultrasonography unless by radiography late in gestation or after birth.
        3. Request of prenatal ultrasonography by an affected parent, having 50% risk of having a similarly affected child, to optimize obstetric management.
        4. Follow pregnancy by a femoral growth curve in the second trimester by serial ultrasound scans to enable prenatal distinction between homozygous, heterozygous, and unaffected fetuses, in case of both affected parents (Patel and Filly 1995).
    2. Prenatal radiography.
        1. Shortened long bones with wide metaphyses
        2. Slim and radiolucent area in the proximal femur
        3. Horizontal acetabular roof
        4. The above features not always detected
    3. Three-dimensional computed tomography scan (3D CT scan) may be used after 30 weeks of gestation (Krakow et al. 2003; Ruano et al. 2004).
        1. Slightly flat vertebral bodies with medial spurs
        2. Pointed femora with proximal extremity
        3. Round and square ilia with an oval radiolucent area in the proximal femur
    4. On computed tomography and postnatal X-ray, proximal femoral metaphysis appeared rounded, with poor, uneven

ossification. Connection to diaphysis was abnormal, with relative overgrowth of the periosteum, creating a new diagnostic sign, called the "collar hoop" sign (Boulet et al. 2009).

5. Prenatal molecular testing.
    1. Molecular technology applied to prenatal diagnosis of a fetus suspected of or at risk for having achondroplasia
    2. Simple methodology requiring only one PCR and one restriction digest to detect a very limited number of mutations causing achondroplasia
    3. Preimplantation genetic diagnosis
        1. Available at present (Moutou et al. 2003)
        2. The initial practice raising questions on the feasibility of such a test, especially with affected female patients

3. Management
    1. Adaptive environmental modifications
        1. Appropriately placed stools
        2. Seating modification
        3. Other adaptive devices
    2. Obesity control
    3. Obstructive apnea
        1. Adenoidectomy and tonsillectomy (Mogayzel et al. 1998)
        2. Continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP) for clinically significant persistent obstruction
        3. Surgical improvement of the airway, including mid-face advancement (Afsharpairman et al. 2013)
        4. Extremely rare for requiring temporary tracheostomy
    4. Experimental growth hormone therapy (Horton et al. 1992; Shohat et al. 1996; Seino et al. 2000)
        1. Resulting in transient increases in growth velocity
        2. Long-term result not conclusive
    5. Hydrocephalus (Pierre-Kahn et al. 1980)
        1. Observation for benign ventriculomegaly
        2. May need surgical intervention for clinically significant hydrocephalus
    6. Kyphosis
        1. Adequate support for sitting in early infancy
        2. Bracing using a thoracolumbosacral orthosis for severe kyphosis in young children
        3. Surgical intervention for medically unresponsive cases
    7. Surgical decompression for unequivocal evidence for cervical cord compression
    8. Decompression laminectomy for severe and progressive lumbosacral spinal stenosis
    9. Limb lengthening through osteotomy and stretching of the long bones (Aldegheri et al. 1988; Lavini et al. 1990; Ganel et al. 1979; Rimoin 1991; Ganel and Horoszowski 1996; Yasui et al. 1997)
        1. Controversial
        2. Difficult to achieve the benefits of surgery
            1. Need strong commitment on the part of the patients and their families for the time in the hospital and the number of operations
            2. A high risk of infection
            3. Occurrence of possible severe permanent sequelae (damage to joint and soft tissue)
            4. May result in poorer quality of life
    10. Potential anesthetic risks related to:
        1. Obstructive apnea
        2. Cervical compression
    11. Risks associated with pregnancy in women with achondroplasia (Lattanzi and Harger 1982)
        1. Cephalopelvic disproportion secondary to marked pelvic contracture the most consistent features
        2. Worsening neurologic symptoms related to increasing hyperlordosis and maternal respiratory failure
        3. Anticipate a scheduled cesarean delivery due to cephalopelvic disproportion

4. Preeclampsia
5. Polyhydramnios
6. Increased fetal wastage and neonatal death

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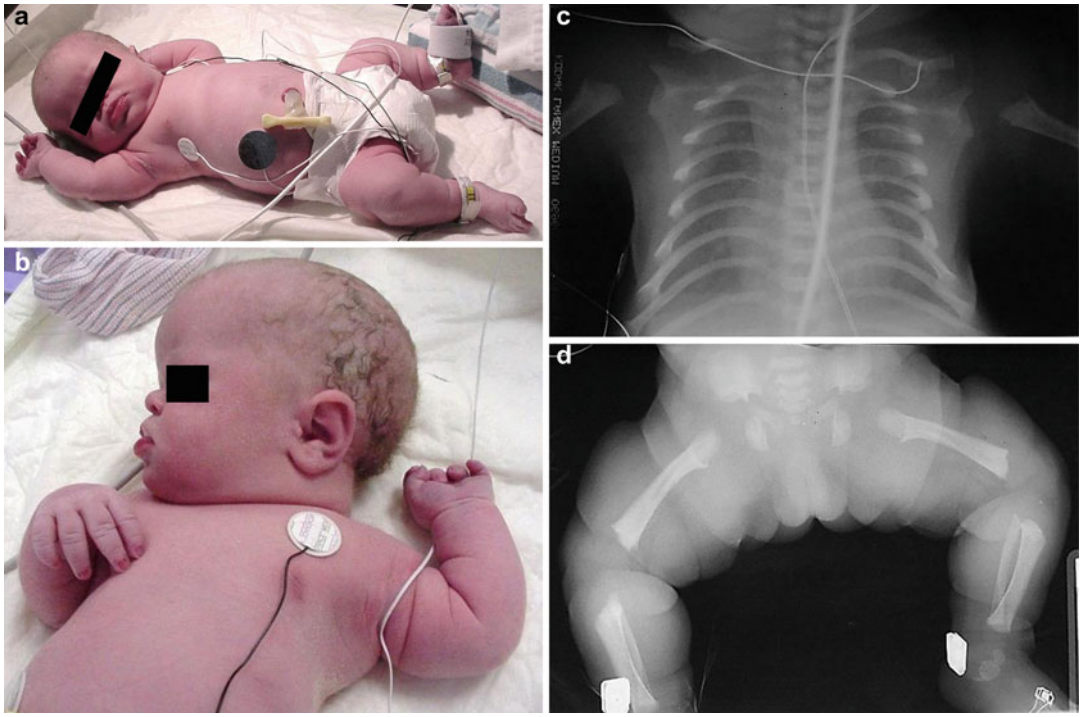


Fig. 1 A newborn with achondroplasia showing large head, depressed nasal bridge, short neck, normal length of the trunk, narrow chest, rhizomelic micromelia, and trident hands (**a**, **b**). The radiographs showed narrow chest, characteristic pelvis, micromelia, and oval radiolucent proximal portion of the femurs (**c**, **d**). Molecular analysis showed 1138 G → C transversion mutation which has been observed in approximately 1.9 % of achondroplasia chromosomes

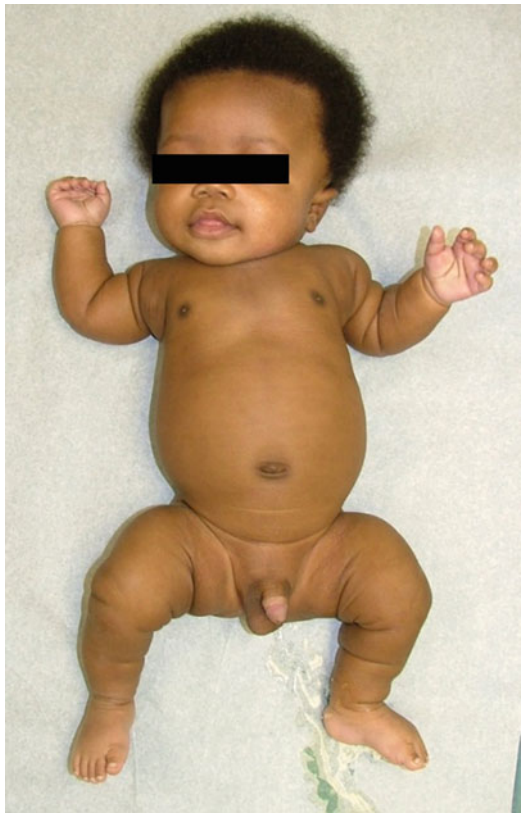


Fig. 2 A 4-month-old boy with achondroplasia showing typical craniofacial features and rhizomelic shortening of limbs (confirmed by radiograms). Molecular study revealed 1138 G-to-A transition mutation which has been observed in approximately 98% of achondroplasia chromosomes

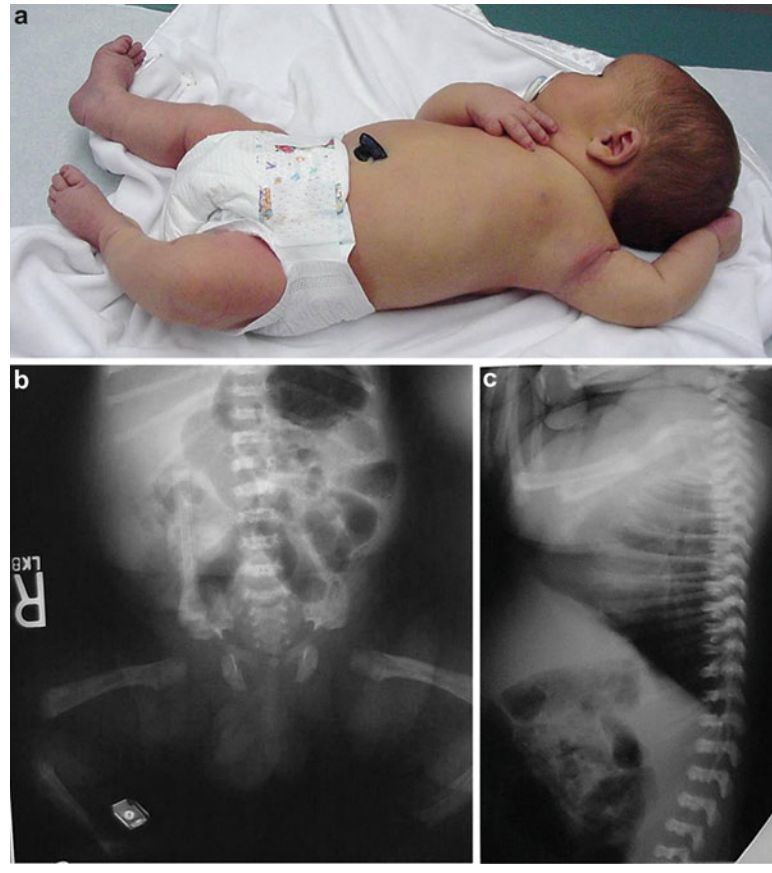


Fig. 3 Another achondroplastic neonate with typical clinical features (**a**) and radiographic findings (**b**, **c**). Note the abnormal vertebral column with wide intervertebral spaces and abnormal vertebral bodies

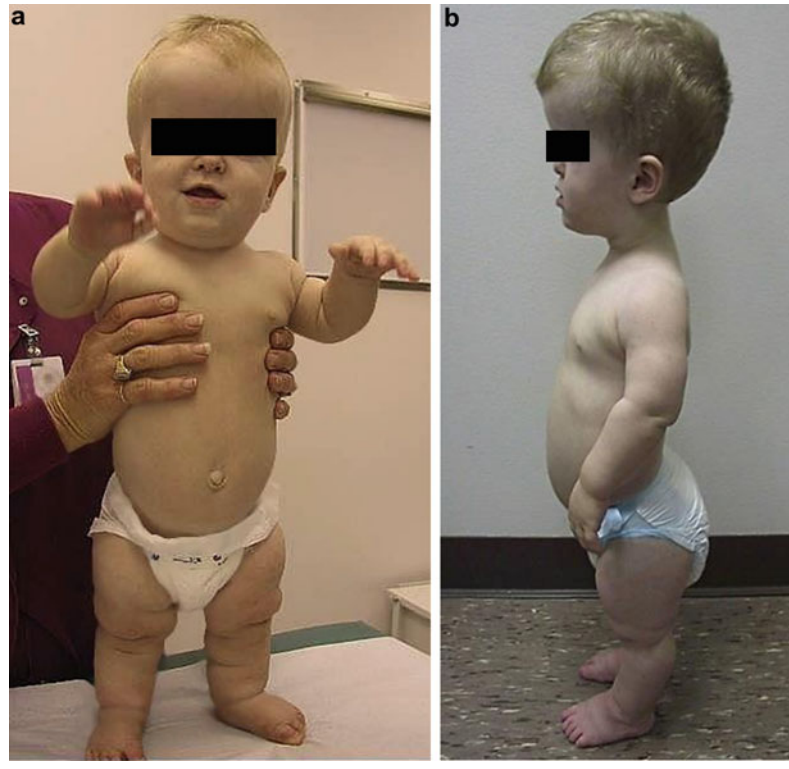


Fig. 4 A boy (7-month (**a**) and 2-year and 7-month old (**b**)) with achondroplasia showing a large head, small chest, normal size of the trunk, rhizomelic micromelia, and exaggerated lumbar lordosis

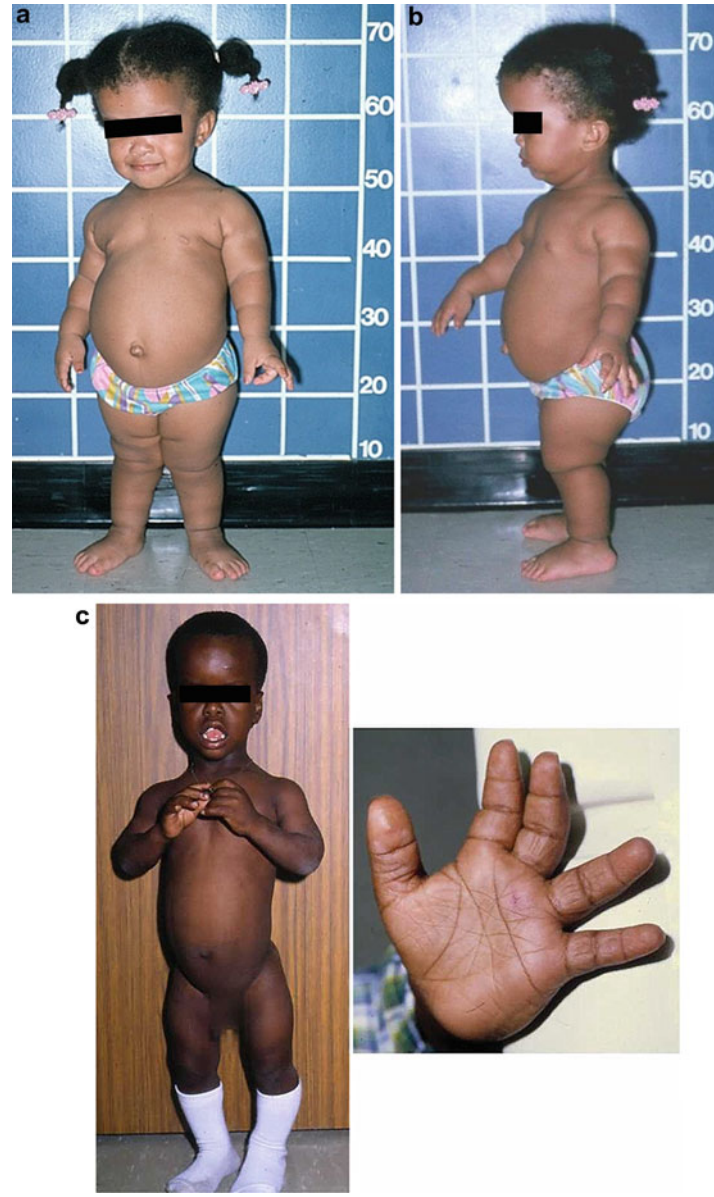


Fig. 5 Two older children with achondroplasia showing rhizomelic micromelia, typical craniofacial features, exaggerated lumbar lordosis (**a**–**c**), and trident hands (**d**)

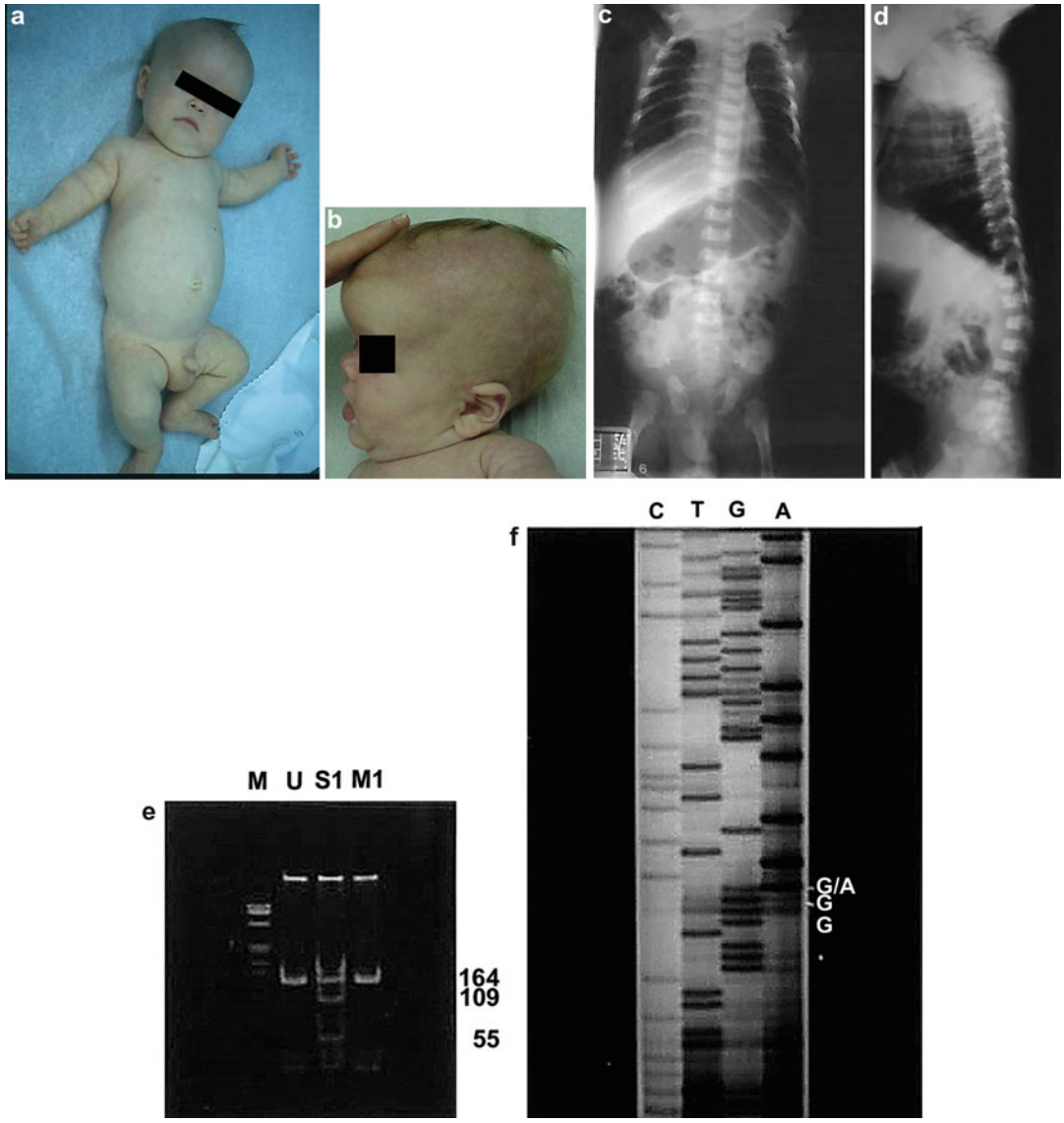


Fig. 6 A boy with achondroplasia and i(21q) Down syndrome presented with diagnostic dilemma. Besides craniofacial features typical for Down syndrome, the skeletal findings of achondroplasia dominate the clinical picture (**a**, **b**). The diagnosis of Down syndrome was based on the clinical features and the cytogenetic finding of i(21q) trisomy 21. The diagnosis of achondroplasia was based on the presence of clinical and radiographic findings (**c**, **d**) and confirmed by the presence of a common *FGFR3* gene mutation (Gly380Arg) detected by restriction enzyme analysis and sequencing of the PCR products (**e**, **f**) (Chen et al. 2000)

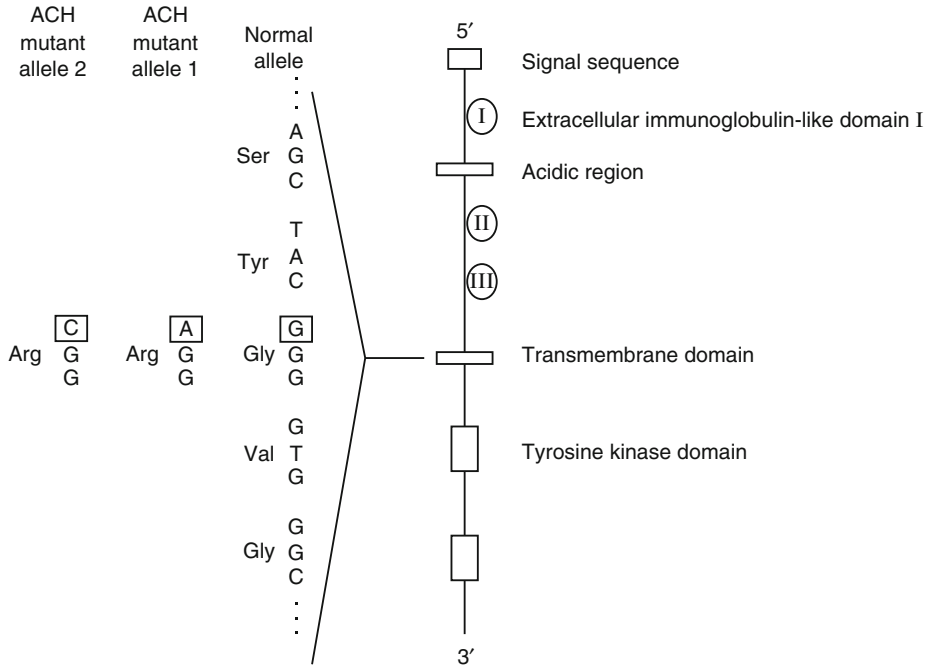


Fig. 7 Schematic of the *FGFR3* gene and DNA sequence of normal allele and mutant FGFR3 achondroplasia allele (Modified from Shiang et al. 1994)

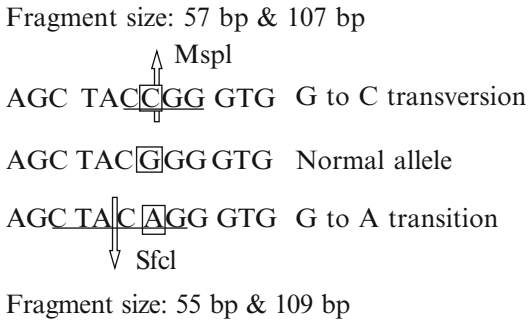


Fig. 8 Nucleotide change in the 1138 C allele creates a Msp1 site and nucleotide change in the 1138A allele creates a Sfc1. The base in the coding sequence that differs in the three alleles is *boxed* (Modified from Shiang et al. 1994)

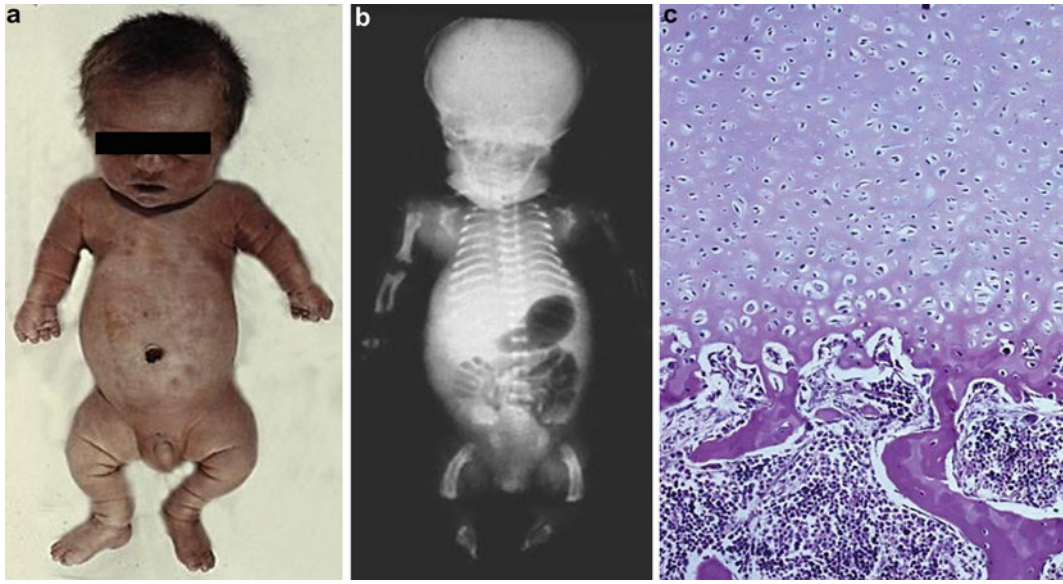
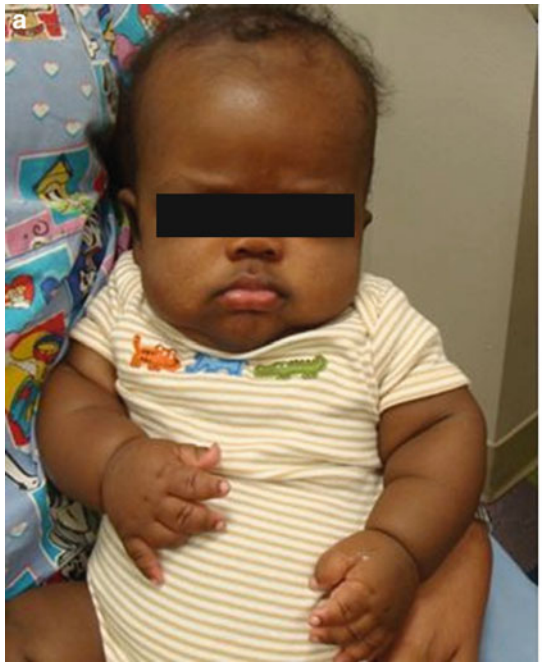


Fig. 9 Homozygous achondroplasia. Both parents are achondroplastic. The large head, narrow chest, and severe rhizomelic shortening of the limbs are similar to those of thanatophoric dysplasia (**a**). Radiograph (**b**) shows severe platyspondyly, small ilia, and short limb bones. Photomicrograph of the physeal growth zone (**c**) shows severe retardation and disorganization, similar to that of thanatophoric dysplasia (Yang and Gilbert-Barnes 1997) (Courtesy of Dr. Samuel Yang)



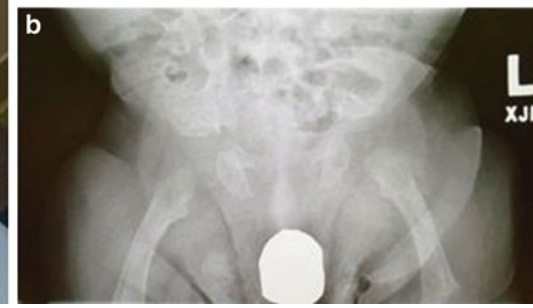


Fig. 10 This 4-month-old boy had typical clinical (**a**) and radiographic (**b**) features of achondroplasia. Molecular testings indicated the presence of a G>A transition at nucleotide 1138 (c.1138G>A) of the fibroblast growth factor receptor 3 (FGFR3) gene. The presence of this mutation is consistent with clinical diagnosis of achondroplasia

Adams-Oliver Syndrome

Contents

In 1945, Adams and Oliver described congenital transverse limb defects associated with aplasia cutis congenita in a three-generation kindred with typical autosomal dominant inheritance and intrafamilial variable expressivity.

Synonyms and Related Disorders

Aplasia cutis congenita with terminal transverse limb defects

Genetics/Basic Defects

1. Genetic heterogeneity
    1. Autosomal dominant in most cases (Burton et al. 1976; Bonafede and Beighton 1979; Küster et al. 1988):
        1. The family described by Adams and Oliver, and revisited by Whitley and Gorlin in 1991, illustrates vertical transmission, with multiple affected members spanning four generations, and includes male-to-male transmission, consistent with autosomal dominant inheritance.
        2. Reports from over 20 further kindreds provide support for the role of a heterozygous autosomal gene mutation (Snape et al. 2009).
    2. Autosomal recessive in some cases (Koiffmann et al. 1988; Klinger and Merlob 1998; Sybert 1989; Tekin et al. 1999; Temtamy et al. 2007):
        1. The combination of aplasia cutis congenita and terminal transverse limb defects within sibships provides evidence for an autosomal recessive mode of inheritance.
        2. Further supported by the occurrence of affected siblings within inbred families.
    3. Recent report of an autosomal recessive Adams-Oliver syndrome caused by homozygous mutation in *EOGT*, encoding an EGF domain-specific O-GlcNAc transferase (Cohen et al. 2014). This study, together with a parallel independent study by Shaheen et al. (2013) which identified three *EOGT* mutations in different Arab families, defines *EOGT* as a novel Adams-Oliver syndrome gene.
    4. Hassed et al. (2012) have identified two mutations in *RBPJ*, the key transcriptional regulator for Notch, in two independent

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kindreds affected by Adams-Oliver syndrome.
5. Mutations in *ARHGAP31* (Southgate et al. 2011) and *DOCK6* (Shaheen et al. 2011) have been reported in AOS-affected kindreds with both autosomal dominant and autosomal recessive inheritance.
6. A large pedigree was reported to exhibit the vast clinical variability of Adams-Oliver syndrome resulting from *ARHGAP31* mutations, ranging from severe and milder phenotypes to complete absence of a recognizable limb defect (Islie et al. 2014).
7. Mutations in *NOTCH1* are the most common cause of Adams-Oliver syndrome and add to a growing list of human diseases that have a vascular and/or bony component and are caused by alterations in the Notch signaling pathway (Stittrich et al. 2014).

2. Pathogenesis (Baskar et al. 2009)
    1. Trauma
    2. Uterine compression
    3. Amniotic band sequelae
    4. Vascular disruption sequence
        1. Concomitant occurrence of Poland sequence
        2. Both Poland sequence and Adams-Oliver syndrome: secondary to vascular disruption due to thrombosis of subclavian and vertebral arteries
    5. Massive thrombus from the placenta occluding the brachial artery
    6. Abnormalities in small vessel structures manifesting during embryogenesis
    7. A developmental disorder of morphogenesis

Clinical Features

1. Marked intrafamilial (Bamforth et al. 1994) and interfamilial variability.
2. Terminal transverse limb defects:
    1. Most common manifestation (84%)
    2. Usually asymmetrical
    3. Tendency toward bilateral lower limb, rather than upper limb involvement
    4. Mild spectrum of defects
        1. Nail hypoplasia
        2. Cutaneous syndactyly
        3. Bony syndactyly
        4. Ectrodactyly
        5. Brachydactyly
    5. Severe spectrum of transverse defects
        1. Absence of the hand
        2. Absence of the foot
        3. Absence of the limb
3. Aplasia cutis congenita:
    1. Second most common defect (almost 75%).
    2. Associated with skull defect (64%): The most common site is the vertex, often with scalp defect extending to the periosteum, skull, and dura:
        1. Small lesion: 0.5 cm in diameter
        2. Intermediate lesion: 8–10 cm involving the vertex
        3. Severe lesion: involves most of the scalp with acrania
    3. Skull defect without scalp defect, often mistaken for an enlarged fontanel.
    4. May involve other areas of the body (Pereira-da-Silva et al. 2000).
    5. Severe end of the spectrum of scalp defects:
        1. Encephalocele
        2. Acrania
    6. Most severe manifestations can be associated with a mortality rate of 20–55% (Bajpai and Pal 2003):
        1. Associated with dilated and tortuous scalp veins with significant morbidity
        2. Associated with hemorrhage (from the sagittal sinus) or infection (Arand et al. 1991)
4. Congenital cardiovascular malformations (13.4–20%) (Zapata et al. 1995; Lin et al. 1998):
    1. Mechanisms proposed to explain the pathogenesis of congenital cardiovascular malformations:
        1. Alteration of mesenchymal cell migration resulting in conotruncal malformations, e.g., tetralogy of Fallot, double outlet right ventricle, and truncus arteriosus

2. Alteration of fetal cardiac hemodynamics resulting in different malformations such as coarctation of the aorta, aortic stenosis, perimembranous VSD, and hypoplastic left heart
3. Persistence of normal fetal vascular channels resulting in postnatal vascular abnormalities

2. Diverse vascular and valvular abnormalities
   1. Bicuspid aortic valve
   2. Pulmonary atresia
   3. Parachute mitral valve
   4. Pulmonary hypertension

5. Other associated anomalies:
   1. Cutis marmorata telangiectatica congenita (25%) (Bork and Pfeifle 1992)
   2. Dilated and tortuous scalp veins (11%)
   3. Poland anomaly (Hoyme et al. 1992)
   4. Encephalocele
   5. Facial features
      1. Hemihypoplasia
      2. Hypertelorism
      3. Epicanthal folds
      4. Microphthalmia
      5. Esotropia
      6. High-arched palate
      7. Cleft palate
   6. Cryptorchidism
   7. Lymphatic abnormalities
      1. Lymphedema of the leg
      2. Chylothorax
      3. Dilated pulmonary lymphatics
      4. Intestinal lymphangiectasia
      5. Marmorata telangiectatica congenita (a cutaneous vascular abnormality)
   8. CNS abnormalities: unusual manifestation
      1. Mental retardation
      2. Learning disability
      3. Epilepsy
   9. Short stature
   10. Renal malformations
   11. Spina bifida occulta
   12. Accessory nipples
6. Major and minor features of Adams-Oliver syndrome (Snape et al. 2009): The presence of two major features is considered sufficient for a diagnosis. The combination of one major and one minor feature should place Adams-Oliver syndrome high in the differential diagnosis of such individuals:
   1. Major features
      1. Terminal transverse limb defects
      2. Aplasia cutis congenita
      3. Family history of Adams-Oliver syndrome
   2. Minor features
      1. Cutis marmorata telangiectatica congenita
      2. Congenital cardiac defect
      3. Vascular anomaly
7. Differential diagnosis (Snape et al. 2009):
   1. Amniotic band sequence
   2. Moebius and Poland syndromes (McGuirk et al. 2001)
   3. Teratogenic agents such as phenytoin, misoprostol, and ergotamine
      1. Asymmetrical bilateral transverse terminal limb defects
      2. Tend to affect the upper limb more severely than the lower limb (Spranger et al. 1980; Holmes 2002)
   4. Limb anomalies
      1. Caused by thalidomide: tends to be symmetrical and longitudinal (Smithells and Newman 1992)
      2. Caused by chorionic villus sampling during pregnancy (Holmes 2002)
   5. Isolated aplasia cutis congenita: substantial heterogeneity based on association with known abnormalities or exposure to teratogens such as methimazole (Frieden 1986)
   6. Cutis marmorata telangiectatica congenita
      1. Common in kindreds with Adams-Oliver syndrome
      2. Can be seen in combination with both terminal transverse limb defects (Maniscalco et al. 2005) and aplasia cutis congenita (Verdyck et al. 2003)
      3. Can be an isolated finding in otherwise unaffected family members (Scribanu and Temtamy 1975; Toriello et al. 1988)
      4. Can be associated with skin atrophy and ulcerations, capillary malformations, capillary and cavernous vascular malformations, under- or overgrowth of the affected extremity, macrocephaly, and glaucoma and in association with

vascular syndromes including Sturge-Weber and Klippel-Trenaunay (Amitai et al. 2000)

Diagnostic Investigations

1. Radiography
   1. Transverse limb defects (Fryns 1987)
   2. Ectrodactyly
   3. Brachydactyly
   4. Syndactyly
   5. Nail hypoplasia
   6. Skull defect
2. CT scan or MRI of the brain (Fryns et al. 1996; Mempel et al. 1999)
   1. Polymicrogyria/pachygyria
   2. Ventriculomegaly
   3. Irregular cortical thickening
   4. Cerebral cortex dysplasia
   5. Microcephaly
   6. Arhinencephaly
   7. Periventricular and parenchymal calcium deposits
3. Gene sequencing to detect various causative gene mutations (*ARHGAP31* and *RBPJ* mutations for certain dominant forms; *DOCK6* and *EOGT* mutations for autosomal recessive forms)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal dominant: not increased unless a parent is affected in which case the risk is 50%
      2. Autosomal recessive: 25%
   2. Patient's offspring
      1. Autosomal dominant: 50%
      2. Autosomal recessive: not increased unless the spouse carries the gene or is affected
2. Prenatal diagnosis by ultrasonography (Becker et al. 2002)
   1. Transverse limb defects
   2. Concomitant skull defect
3. Management
   1. Treat minor scalp lesions with daily cleansing of the involved areas with applications of antibiotic ointment.
   2. Surgically close larger lesions and exposed dura with minor or major skin grafting procedure (split thickness or full thickness).
   3. Prevent sepsis and/or meningitis from an open scalp lesion which is highly vascular and rarely involves the sagittal sinus predisposing to episodes of spontaneous hemorrhage.
   4. Urgent surgical intervention may be required with operative measures that include primary closure, skin grafting, local scalp flaps with or without tissue expansion, and cranial vault reconstruction using split rib grafts and free latissimus dorsi muscle flap (Bajpai and Pal 2003).
   5. Orthopedic care for various degrees of limb defects.

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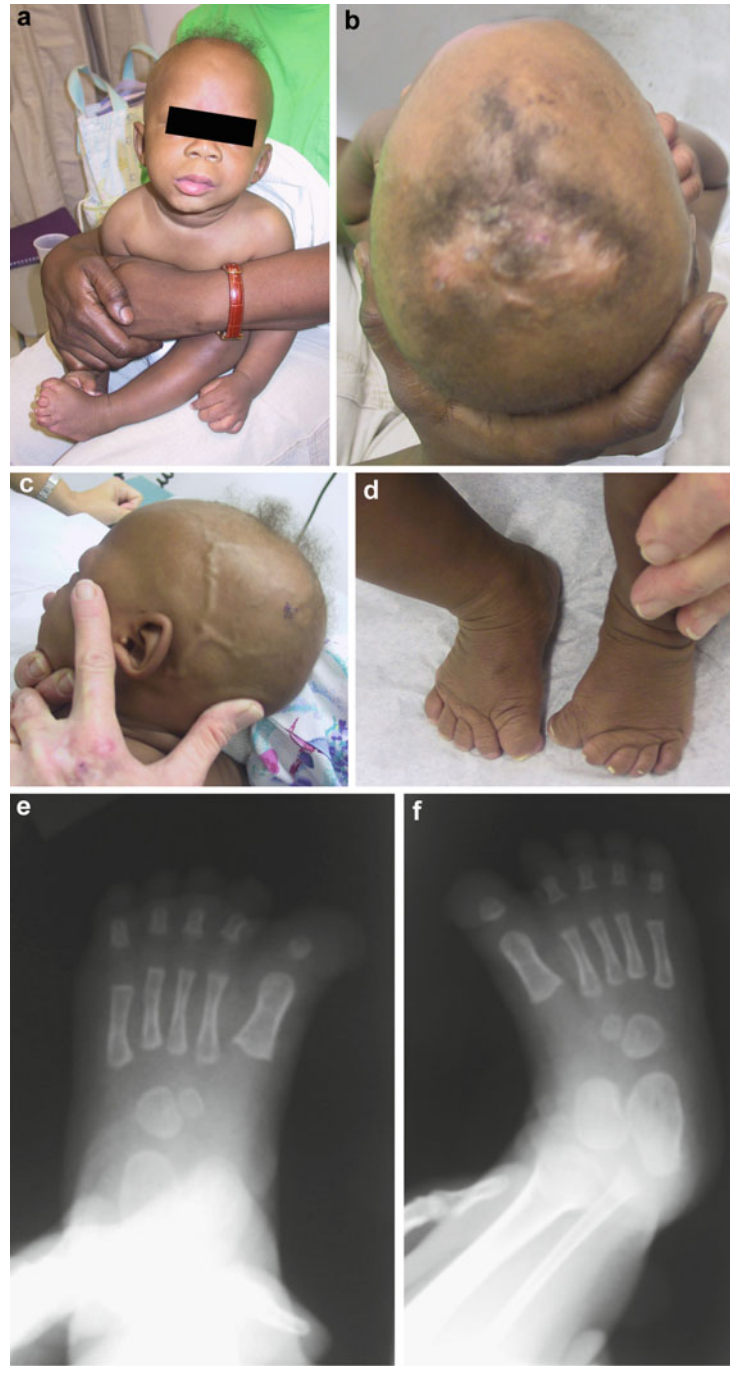

Fig. 1 A 9-month-old boy with Adams-Oliver syndrome showing alopecia, absent eyebrows and eyelashes (**a**), scalp defect (**b**), tortuous scalp veins (**c**), and limb defects (brachydactyly, syndactyly, broad great toes, and nail hypoplasia) (**d**). Radiographs (**e**, **f**) showed absent middle and distal phalanges of second to fifth toes and absent distal phalanges of the great toes

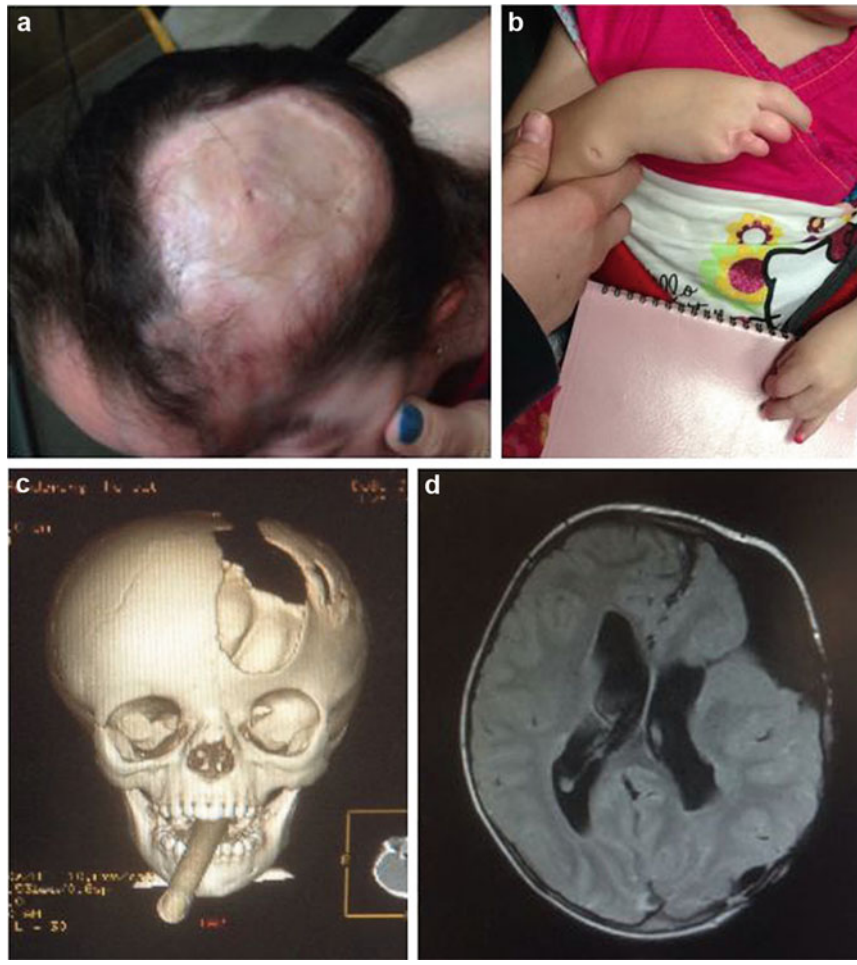

Fig. 2 This 3-year-and-7-month-old girl was evaluated for scalp defect (**a**) and terminal transverse limb defect (**b**). CT of the craniofacial bones (**c**) showed a large calvarial defect overlying the left frontal and parietal bones. MRI of the brain without contrast (**d**) showed a prominent axial cystic collection overlying the left frontal lobe directly overlying the schizencephaly, most comparable with arachnoid cyst. Mass effect from the extra-axial cystic focus results in approximately 5 mm of rightward midline shift. Continued abnormal configuration of the craniocervical junction with approximately 2.7 cm inferior extension of the cerebellar tonsils below the foramen magnum, concerning for underlying Chiari malformation (Courtesy of Dr. Ghali Ghali)

Agnathia

Contents

Agnathia is an extremely rare lethal neurocristopathy. The disorder has also been termed agnathia-holoprosencephaly spectrum, agnathia-otocephaly complex, agnathia-astomia-synotia, or cyclopia-otocephaly association. The incidence is estimated to be 1 in 70,000 infants (Schiffer et al. 2002).

The spectrum of agnathia ranges from isolated agnathia, or virtual absence of the mandible, to otocephaly, which refers to a broader malformation of mandibular hypoplasia or agnathia, downward displacement of the ears, and/or synotia (approximation of the ears in the midline), with or without aglossia (no tongue), and microstomia (small mouth) (Petrikovsky 1999). Agnathia-otocephaly is a lethal malformation complex characterized by absence of the mandible, microstomia, aglossia, and positioning of the ears toward the midline (Pauli et al. 1981; Bixler et al. 1985). Although ear positioning is variable and the use of the term "otocephaly" does not seem always justified, otocephaly is commonly used to assemble all ear abnormalities with displacement toward the midline (Schiffer et al. 2002; Faye-Petersen et al. 2006). Agnathia-otocephaly can occur alone or in combination with a variety of associated malformations, holoprosencephaly being the most commonly reported association.

Synonyms and Related Disorders

Agnathia-holoprosencephaly spectrum; Agnathia-otocephaly complex

Genetics/Basic Defects

1. Typically sporadic and often suspected during second-trimester ultrasound scans (Gekas et al. 2010).
2. Genetically heterogeneous (Sergouniotis et al. 2015).
    1. Rare autosomal recessive inheritance: two siblings with isolated dysgnathia complex who survived infancy (Baker et al. 2004); two stillborn sisters, both with agnathia and holoprosencephaly (Pauli et al. 1983).
    2. Possible autosomal dominant inheritance.
        1. Supported by an observation of dysgnathia in mother and daughter (Erlich et al. 2000).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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   2. Possibility of a defect in the *OTX2* gene as the basis of the disorder (Matsuo et al. 1995).
   3. Mutations in two genes, *PRRX1* (recessive or dominant) and *OTX2* (dominant), explain only a small subset of cases (Gekas et al. 2010; Chassaing et al. 2012; Donnelly et al. 2012; Patat et al. 2013).
3. Teratogenic factors have been described in humans (Cohen 1989).
   1. Salicylate (Benawra et al. 1980)
   2. Amidopyrine (Mollica et al. 1979)
   3. Theophylline (Ibba et al. 2000)
4. A prechordal mesoderm inductive defect affecting neural crest cells (Carles et al. 1987)
   1. A developmental field defect
   2. Different etiologic agents (etiological heterogeneity) acting on the same developmental field producing a highly similar complex of malformations
5. Possible existence of a mild form of agnathia without brain malformation (holoprosencephaly)
   1. Situs inversus-congenital hypoglossia
   2. Severe micrognathia, aglossia, and choanal atresia
6. Agnathia-holoprocephaly: a midline malformation association (Hanekam 1990)
7. Otocephaly-holoprosencephaly malformation association (Hersh et al. 1989)
8. A well-recognized malformation complex in the mouse (Juriloff et al. 1985), guinea pig (Wright 1934), rabbit, sheep, and pig

Clinical Features

1. Polyhydramnios due to persistence of oropharyngeal membrane or blind-ending mouth
2. Agnathia (absence of the mandible)
3. Microstomia or astomia (absence of the mouth)
4. Aglossia (absence of the tongue)
5. Blind mouth
6. Ear anomalies
   1. Otocephaly (variable ear positions)
   2. Synotia (external ears approaching one another in the midline)
   3. Dysplastic inner ear
   4. Atretic ear canal
7. Down-slanting palpebral fissures
8. Variable degree of holoprosencephaly: nearly 100 patients reported as having holoprosencephaly and features consistent with the spectrum of agnathia (Kauvar et al. 2010).
   1. Cyclopia
   2. Synophthalmia
   3. Arrhinencephaly
9. Other brain malformations
   1. Cerebellar hypoplasia
   2. Septum pellucidum cavum
   3. Absence of cranial nerves (I-IV)
   4. Absence of the corpus callosum
   5. Meningocele
10. Intrauterine growth retardation
11. Cleft lip/palate
12. Occular malformations
   1. Microphthalmos/anophthalmia
   2. Proptosis (protruding eyes)
   3. Absence of the eyelids
   4. Epibulbar dermoid
   5. Aphakia
   6. Retinal dysplasia
   7. Microcornea
   8. Anterior segment dysgenesis
   9. Uveal colobomas
13. Nasal anomalies
   1. Absence of the nasal cavity
   2. Cleft nose
   3. Blind nasal pharynx
14. Various visceral malformations
   1. Choanal atresia
   2. Tracheoesophageal fistula
   3. Absence of the thyroid gland
   4. Absence of the submandibular and parotid salivary glands
   5. Abnormal glottis and epiglottis
   6. Thyroglossal duct cyst
   7. Carotid artery anomalies
   8. Situs inversus (Leech et al. 1988; Meinecke et al. 1990; Ozden et al. 2000)
   9. Cardiac anomalies
   10. Unlobulated lungs
   11. Renogenital anomalies
      1. Unilateral renal agenesis
      2. Renal Ectopia

3. Cystic kidneys
4. Horseshoe kidneys
5. Solitary kidney
6. Mullerian duct agenesis
7. Cryptorchidism

15. Skeletal anomalies
    1. Vertebral anomalies
    2. Rib anomalies
    3. Tetramelia
16. Anatomical variations
    1. Ears
        1. Absence of the tragus
        2. Synotia
    2. Mandible
        1. Rudimentary
        2. Absent
        3. Two small separate masses
    3. Mouth: microstomia with vertical orientation
    4. Buccopharyngeal membrane: absent to present
    5. Tongue
        1. Small to absent body
        2. Present in (hypo)pharynx
    6. Absent submandibular glands
    7. Other skull bones: approximated maxillae, palatine, zygomatic, and temporal

Diagnostic Investigations

1. Radiography
    1. Reduced maxilla
    2. Absence of the zygomatic process
    3. Absence of the hyoid bone
    4. Vertebral anomalies
    5. Absence of the ribs
    6. Sprengel deformity
2. Cranial ultrasonography to define holoprosencephaly
3. Postnatal reconstructed CT for detailed 3D structure of the cranium in agnathia-otocephaly (Hinojosa et al. 1996)
4. Chromosome analysis (Krassikoff & Sekhon 1989)
    1. Normal in majority of cases
    2. Unbalanced der(18),t(6;18)(pter → p24.1; p11.21 → qter) in two female sibs with agnathia-holoprosencephaly
5. Utilization of exome sequencing as a means of elucidating the molecular pathology in fetuses with agnathia-otocephaly complex (Sergouniotis et al. 2015)
6. Autopsy to define postmortem findings

Genetic Counseling

1. Recurrence risks
    1. Risk to patient's sib: not increased unless in a rare autosomal recessive inheritance
    2. Risk to patient's offspring
        1. Not applicable to lethal cases since the patients do not survive to reproductive age
        2. Autosomal dominant (some cases may survive to reproductive age): 50%
2. Prenatal diagnosis by ultrasonography (Rolland et al. 1991; Ducarme et al. 2007; Tantbirojn et al. 2008). 3-D imaging by helical computed tomography (CT) (Ebina et al. 2001), and/or MRI imaging (Chen et al. 2003, 2007)
    1. Polyhydramnios: secondary to an atretic, constricted, or obstructed oropharynx that prevents the fetus from swallowing amniotic fluid efficiently or at all
    2. Intrauterine growth retardation
    3. Mandibular absence (agnathia) or major hypoplasia
    4. Holoprosencephaly: associated with agnathia-otocephaly (10%) (Blaas et al. 2002)
    5. Cyclopia, marked hypotelorism, or frontal proboscis
3. Management
    1. Although a lethal entity, several survivals beyond infancy have been reported (Brecht and Johnson 1985; Kamiji et al. 1991; Walker et al. 1995; Shermak and Dufresne 1996; Baker et al. 2004). Our third case with agnathia is still surviving with normal neurological development at 20 years of age.

2. All survivors required tracheotomy immediately soon after delivery since no laryngeal opening is most likely present for endotracheal tube insertion.
3. EXIT (*ex utero* intrapartum treatment) procedure, a technique for safely managing airway obstruction at birth, in which placental support is maintained until the airway can be evaluated and secured (Umekawa et al. 2007).

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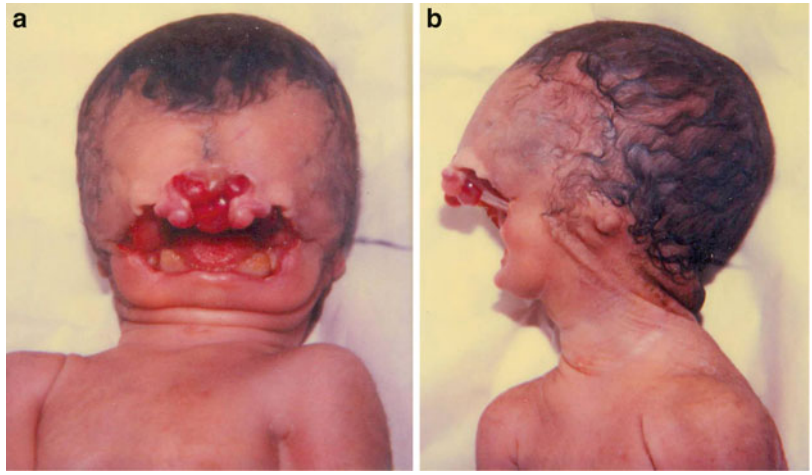

Fig. 1 (**a**, **b**) A neonate (28 week gestation) with agnathia-holoprosencephaly complex showing a large defect involving entire midface area with almost total absence of jaw, absence of eyes and nose, and severe microtia. Absence of olfactory bulbs and grooves (arrhinencephaly) was demonstrated by necropsy. Additional anomalies included 13 pairs of ribs, atresia of left ureter with resultant hydronephrosis, and left renal cortical cysts. Maternal hydramnios was present

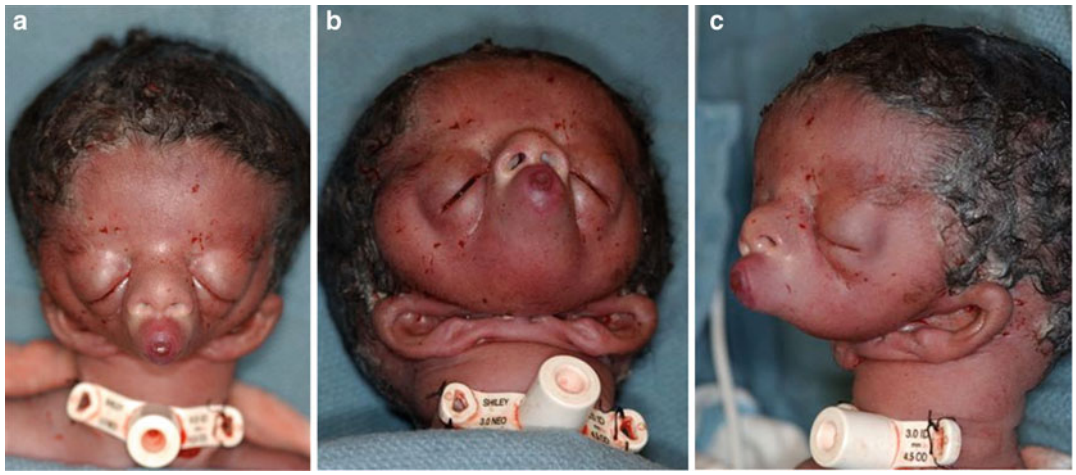

Fig. 2 (**a**–**c**) The female infant was born via elective cesarean section with Apgar scores of 1, 1, and 1 at 1, 5, and 10 min respectively. After a failed attempt at nasotracheal intubation, an emergent tracheostomy was performed. However, the infant expired shortly after placement. Postmortem examination of the baby revealed congenital absence of the mandible (agnathia), microstomia with a slit-like oral opening, posterior choanal atresia, proptosis, and external ears placed ventrally with posterior rotation approaching each other in the midline. Amniocentesis revealed normal chromosomes

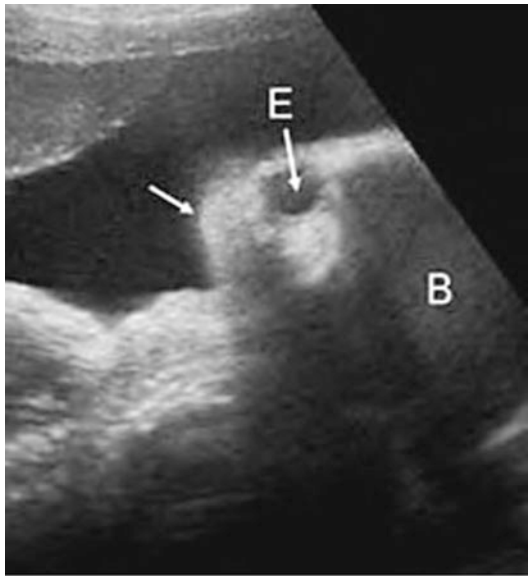

Fig. 3 Prenatal ultrasound showed absence of fetal jaw (*arrow*) (*E* fetal eye, *B* fetal brain)

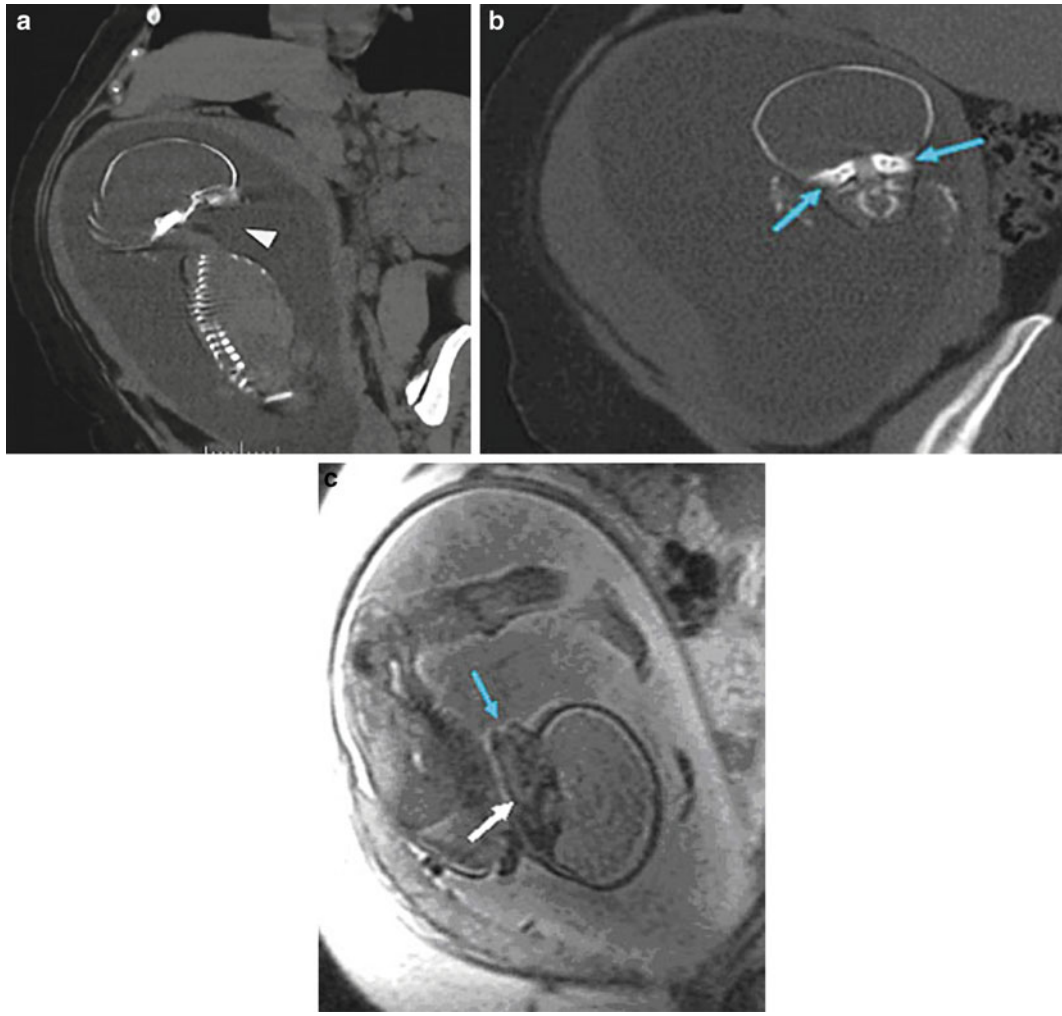

Fig. 4 (**a**–**c**) Maternal abdominal T2 MRI showed agnathia (*blue arrow*) and the lower end of the large horizontal ear meeting at the jaw area (*white arrow*)

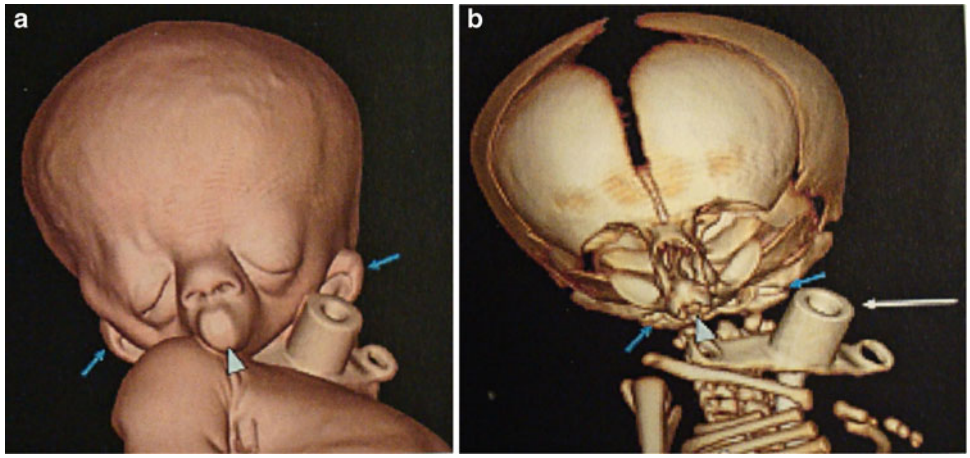

Fig. 5 (**a**, **b**) Postmortem CT scan demonstrated mandibular agnathia with synotia (posterior rotation with ventromedial displacement of the external ear structures approaching fusion near the midline), hypoplasia of the superior maxillary bone, and persistence of the inner ears in their initial fetal position

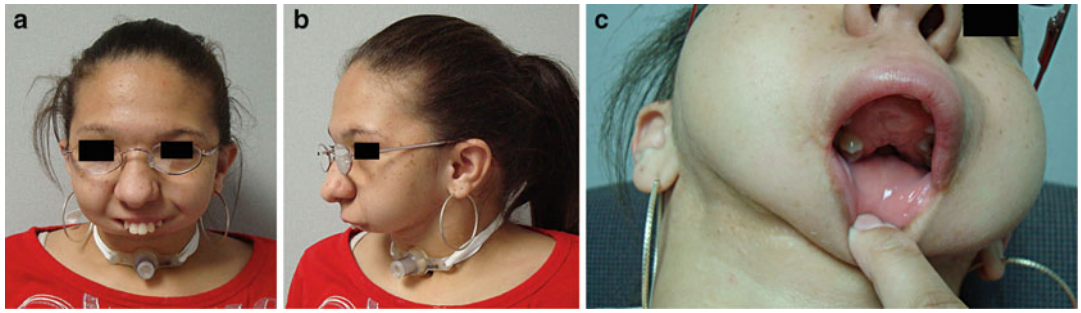

Fig. 6 (**a**–**c**) A 20-year-old female with agnathia with tracheotomy. She has severe microretrognathia due to absence of mandible, cleft palate, Arnold-Chiari malformation, severe bilateral hearing loss, Klippel-Feil syndrome, and scoliosis (Courtesy of Dr. Ghali Ghali)

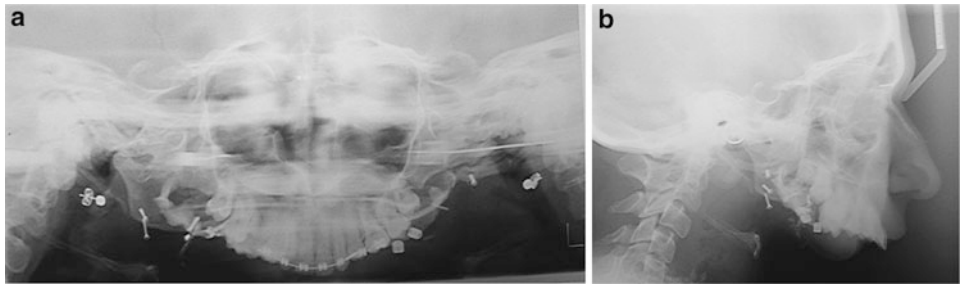

Fig. 7 (**a**, **b**) Radiographs of orofacial structures showed absence of mandible

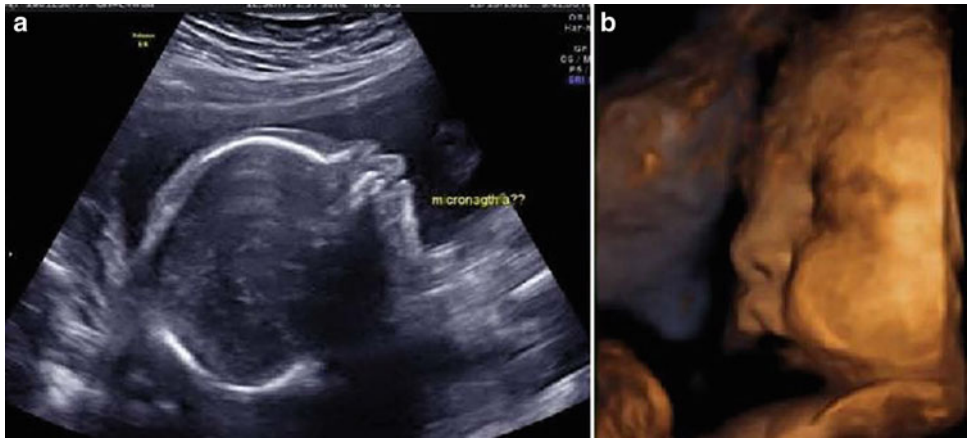

Fig. 8 (**a**, **b**) The newborn baby was born to an 18-year-old G2P1 mother at 39 weeks of gestation. Because of prenatal ultrasound findings at 24 weeks of gestation (courtesy of Dr. Rose Brouiellette) of severe retro/micrognathia by 2D ultrasound (**a**) and 4D real-time ultrasound (**b**), the baby had EXIT (ex utero intrapartum treatment) procedure, a technique for safely managing airway obstruction at birth, in which placental support is maintained until the airway can be evaluated and secured (Umekawa et al. (2007)). The EXIT procedure along with tracheostomy was performed successfully (Dr. ghali Ghali)

Fig. 9 (**a**, **b**) The baby at birth was ventilated with tracheostomy tube in place. There was virtual absence of mandible (agnathia) with severe retromicrognathia, microstomia, a small tongue without cleft palate, and slightly low-set and posteriorly rotated ears. No otocephaly was present

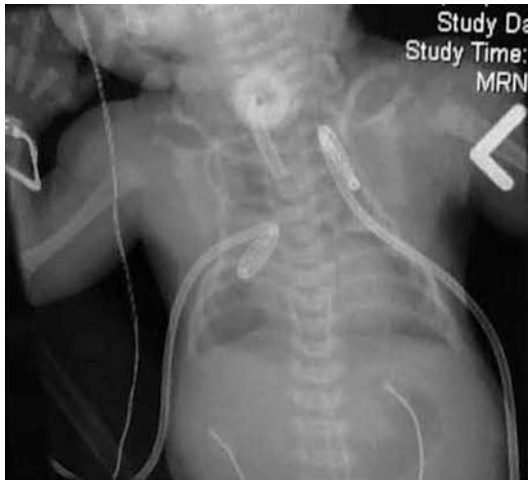

Fig. 10 Chest radiograph showing a narrow chest, especially upper chest associated with poorly defined and shortened ribs and tracheostomy in place

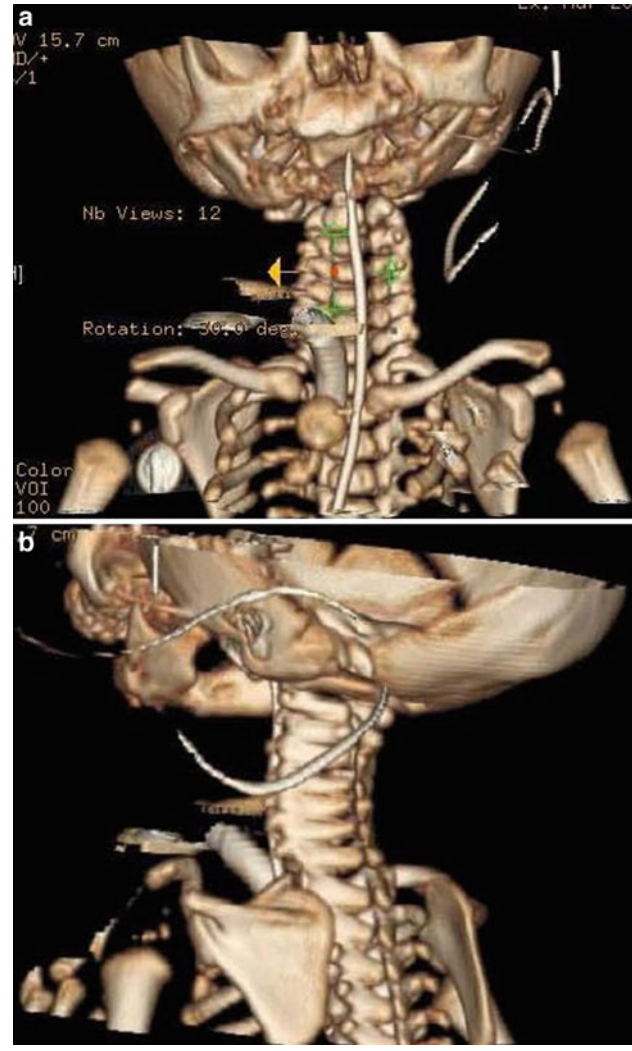

Fig. 11 (**a**, **b**) CT without contrast of the face showed micrognathia and gap in the anterior aspect of the mandible. There is no obvious airway in the area corresponding to the hypopharynx, larynx, and upper trachea (Courtesy of Dr. Ghali Ghali)

Aicardi Syndrome

Contents

In 1965, Aicardi et al. reported a new syndrome consisting of spasms in flexion, callosal agenesis, and ocular abnormalities. Actual frequency of the condition is not known, but about 1–4% of cases of infantile spasms from tertiary referral centers may be due to Aicardi syndrome.

Synonyms and Related Disorders

Agenesis of corpus callosum with chrioretinal abnormality

Genetics/Basic Defects

1. Inheritance (Aicardi 2005)
    1. An X-linked dominant, lethal in males (Donnenfeld et al. 1989; Aicardi 1999)
    2. Almost exclusively affects females with two X chromosomes (heterozygous for a particular mutant X-chromosome gene to manifest)
3. Exceptions
    1. Boys with XXY chromosome constitution (Hopkins et al. 1979; Aicardi 2005; Glasmacher et al. 2007; Chen et al. 2009) allowing heterozygous expression of the gene as in the female
    2. Two phenotypic boys with 46,XY males (Curatolo et al. 1980; Aggarwal et al. 2000): Aicardi has disputed the observations that are too atypical for classification as Aicardi syndrome due to the presence of lissencephaly or chorioretinal lesions not reminiscent of lacunae (Aicardi 1980)
    3. A 5-year-old male was reported to have clinical triad of Aicardi syndrome (Chappelow et al. 2008): Routine cytogenetic analysis showed 46, XY. A chromosome microarray analysis failed to detect any known microdeletion or microduplication. The possibility of low mosaic for 47, XXY Klinefelter cannot be ruled out
4. Not known to be a familial condition, except an isolated familial instance involving two sisters (Molina et al. 1989)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_6

5. The mutation
    1. Seems to arise de novo, accounting for the almost complete absence of familial cases
    2. Could occur as a postzygotic event in early embryonic development as suggested by the observation of a monozygotic twin in a pair in which only one twin had Aicardi syndrome, the other being unaffected (Costa et al. 1997)
2. A gene responsible for Aicardi syndrome has not been identified
3. Gene map postulated on chromosome Xp22.3 from an observation in an affected girl with t(X;3)(p22;q12) (Ropers et al. 1982)
4. Nonrandom X-inactivation in lymphocytes and possible other tissues in patients with Aicardi syndrome may reflect heterogeneity of thier molecular basis (Neidich et al. 1990)

Clinical Features

1. Classic triad
    1. Pathognomonic chorioretinal lacunae
        1. Multiple, rounded, unpigmented, and yellow-white lesions
        2. Occasionally unilateral
        3. May be absent in rare cases
    2. Infantile spasms: the most characteristic type of seizure
        1. Frequently asymmetric or even unilateral (Bour et al. 1986)
        2. Often preceded or precipitated by a focal clonic or tonic seizure limited to the side in which the spasms predominate
    3. Agenesis of the corpus callosum
2. Other CNS abnormalities
    1. Ependymal cysts
    2. Choroid plexus papillomas (Robinow et al. 1984; Trifiletti et al. 1995)
    3. Cortical migration abnormalities
    4. Optic disc coloboma
    5. Hydrocephaly
    6. Porencephaly
    7. Cerebellar agenesis
    8. Heterotopias
3. Variable neurologic abnormalities
    1. Hemiparesis or hemiplegia
        1. The most frequent abnormality
        2. Often on the side where the spasms predominate
    2. Quadriplegia
    3. Hypotonia
    4. Hypertonia
    5. Development of microcephaly, though head circumference is normal at birth
4. Microphthalmia
5. Extra-CNS tumors
    1. Soft palatal benign teratoma
    2. Hepatoblastoma
    3. Parapharyngeal embryonal cell carcinoma
    4. Limb angiosarcoma
    5. Scalp lipoma
    6. Multiple gastrointestinal polyps (Trifiletti et al. 1995)
6. Scoliosis or costovertebral anomalies
7. Severe cognitive and physical handicaps
    1. Global developmental delay
    2. Moderate to severe mental retardation in most patients
    3. Unable to ambulate in most children
    4. Limited visual ability
8. New diagnostic criteria (Aicardi 1999, 2005)
    1. Classic triad
        1. Infantile spasms
        2. Chorioretinal lacunae
        3. Agenesis/dysgenesis of the corpus callosum
    2. New major features (present in most patients studied by MRI)
        1. Cortical malformations, mostly microgyria (probably constant but may not be possible to evidence)
        2. Periventricular and subcortical heterotopia
        3. Cysts around the third ventricle and/or choroid plexuses
        4. Papillomas of choroid plexuses
        5. Optic disc/nerve coloboma
    3. Supporting features (present in some cases)
        1. Vertebral and costal abnormalities

2. Microphthalmia and/or other eye abnormalities
3. "Split-brain" EEG (associated suppression-burst tracing)
4. Gross hemispheric asymmetry

9. Estimated survival rate (Menezes et al. 1994)
   1. 76% at 6 years of age
   2. 40% at 15 years of age

Diagnostic Investigations

1. Ophthalmological examination
   1. Choroid retinal lacunae
   2. Optic disc coloboma
2. Electroencephalograms
   1. "Split-brain" EEG (Dennis and Bower 1972)
   2. Asymmetry or asynchrony
   3. Quasiperiodicity
   4. Hypsarrhythmia
3. CT or MRI of the brain (Hopkins et al. 2008)
   1. Agenesis or partial agenesis of the corpus callosum
   2. Choroid plexus papillomas
   3. Cerebellar dysgenesis
   4. Cortical heterotopias
   5. Porencephaly
   6. Agenesis or hypoplasias of the cerebellar vermis
4. Radiography for skeletal malformations
5. Chromosome analysis in case of Klinefelter syndrome
6. Not caused by copy number variants detectable with currently used high-resolution array platform (Wang et al. 2009)
7. Histopathology (Sunderkrishnan 2014)
   1. Multiple brain malformations
      1. Complete or partial agenesis of the corpus callosum
      2. Cortical heterotopias
      3. Gyral malformation
      4. Cysts of posterior fossa (de Jong et al. 1976)
      5. Microscopic evaluation of the parenchyma
         1. Disordered cellular organization
         2. Disruption of the normal layered appearance of the cortex
   2. Chorioretinal lacunae
      1. Well-circumscribed, punched-out lesions in the retinal pigment epithelium and choroid
      2. Severely disrupted retinal architecture
         1. All layers are thinned.
         2. Decreased choroidal vessel number and caliber are decreased
         3. Presence of pigmentary ectopia and pigmentary epithelial hyperplasia

Genetic Counseling

1. Recurrence risk
   1. Patient's sibs: recurrence not likely (exception with one report of two affected sibs, likely due to gonadal mosaicism in one of the parent).
   2. Patient's offspring: 50% of offspring of affected females are expected to carry the abnormal X chromosome but affected individuals are not expected to survive to reproduce.
2. Prenatal diagnosis (Bromley et al. 2000): The prenatal ultrasonographic findings include:
   1. Arachnoid cysts
   2. Agenesis of the corpus callosum (development of the corpus callosum may not be complete until 22 weeks of gestation)
   3. Ventriculomegaly
3. Management
   1. Anticonvulsants for control of seizures
   2. Specific therapy for infantile spasm
      1. Adrenocorticotropic hormone (ACTH): effective for some patients
      2. Vigabatrin, a more recently introduced therapy for infantile spasm
         1. An enzyme that breaks down GABA, the major inhibitory neurotransmitter in the brain
         2. Effective for infantile spasm without the serious life-threatening adverse effects of ACTH

3. Possible ophthalmologic sequelae of constriction of the visual fields
4. Not currently approved for use in the USA

3. A multidisciplinary team approach to developmental handicaps
4. Orthopedic surveillance and treatment of scoliosis
5. Vigorous treatment of any infection as pulmonary problems are the commonest cause of death (Figs. 1 and 2)

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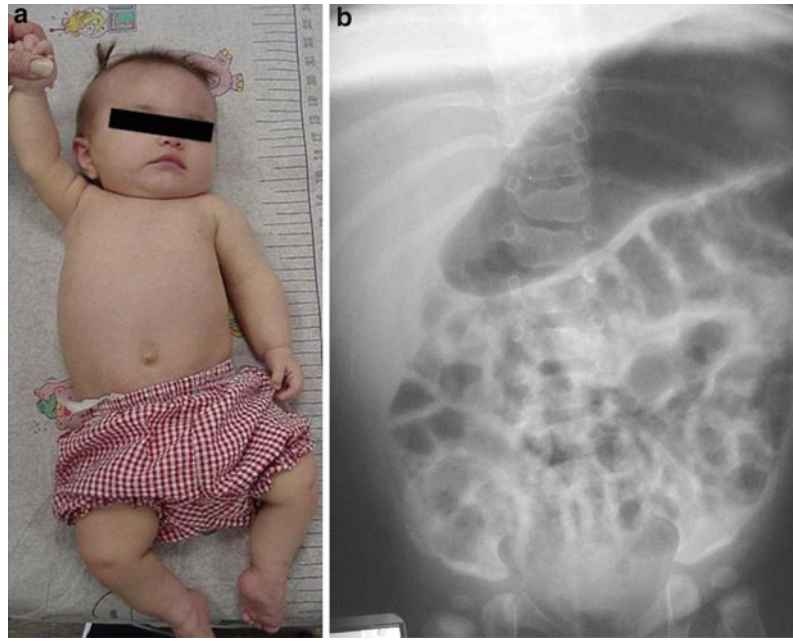

Fig. 1 (**a**, **b**) An 8-month-old girl with Aicardi syndrome characterized by infantile spasms, chorioretinopathy, brain malformation, and costovertebral anomalies

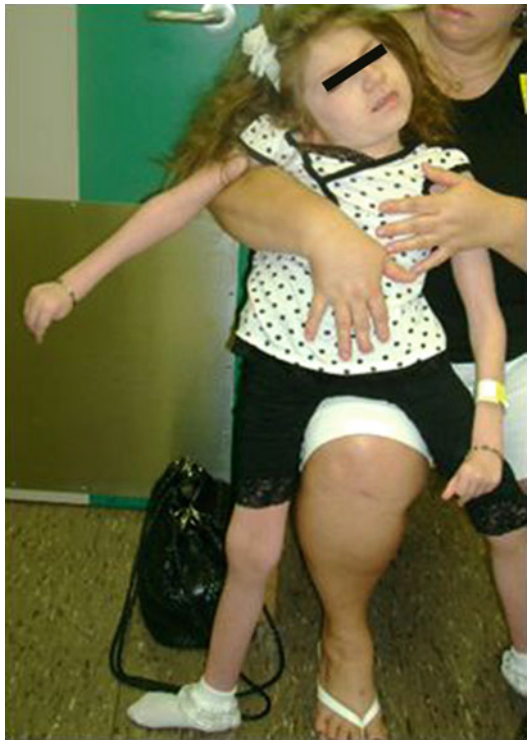

Fig. 2 This 10-year-old Caucasian female was evaluated for seizures, scoliosis, cerebral palsy, and global developmental delay. Evaluation of the intraorbital contents demonstrated bilateral colobomas at the optic nerve head insertion. On the left, subretinal effusion with detachment was present with abnormality extending into the coloboma. The MRI of the brain showed absence of the corpus callosum associated with an interhemispheric cyst. The cerebral hemispheres are also markedly abnormal with multiple foci of gray matter heterotopia identified along both ependyma. There was cortical dysplasia identified involving much of the left frontal lobe in a pattern most compatible with polymicrogyria. The underlying white matter appeared dysplastic. Areas of polymicrogyria also appeared to be present within the superior right frontal lobe. There was cerebellar volume loss. No definite olfactory bulbs were appreciated. An olfactory sulcus may be present on the right. The hippocampal formations appear within normal limits, other than atrophic. There are no areas of diffusion restriction. There are no areas demonstrating abnormal enhancement following contrast administration. Small choroid plexus cysts appeared present bilaterally at the level of the glomus. The constellation of findings of frontal cortical dysplasia, callosal agenesis with small interhemispheric cyst, and bilateral colobomas with retinal detachment is compatible with Aicardi syndrome

Alagille Syndrome

Contents

In 1969, (Alagille et al. 1969) described a syndrome characterized by chronic cholestasis resulting from paucity of interlobular bile ducts, peripheral pulmonary stenosis, butterfly-like vertebral arch defect, posterior embryotoxon, and peculiar facies. The syndrome is also known as arteriohepatic dysplasia.

Alagille syndrome occurs in approximately 1 in 60,000 live births based on the presence of neonatal cholestasis (Danks et al. 1977). This may be an underestimate as molecular testing has demonstrated that many individuals with a disease-causing mutation do not have neonatal liver disease (Kamath and Poccoli 2003).

Synonyms and Related Disorders

Arteriohepatic dysplasia; *JAG1*-related Alagille syndrome; *NOTCH2*-related Alagille syndrome

Genetics/Basic Defects

1. Inheritance
   1. Sporadic in 45–50% of cases
   2. Autosomal dominant
      1. Reduced penetrance
      2. Variable expressivity
   3. Alagille syndrome gene mapped to 20p12 (Anad et al. 1990; Li et al. 1996)
2. Molecular defect
   1. Caused by mutations or deletions of Jagged-1 gene (*JAG1*), encoding a ligand for the NOTCH transmembrane receptor, implicated in cell differentiation (Li et al. 1997)
   2. More than 120 described intragenic mutations of the *JAG1* gene
   3. Chromosome microdeletions: rare (Desmaze et al. 1992; Deleuze and Hadchouel 1996)
   4. Alagille syndrome type 1 (*JAG1*-associated) (Tumpenny and Ellard 2012)
      1. Detected in about 90% of cases due to mutations in JAG1 (20p12).
      2. JAG1 mutations include total gene deletions, protein truncating, splicing, and missense mutations (Krantz et al. 1999).
   5. Parental mosaicism in *JAG1* mutations in a phenotypically normal parent (Giannakudis et al. 2001)
   6. No clear genotype-phenotype correlation in Alagille syndrome (Colliton et al. 2001)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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7. *NOTCH2* mutations that were identified in 2/11 individuals with classic Alagille syndrome who do not have an identifiable *JAG1* mutation (McDaniell et al. 2006)
8. Alagille syndrome type 2 (*NOTCH2*-associated): detected in about 1% of cases due to mutations in NOTCH2 (1p13) (Tumpenny and Ellard 2012)

Clinical Features

1. High variability of phenotypic findings (Shulman et al. 1984; Krantz et al. 1997a; Crosnier et al. 2000a)
2. Major features
    1. Neonatal chronic cholestasis
        1. Episodes of jaundice separated by periods of remission
        2. Pruritus
        3. Hepatomegaly
        4. Splenomegaly: may be associated with portal hypertension
        5. Xanthoma, progressive and observed in:
            1. Extensor surface of the fingers
            2. Palmar creases
            3. Nape of the neck
            4. Anal folds
            5. Popliteal fossa
            6. Inguinal areas
    2. Facial features (Kamath et al. 2002)
        1. Broad prominent forehead
        2. Deep-set, widely spaced eyes
        3. Long, straight nose
        4. Bullous tip of the nose
        5. Underdeveloped mandible
        6. Sharply pointed chin
    3. Complex congenital cardiovascular anomalies
        1. Pulmonary artery stenosis (67%)
        2. Ventricular septal defects
        3. Patent ductus arteriosus
        4. Pulmonary valve atresia
        5. Tetralogy of Fallot (7–16%)
        6. Tricuspid regurgitation
        7. Right ventricular hypertrophy
    4. Vertebral arch anomalies (butterfly-like vertebrae)
    5. Posterior embryotoxon (prominent Schwalbe's ring)
3. Less frequently associated features
    1. Growth retardation
    2. Neurological complications from vitamin E deficiency
    3. Mental retardation (2–30%)
    4. Systemic vascular malformations
        1. Coarctation of the aorta
        2. Middle aortic syndrome
        3. Arterial hypoplasia/dysplasia (hepatic, renal, carotid, celiac) (Crosnier et al. 2000b)
        4. Artery stenosis (renal, subclavian)
        5. Moyamoya disease (Connor et al. 2002; Baird et al. 2015)
        6. Carotid artery aneurysm
        7. Intracranial hemorrhage
        8. Hypoplastic portal vein branch
    5. Renal involvement: occurs in 40% of *JAG1*-mutation-positive individuals (Kamath et al. 2013)
        1. Interstitial nephritis
        2. Glomerular intramembranous and mesangial lipidosis
        3. Tubular dysfunction
        4. Renal hypoplasia
        5. Renal agenesis
        6. Horseshoe kidney
        7. Cystic disease
    6. Small bowel atresia or stenosis
    7. Pancreas
        1. Diabetes
        2. Exocrine pancreatic insufficiency
    8. Lung: tracheal and bronchial stenosis
    9. Larynx: high-pitched voice
    10. Eye abnormalities (Brodsky and Cunniff 1993; Hingorani et al. 1999; Kim and Fulton 2007)
        1. Posterior embryotoxon (prominence of Schwalbe's ring at the junction of the iris and cornea)
        2. Optic disk drusen
        3. Angulated retinal vessels
        4. Pigmentary retinopathy

5. Nanophthalmia
6. Iris strands/hypoplasia
7. Cataract
8. Myopia
9. Strabismus
10. Glaucoma
11. Microcornea
12. Corneal pannus
13. Corectopia
14. Band keratopathy
15. Axenfeld anomaly
16. Fundus hypopigmentation
17. Congenital macular dystrophy

11. Skeletal abnormalities
    1. Lack of normal progression of interpedicular distance in the lumbar spine
    2. Spina bifida
    3. Shortening of distal phalanges and metacarpal bones
    4. Clinodactyly
12. Hepatocellular carcinoma: a rare complication of Alagille syndrome (Bhadri et al. 2005)
13. Immune dysregulation: a new feature of the evolving phenotype (Tilib Shamoun et al. 2015)

4. Prognosis
    1. Characterized by recurrent episodes of cholestasis
    2. Often associated with common respiratory tract infections, especially during the first year of life
    3. Pregnancy
        1. Possible but rare as in other chronic liver diseases because of decreased fertility, voluntary abortion, and miscarriages
        2. Few cases of successful pregnancy in mothers with Alagille syndrome reported (Ferrarese et al. 2015)
    4. Good long survival but mortality rate may be up to 25%
5. Other hereditary causes of cholestasis (Hartley et al. 2013)
    1. Progressive familial intrahepatic cholestasis
    2. Bile acid synthesis defects
        1. 3-Beta-hydroxy-delta-5-C27-steroid oxidoreductase deficiency (MIM #607765)
        2. Delta(4)-3-oxosteroid 5-beta-reductase deficiency (MIM #235555)
    3. Niemann-Pick type C disease
    4. Citrullinemia type II
    5. Arthrogryposis-renal dysfunction-cholestasis syndrome
    6. Aagenaes syndrome
    7. Alpha-1 antitrypsin deficiency
    8. North American Indian childhood cirrhosis
    9. Zellweger syndrome
    10. Ciliopathies
    11. Smith-Lemli-Opitz syndrome

Diagnostic Investigations

1. Biochemical studies (Alagille et al. 1987; Scheimann 2013)
    1. Hypercholesterolemia: cholesterol levels ranging from 220 to 1,600 mg% in all children with xanthomas (Garcia et al. 2005).
    2. Hyperphospholipidemia.
    3. Hypertriglyceridemia (500–2,000 mg/dL).
    4. Prominent increase in the pre–βlipoprotein and apolipoprotein B levels.
    5. Very high total bile acid, gamma-glutamyl transferase, and alkaline phosphatase blood levels.
    6. Fat-soluble vitamin deficiencies: frequently observed.
    7. Prolongation of prothrombin time (PT) or activated partial thromboplastin time (aPTT): often observed.
    8. Conjugated hyperbilirubinemia.
    9. Total bilirubin level: generally 4–14 mg/dL with a direct fraction generally 30% of total bilirubin. In most children, conjugated hyperbilirubinemia improves with time.
2. Ophthalmologic assessment for posterior embryotoxon and other ocular anomalies

3. Ultrasonography: allows hepatobiliary disease assessment and helps to establish indications for hepatic transplantation (Berrocal et al. 1997)
    1. Portal hypertension
    2. Cirrhosis
    3. Renal hypoplasia
4. Radiography: not specific (Berrocal et al. 1997)
    1. Abnormal "butterfly" vertebrae
    2. Ulnar or phalangeal shortening
5. MRI or MRA: identifies intracranial vascular anomalies
6. Other imagings
    1. Dimethyl iminodiacetic acid scanning
    2. Magnetic resonance cholangiopancreatography
    3. Endoscopic retrograde cholangiopancreatography
    4. Cholangiography: demonstrates the patency of the extrahepatic biliary tree (Hartley et al. 2013)
7. Echocardiography for cardiovascular malformations, especially pulmonary stenosis
8. Histology (liver biopsy) (Emerick et al. 1999)
    1. Paucity of interlobular bile ducts (85%)
    2. Cholestasis in hepatocytes and canaliculi (96%)
9. Cytogenetic analysis
    1. Cytologically balanced t(2;20) in a two-generation family with Alagille syndrome (Spinner et al. 1994)
    2. Detects cytogenetic abnormalities of 20p12 in 3.6% of patients with Alagille syndrome (Krantz et al. 1997b)
10. Molecular genetic analysis
    1. Sequence analysis of the *JAG1* gene detects mutations in approximately 70% of individuals who meet clinical diagnostic criteria.
    2. The ability to provide molecular confirmation for Alagille syndrome will be of great benefit to families with an affected child. The expression of Alagille syndrome is extremely variable both between and within families. A molecular assay will permit identification of family members with microforms of this disorder, greatly improving ability to appropriately counsel affected families (Krantz et al. 1998).
    3. FISH detects a microdeletion of 20p12, including the entire *JAG1* gene, in approximately 5–7% of cases (Spinner et al. 2001).
    4. Mutations in NOTCH2 gene have been observed in fewer than 1% of individuals with Alagille syndrome (McDaniell et al. 2006).
    5. Exome sequencing determines genetic etiology in patients lacking mutations in those genes commonly associated with their clinically diagnosed disorders, such as Alagille syndrome (Grochowski et al. 2015).

Genetic Counseling

1. Recurrence risk (Spinner et al. 2013)
    1. Patient's sib
        1. A low but slightly increased risk due to parental germ line mosaicism in clinically normal-appearing parents (Giannakudis et al. 2001; Laufer-Cahana et al. 2002)
        2. A 50% risk if a parent is affected
    2. Patient's offspring: a 50% risk of having an offspring with Alagille syndrome
2. Prenatal diagnosis
    1. Several issues to be considered before attempting pregnancy (Ferrarese et al. 2015):
        1. Severity of liver disease and the degree of portal hypertension: could worsen during pregnancy
        2. Degree of cardiac dysfunction, in particular the severity of pulmonary hypertension
        3. High probability of Alagille mutation in the fetus, although with variable phenotypic manifestations
    2. Prenatal ultrasonography (Albayram et al. 2002):

1. Severe pulmonary artery stenosis
2. Progressive severe intrauterine growth retardation
3. 2D and 3D ultrasound in the second trimester: identification of hemivertebrae and butterfly vertebrae (Wax et al. 2014)

3. Prenatal molecular diagnosis on fetal DNA obtained from amniocentesis or CVS (Witt et al. 2004) is available if a disease-causing mutation (demonstrated by molecular genetic testing) or a deletion (detected by FISH) is identified in an affected family member (Witt et al. 2004):
   1. *JAG1*: sequence analysis/mutation scanning, sequence analysis of select exons, and deletion/duplication analysis (including DISH)
   2. *NOTCH2*: sequence analysis and deletion/duplication analysis
4. Preimplantation genetic diagnosis (Renbaum et al. 2007):
   1. A polar body (PB)-based multiplex fluorescent PCR reaction for a female affected with Alagille syndrome.
   2. The protocol included analysis of the Jagged-1 (*JAG1*) familial mutation and four closely linked highly polymorphic markers (D20S162, D20S901, D20S894, and D20S186).
   3. A reliable diagnosis was possible in all developing embryos.

3. Management
   1. Medical care (Alagille et al. 1987)
      1. Low-fat diets with medium-chain triglyceride supplementation
      2. Hypercaloric diets to severely malnourished patients
      3. Vitamin supplements
      4. Cholestasis: ursodeoxycholic acid which may improve the biochemical cholestasis (Balistreri 1997)
      5. Pruritus
         1. Antihistamine agents
         2. Cholestyramine or rifampin in management of bile acid-induced pruritus
      6. Monitoring of oral hygiene and caries control: mandatory (Berniczei-Royko et al. 2014)
   2. Surgical care for patients with refractory disease
      1. Possible to perform orthodontic treatment combined with aesthetic restorative procedures or surgery in patients with less severe general manifestations (Berniczei-Royko et al. 2014)
      2. Biliary diversion
      3. Surgical revascularization in patients with Alagille syndrome with moyamoya (Baird et al. 2015)
      4. Eventual orthotopic liver transplantation (Cardona et al. 1995; Emerick et al. 1999; Kasahara et al. 2003; Englert et al. 2006; Arnon et al. 2010)
         1. Indications: progressive hepatic dysfunction, severe portal hypertension, failure to thrive, intractable pruritus, and osteodystrophy.
         2. Associated with good long-term graft survival, although it is lower than that in biliary atresia.
         3. Death from graft failure and neurological and cardiac complications was significantly higher than in patients with biliary atresia.
         4. The higher rate of mortality and graft failure may be related to the multisystem involvement of Alagille syndrome.
      5. Cardiac surgery for complex congenital heart defects

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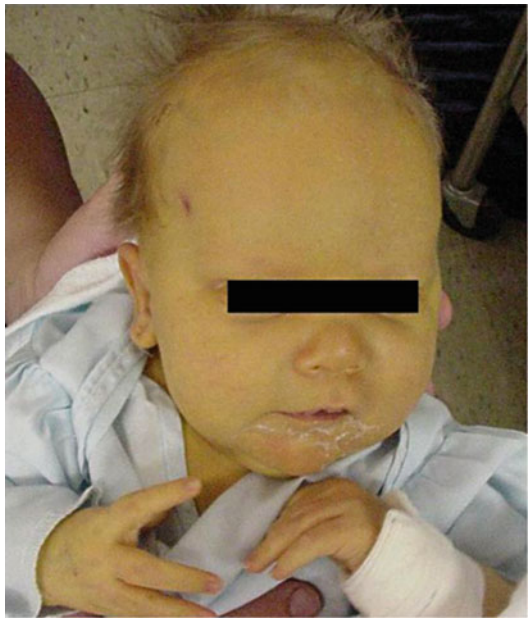

Fig. 1 An infant with Alagille syndrome showing neonatal jaundice, broad forehead, and underdeveloped mandible. This infant had peripheral pulmonary artery stenosis and paucity of interlobular bile ducts

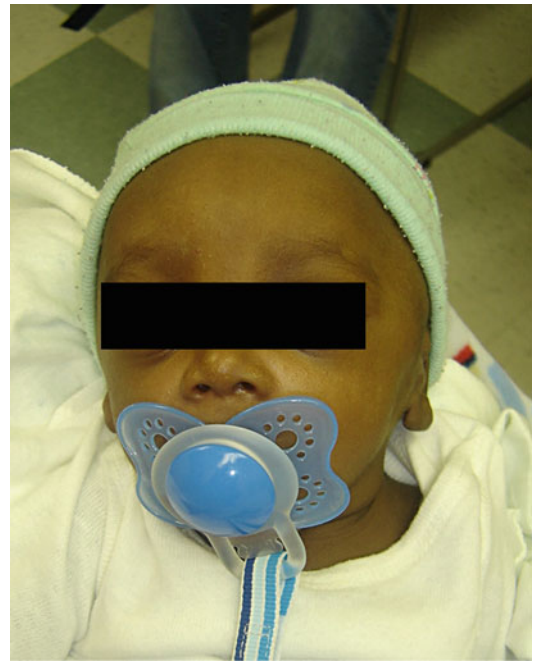

Fig. 2 A 2-month-old boy with Alagille syndrome showing neonatal jaundice (conjugated hyperbilirubinemia). Liver biopsy showed paucity of the bile ducts. He was put on Mephyton 2.5 mg qd

Albinism

Contents

Albinism, derived from the Latin *albus*, is a group of inherited disorders in which melanin biosynthesis is reduced or absent. It involves the skin, hair, and eyes (oculocutaneous albinism) or may be limited primarily to the eyes (ocular albinism). Current classification of albinism is determined by the affected gene, making the previously used terms "partial or complete" and "tyrosinase positive or tyrosinase negative" obsolete (King and Oetting 2007; Summers et al. 1996). The prevalence of all forms of albinism varies considerably worldwide, estimated at approximately 1/17,000 and about 1 in 70 people carry a gene for oculocutaneous albinism (OCA) (Grønskov et al. 2007).

Synonyms and Related Disorders

Chediak-Higashi syndrome; Griscelli syndrome; Hermansky-Pudlak syndrome; OCA, X-linked; OCA type 2 (tyrosinase-positive OCA); OCA type 3 (brown albinism); Oculocutaneous albinism (OCA) type 1 (tyrosinase-negative OCA, tyrosinase-related OCA)

Genetics/Basic Defects

1. Classification of albinism (genetic heterogeneity) (King and Summers 1988; Carden et al. 1998; Biswas and Lloyd 1999):
    1. Oculocutaneous albinism (OCA): a common phenotype for a group of recessive genetic disorders of melanin synthesis. Reduction in melanin synthesis can involve the skin, hair follicle, and eye. Mutations in at least 12 genes are responsible for this phenotype. Mutations in OCA-related genes result in reduction of melanin synthesis by the melanocytes:
        1. Common types of OCA with cutaneous and ocular hypopigmentation without significant involvement of other tissue:
            1. Oculocutaneous albinism 1 (OCA1): subdivided into OCA1A, OCA1B, OCA1ts
            2. Oculocutaneous albinism 2 (OCA2)
            3. Oculocutaneous albinism 3 (OCA3)
        2. Less common types of OCA with more complex manifestations:
            1. Hermansky-Pudlak syndrome
            2. Chediak-Higashi syndrome
    2. Ocular albinism: reduction in melanin synthesis localized primarily to the eye:

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1. Ocular albinism 1 (OA1): X-linked recessive (Lang et al. 1990)
2. Autosomal recessive ocular albinism (AROA)

2. Molecular defects causing four known types of OCA (Oetting and King 1999; Grønskov et al. 2007)
   1. OCA1 (tyrosinase-related albinism) (Oetting 2002; Oetting et al. 2003):
      1. Inherited in an autosomal recessive manner.
      2. Caused by mutations of tyrosinase (*TYR*) gene located at 11q14.3.
      3. Several different types of mutations to the tyrosinase gene (missense, nonsense, and frameshift) are responsible for producing OCA1A and OCA1B.
      4. OCA1A ("tyrosinase-negative" albinism with inactive enzyme) produced by null mutations of the *Tyr* gene:
         1. 0% tyrosinase enzyme activity
         2. Over 100 mutations spanning all parts of the gene reported
         3. Compound heterozygotes with different maternal and paternal alleles in majority of patients
      5. OCA1B (tyrosinase-related albinism with partially active enzyme) produced by leaky mutations of the *Tyr* gene:
         1. "Yellow" mutant of albinism with 5–10% activity of tyrosinase.
         2. A base substitution within the gene may result in reduced rather than completely abolished enzyme activity.
      6. OCA1ts (tyrosinase-related albinism with thermolabile enzyme):
         1. A temperature-sensitive tyrosinase is only partly functional.
         2. The first reported cases had a missense substitution within the tyrosinase gene.
   2. OCA2 ("tyrosinase-positive" albinism) (Oetting et al. 1998), brown OCA in Africans:
      1. *OCA2* gene: the pink-eyed dilution gene (*p*) located at 15q11.2-q12.
      2. Caused by mutations of the P gene on the chromosome 15, homologous to the mouse pink-eyed dilution, or p gene.
      3. Inherited in an autosomal recessive manner.
      4. The mutated region is also deleted in Prader-Willi syndrome (PWS) and Angelman syndrome (AS), accounting for close linkage of OCA2 to PWS and AS.
   3. OCA3 (brown albinism):
      1. *OCA3* gene: tyrosinase-related protein-1 gene (*TRP1*) (Sarangarajan and Boissy 2001) located at 9p23
      2. The gene homologous to the mouse "brown" gene
      3. Mutation of the gene possibly synergistic with a polymorphism or partially active mutation in OCA1 or OCA2
      4. 1 in 8,500 in Africans
      5. Rare in white Europeans and Asians
   4. OCA4:
      1. Resulting from mutation in the *SLC45A2* gene, formerly called membrane-associated transporter protein gene (*MATP*), located at 5p13.3
      2. 1 in 85,000 in Japanese
      3. Rare in white Europeans
3. Molecular defects causing other types of albinism
   1. XLOA (X-linked ocular albinism, OA1):
      1. *GPR143*, located at Xp22.3-22.2, is the only gene known to be associated with XLOA.
      2. Intragenic deletions, frameshift mutations, and point mutations identified (Rosenberg and Schwartz 1998).
      3. Affects males because of X-linked recessive inheritance.
      4. Eighty-five to 90% of obligate carriers show pigmentary mosaicism in the fundi, representing the lionization effect (X-inactivation), although there are no functional sequelae.
   2. OAR (autosomal recessive ocular albinism):
      1. Gene mapping: 6q13–q15

2. May not be a clinical entity
3. Tyrosinase in some cases
4. P protein in some cases

3. Hermansky-Pudlak syndrome (HPS): a bleeding disorder due to absence of dense bodies in platelets:
   1. Hermansky-Pudlak syndrome 1 is caused by mutations of the *HPS1* gene which is localized to 10q23.
   2. *HPS2* gene was localized to 5q13. Hermansky-Pudlak syndrome 2 is caused by mutation of the *APB1* gene, which is localized to 5q13, resulting in a defect in adapter complex 3 AP-3, β3A subunit.
4. Chediak-Higashi syndrome (Nagle et al. 1996):
   1. Immunodeficiency associated with neurologic problems
   2. Defect in *CHS1* gene (lysosomal trafficking regulator gene) located at 1q42–44
5. Griscelli syndrome: resulting from mutations in the *RAB27A* gene or *MYO5A* gene, both located at 15q21.

4. Pathophysiology
   1. Melanin in the skin:
      1. Melanin, a photoprotective pigment in the skin, absorbs UV light from the sun, thus preventing skin damage.
      2. Normal skin tans upon sun exposure due to increased melanin pigment in the skin.
      3. Patient with albinism develops sunburn because of the lack of melanin.
   2. Consequence of the absence of melanin during the development of the eye:
      1. Hypoplasia of fovea
      2. Alteration of neural connections between the retina and the brain
   3. Melanin pathway:
      1. Consisting of a series of reactions that converts tyrosine into two types of melanin, black-brown eumelanin and red-blond pheomelanin.
      2. Tyrosinase: a major enzyme in a series of conversions to melanin from tyrosine and it is also responsible for converting tyrosine to DOPA and then to dopaquinone, which subsequently converts to either eumelanin or pheomelanin.
      3. Two other enzymes involved in the formation of eumelanin: tyrosinase-related protein 1 (TRP1, DHICA oxidase) and tyrosinase-related protein 2 (TRP2, dopachrome tautomerase). Mutation of the TRP1 results in OCA3; mutation of the TRP2 does not cause albinism.
      4. P protein, a melanosomal membrane protein, believed to be involved in the transport of tyrosine prior to melanin synthesis. Mutation of this *P* gene causes OCA2.

5. Pathogenesis of the ocular features:
   1. Development of the optic system highly dependent on the presence of melanin
   2. Ocular features appear if melanin is reduced or absent
   3. Mechanisms
      1. Misrouting of the retinogeniculate projections resulting in abnormal decussation of optic nerve fibers
      2. Sensation of photophobia and decreased visual acuity caused by light scattering within the eye
      3. Light-induced retinal damage postulated as a contributing mechanism to decreased visual acuity
      4. Foveal hypoplasia: the most significant factor causing decreased visual acuity.

Clinical Features

1. General clinical features of albinism (Abadi and Pascal 1989; Oetting 1999; King et al. 2001; Bashour et al. 2014; Boissy and Nordlund 2014; Peracha et al. 2015):
   1. Skin, hair, and eye discoloration caused by abnormalities of melanin metabolism (might not be obvious in ocular albinism)
   2. Reduced visual acuity due to foveal hypoplasia (common to all types of albinism, even though a rudimentary annular reflex

has been described in a few patients with better visual acuity) (Creel et al. 1990; Summers 2009)
3. Translucent iris due to reduction in iris pigment
4. Visible choroid vessels due to reduction in retinal pigment
5. Photophobia due to iris pigmentary abnormalities
6. Anomalous visual pathway projections due to misrouting of the optic nerves at the chiasm
7. Nystagmus (Summers 2009)
    1. Due to abnormal decussation of optic nerve fibers.
    2. Typically pendular in nature.
    3. More noticeable with fatigue and illness.
    4. Amplitude of nystagmus diminishes as child matures.
8. Alternating strabismus.
9. Hyperopia, myopia, and astigmatism.

2. Oculocutaneous albinism 1 (OCA1) (Lewis 2013):
    1. Incidence: approximately 1 in 40,000 individuals
    2. Oculocutaneous albinism 1A (OCA1A)
        1. Classic "tyrosinase-negative" OCA: complete lack of melanin production throughout life
        2. Most severe form of OCA
        3. White hair and white skin that does not tan
        4. Blue and translucent irides that do not darken with age
        5. Foveal hypoplasia
        6. No tanning potential
        7. At risk for sun burning and skin cancer
        8. Diminished visual acuity as low as 20/400
        9. Photophobia and nystagmus worst in this subtype
    3. Oculocutaneous albinism 1B (OCA1B):
        1. Yellow mutant type OCA, referred to as Amish albinism, or xanthous albinism.
        2. Variable pigmentation ranging from very little cutaneous pigmentation to nearly normal skin pigmentation.
        3. Increased skin, hair, and eye pigment with age and tan with sun exposure.
        4. Yellow hair pigment develops in the first few years of life and continuously accumulates pigment, principally yellow-red pheomelanin, in the hair, eyes, and skin in the later life.
        5. Decreased visual acuity improving with age.
    4. Temperature-sensitive albinism (OCA1ts):
        1. A subtype of OCA1B.
        2. Mutation of the tyrosinase gene that produces a temperature-sensitive tyrosinase enzyme.
        3. The heat-sensitive tyrosinase enzyme activity is approximately 25% of the normal tyrosinase activity at 37 °C. The activity improves at lower temperatures.
        4. Dark hair pigment in the arms and legs (cooler areas of the body), while axillary and scalp hair remains white.
        5. Pigment is absent in the fetus because of high fetal temperature.
3. Oculocutaneous albinism 2 (OCA2):
    1. "Tyrosinase-positive" OCA
    2. Incidence: approximately 1 in 15,000 individuals
    3. Most prevalent type of albinism in all races and especially frequent among African-American population (1 in 10,000)
    4. Phenotypic variability:
        1. Ranging from absence of pigmentation to almost normal pigmentation
        2. Absence of black pigment (eumelanin) in the skin, hair, or eyes at birth
        3. Gradual development of pigmentation with age
        4. Increased pigmentation resulting in improved vision
4. Oculocutaneous albinism 3 (OCA3):
    1. Previously known as red/rufous OCA
    2. Incidence of the disease unknown

3. Phenotype in African patients:
   1. Light brown skin and hair
   2. Blue-brown irides
   3. Ocular features not fully consistent with diagnosis of OCA (no iris translucency, nystagmus, strabismus, or foveal hypoplasia)
4. Phenotype in Caucasians and Asians: not known.

5. Oculocutaneous albinism 4 (OCA4):
   1. Cannot be distinguished from OCA2 on clinical findings
   2. Hypopigmentation of the skin and hair
   3. Characteristic ocular changes found in all other types of albinism:
      1. Nystagmus
      2. Reduced iris pigment with iris translucency
      3. Reduced retinal pigment with visualization of the choroidal blood vessels on ophthalmoscopic examination
      4. Foveal hypoplasia associated with reduction in visual acuity
      5. Misrouting of the optic nerves at the chiasm associated with alternating strabismus
      6. Reduced stereoscopic vision
      7. An altered visual-evoked potential (VEP)

6. Ocular albinism 1 (OA1) (Shen et al. 2001; Lewis 2015):
   1. X-linked recessive OA (XLOA)
   2. Incidence of the disease approximately 1 in 50,000 individuals
   3. Extreme variability in clinical expression
   4. Involving eyes only:
      1. Decreased visual acuity
      2. Refractive errors: typical findings:
         1. Hypermetropia
         2. Astigmatism
      3. Hypopigmentation of the fundus and the iris
      4. Absent foveal reflex (foveal hypoplasia)
      5. Congenital nystagmus
      6. Photophobia
      7. Strabismus
      8. Iris translucency
      9. Posterior embryotoxon
      10. Loss of stereoscopic vision due to misrouting of the optic tracts
   5. Normal skin.
   6. Male manifesting complete phenotype.
   7. Carrier females:
      1. Normal vision
      2. Hypopigmented streaks (characteristic patchy hypopigmentation as a result of mosaic inactivation of the affected X chromosomes) in the periphery
      3. Marked iris translucency
   8. Severity depending on ethnic background: less severe in races exhibiting very dark constitutive skin pigmentation than those more lightly pigmented.

7. Autosomal recessive ocular albinism (OAR):
   1. Children with ocular features of albinism and normal cutaneous pigmentation born to normally pigmented parents
   2. Classified as autosomal recessive because both males and females are affected
   3. Not considered a clinical entity

8. Hermansky-Pudlak syndrome:
   1. A group of related disorders:
      1. Common oculocutaneous albinism
      2. A platelet storage disorder
      3. Ceroid-lipofuscin lysosomal storage disease
   2. An autosomal recessive disorder with very variable expression.
   3. Incidence of the disease: rare, except in Puerto Rico where its frequency is 1 in 1,800 individuals (Witkop et al. 1990).
   4. Bleeding diathesis resulting from a platelet storage pool deficiency.
   5. Patients exhibit severe immunologic deficiency with neutropenia and lack of killer cells (DePinho and Kaplan 1985).
   6. Ceroid storage disease:
      1. Accumulation of a ceroid-lipofuscin material in various organ systems
      2. Interstitial pulmonary fibrosis
      3. Granulomatous colitis and gingivitis
      4. Kidney failure
      5. Cardiomyopathy

9. Chediak-Higashi syndrome (Russell-Eggitt 2001):

1. An autosomal recessive disorder with variable expression
2. Consisting of a very rare group of conditions
3. Severe immune disorder:
    1. Abnormal intracellular granules in most cells, especially white cells
    2. Susceptible to bacterial infections
    3. Defective neutrophils function
    4. Episodes of macrophage activation known as accelerated phases:
        1. Fever
        2. Anemia
        3. Neutropenia
        4. Occasionally thrombocytopenia
        5. Hepatosplenomegaly
        6. Lymphadenopathy
        7. Jaundice
4. Hypopigmentation of the skin, hair, irides, and ocular fundi.
5. Bleeding diathesis:
    1. Easy bruising
    2. Mucosal bleeding
    3. Epistaxis
    4. Petechiae
6. Eye symptoms:
    1. Photophobia
    2. Nystagmus
    3. Reduced stereoacuity
    4. Strabismus
7. Often succumb during childhood to severe viral and bacterial infections, bleeding, or development of the accelerated phase.
8. May develop a peripheral and cranial neuropathy in survivors:
    1. Autonomic dysfunction
    2. Weakness and sensory deficits
    3. Loss of deep tendon reflexes
    4. Clumsiness with a wide-based gait
    5. Seizures
    6. Abnormal EEG
    7. Abnormal EMG with decreased motor nerve conduction velocities
10. Griscelli syndrome (Mancini et al. 1998):
    1. A rare disorder.
    2. Immune impairment.
    3. Neurological deficit.
    4. Hypopigmentation of skin and hair.
    5. Presence of large clumps of pigment in hair shafts.
11. Waardenburg syndrome: a syndrome of sensory deafness and partial albinism, referred to as the albinism-deafness syndrome (Waardenburg 1951).

Diagnostic Investigations

1. Ophthalmologic examination for detection of reduced retinal pigment with visualization of the choroidal blood vessels (OCA1) and foveal hypoplasia.
2. Ophthalmic images in oculocutaneous albinism (Goldberg et al. 2015):
    1. One-piece acrylic intraocular lens in the capsular bag, visualized through an undilated pupil by transillumination of the iris.
    2. Slit-lamp photograph: demonstrates miotic pupil, poliosis, and hypopigmented iris.
3. Visual acuity reduction.
4. Hair bulb incubation assay for tyrosinase activity:
    1. OCA1A: no tyrosinase activity.
    2. OCA1B: greatly reduced activity of tyrosinase but still present.
5. Visual-evoked potential (VEP): an accurate diagnostic test for albinism by demonstrating an asymmetry of VEP between the two eyes secondary to misrouting of optic pathways.
6. Electron microscopy of skin and hair bulb: not routinely performed but probably the best diagnostic method for albinism.
7. Ultrastructural examination of skin: The presence of macromelanosomes in the skin is considered specific for OA1.
8. Molecular genetic analysis: clinically available:
    1. OCA1 (Lewis 2013):
        1. Sequence analysis to detect sequence variants for OCA1A or OCA1B
        2. Deletion/duplication analysis to detect *TYR* exonic or whole-gene deletions for both forms

2. OCA2:
    1. Targeted mutation analysis to detect 2.7-kb deletion (most individuals of sub-Saharan African heritage)
    2. Sequence analysis/mutation scanning of OCA2 sequence variations other than 2.7-kb deletion
3. OCA3: sequence analysis of the entire coding region of *OCA3* gene
4. OCA4: sequence analysis to detect *MATP* mutations
5. XLOA: analysis of the *GPR143* gene

9. Hermansky-Pudlak syndrome:
    1. Simple blood clotting tests
    2. Electron microscopic examination of platelets for identification of the absence of dense bodies (delta granules)
10. Chediak-Higashi syndrome:
    1. Blood smear: identification of neutrophils containing giant cytoplasmic granules
    2. Defective neutrophils chemotaxis or killing
    3. Prolonged bleeding time caused by impaired platelet function
11. Griscelli syndrome:
    1. Immunological function evaluation
    2. CT and MRI for neurological abnormalities

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib:
        1. Autosomal recessive oculocutaneous albinism: 25% recurrence risk of being affected (Lewis 2013)
        2. X-linked recessive ocular albinism:
            1. If the mother is a carrier: 50% of brothers affected and 50% of sisters carriers.
            2. If the mother is not a carrier: The recurrence risk is low but still exists since the risk of germ line mosaicism in mothers is not known but is likely rare.
    2. Patient's offspring:
        1. Autosomal recessive oculocutaneous albinism: recurrence risk not increased unless the spouse is also a carrier in which case, there is a 50% recurrence risk (as in the pseudodominance).
        2. X-linked recessive ocular albinism: None of the sons will be affected; all daughters will be carriers.
2. Prenatal diagnosis:
    1. Important to perform segregation analysis of mutation on both parents to exclude two mutations located at the same allele (Hsieh et al. 2001).
    2. Genetic sequence diagnosis possible on fetal DNA obtained from amniocentesis or CVS for pregnancies at 25% risk when the disease-causing mutations of the *TYR* gene in an affected family member is known:
        1. OCA1: available clinically in families with an identified *OCA1* mutation
        2. OCA2: possible in families with an identified *OCA2* mutation
        3. XLOA: available clinically in families with an identified *OA1* mutation (Lewis 2015)
    3. Fetoscopy (a high-risk procedure) to obtain fetal skin biopsy to demonstrate the lack of melanin in skin melanocytes: an invasive procedure not recommended clinically.
3. Management:
    1. Albinism (Okulicz et al. 2003):
        1. Skin care: avoid prolonged sun exposure to protect skin from sunburned, ultraviolet radiation and minimize the risk of malignancy:
            1. Protective clothing
            2. Sunscreens with at least a sun protection factor of 1.5
        2. Ophthalmologic care:
            1. Use of sunglasses for photophobia
            2. Correction of refractory errors secondary to hyperopia, myopia, or astigmatism to improve visual acuity
            3. Considering strabismus surgery for better ocular alignment
        3. Ensure full benefits of a good education:
            1. Provide large-print and high-contrast written textbooks

   2. Seating at the front of classroom
2. Hermansky-Pudlak syndrome:
   1. Treat extreme bleeding diathesis with platelet and blood transfusions
   2. High dose of steroids for granulomatous colitis or pulmonary fibrosis
3. Chediak-Higashi syndrome:
   1. Treat infections.
   2. Bone marrow transplantation: improves immunological status but no effect on ocular and cutaneous albinism.

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Fig. 1 (**a**–**e**) Oculocutaneous albinism in different age groups including one set of identical twins

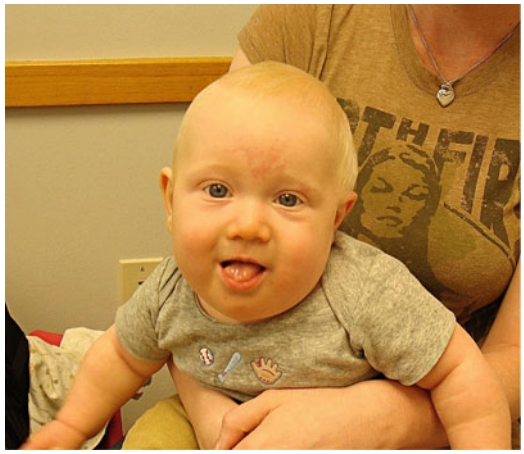

Fig. 2 A 7-month-old infant boy with light skin color, silverish white scalp hair, eyebrows, and eyelashes and absence of nystagmus or strabismus. The infant possesses one detectable mutation in the *OCA2* gene encoding the P protein, namely, V433I: c.1327G > A. This mutation has been reported in the literature and is a known cause of OCA2. The second variation, IVS12-44C > T, was noted. A homozygous sequence change (IVS7-17insA) was observed in the *OCA3* gene. The intronic sequence changes in the *OCA2* and *OCA3* genes have not been reported in the literature and therefore clinical significance is unknown. No mutations were observed in the *OCA1* gene, the *OCA4* gene, or the *OA1* gene

Alpha-Thalassemia X-Linked Mental Retardation Syndrome

Contents

Alpha-thalassemia X-linked mental retardation (ATRX) syndrome, one form of X-linked mental retardation, is characterized by severe mental retardation, typical dysmorphic facies, genital abnormalities, and an unusually mild form of hemoglobin H disease (Gibbons et al. 1995a).

Synonyms and Related Disorders

Alpha-thalassemia X-linked intellectual disability syndrome; ATRX syndrome; X-linked mental retardation-hypotonic face syndrome

Genetics/Basic Defects

1. An X-linked recessive disorder (Donnai et al. 1991).
2. The gene involved in the disease, *ATRX*, is mapped to Xq13.3 (Gibbons et al. 1995b; Carpenter et al. 1999).
3. X-chromosome inactivation.
    1. Skewed X inactivation: common feature of ATRX syndrome (Lossi et al. 1999; Plenge et al. 2002).
    2. Non-skewed X inactivation may cause mental retardation in female carriers of ATRX syndrome (Wada et al. 2005).
4. The ATRX protein belongs to the family of SWI/SNF DNA helicases involved in chromatin remodeling (Ratnakumar and Bernstein 2013; Lacoste et al. 2014).
5. Genetically related (allelic) disorders.
    1. Several X-linked mental retardation (XLMR) syndromes: These disorders should be considered to be in the phenotypic spectrum of ATRX syndromes, and there are no compelling reasons to maintain the syndromic names.
        1. Carpenter-Waziri syndrome (Abidi et al. 1999)
        2. Holmes-Gang syndrome (Stevenson et al. 2000)
        3. Chudley-Lowry syndrome
        4. XLMR with spastic paraplegia
        5. XLMR with epilepsy
        6. Nonsyndromic XLMR
    2. ATRX mutations are identified in the following two syndromes but not in the original reported families; therefore, the relationship between ATRX syndrome and these two syndromes is unclear.
        1. Juberg-Marsidi syndrome (Saugier-Veber et al. 1995; Villard et al. 1996)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_9

2. Smith-Fineman-Myers syndrome (Villard et al. 2000)

Clinical Features

1. Central nervous system features
   1. Global developmental delay
      1. Limited expressive language
      2. Delayed walking until late childhood or unable to ambulate
   2. Generalized hypotonia, a hallmark of the condition, in early childhood, contributing to facial manifestations, drooling, and developmental retardation
   3. Seizures (30%)
2. Characteristic craniofacial features (Gibbons 2006)
   1. Microcephaly (75%)
   2. Characteristic and recognizable facial gestalt during infancy (>90%)
      1. Upsweep of the frontal hair
      2. Hypotonic facies
      3. Telecanthus or ocular hypertelorism
      4. Small triangular nose with retracted columella
      5. Tented upper lip
      6. Prominent or everted lower lip
      7. Open mouth
   3. Other features
      1. Irregular anatomy of the pinnae
      2. Wide spacing of the teeth
      3. Tongue protrusion
      4. Coarse facial appearance particularly after the first few years of life
3. Abnormal external genitalia (80%): broad spectrum of possible genital anomalies but the type of genital anomaly appears to be consistent within a family
   1. Often minor anomalies
      1. First-degree hypospadias
      2. Undescended testes
      3. Underdevelopment of the scrotum
   2. More severe defects
      1. Second- and third-degree hypospadias
      2. Micropenis
      3. Ambiguous genitalia
   3. Occasional gonadal dysgenesis (Jezela-Stanek et al. 2009) resulting in inadequate testosterone production and ambiguous genitalia or normally appearing female external genitalia
4. Skeletal anomalies
   1. Short stature (65%)
   2. Digital anomalies
      1. Brachydactyly
      2. Clinodactyly
      3. Tapered digits
   3. Joint contractures
   4. Spine anomalies
      1. Pectus carinatum
      2. Kyphosis
      3. Scoliosis
      4. Dimples over the lower spine
   5. Foot anomalies
      1. Varus and valgus foot deformation
      2. Pes planus
5. Gastrointestinal features (Martussiello et al. 2006)
   1. Gastroesophageal reflux (two-thirds of cases) may cause aspiration with a fatal complication.
   2. Abdominal pain/distention.
   3. Chronic constipation (one-third of cases).
   4. Report of pseudo-obstruction (gastric pseudovolvulus) resulting from abnormal suspension of the stomach and constipation from colon hypoganglionosis.
6. Major malformations: uncommon
   1. Ocular coloboma
   2. Cleft palate
   3. Cardiac defects (20%)
   4. Inguinal hernia
   5. Heterotaxy
   6. Asplenia

Diagnostic Investigations

1. Diagnosis is suspected on the basis of characteristic craniofacial, genital, skeletal, other somatic features, and hematological findings and should be confirmed by molecular genetic testing.

2. Hematologic studies: demonstration of evidence of alpha thalassemia (Stevenson 2014).
    1. Light microscopy: demonstration of HbH inclusions in red blood cells after incubation with brilliant cresyl blue confirms the diagnosis (Gibbons et al. 1995a; Gibbons and Higgs 2000).
    2. HbH inclusions (β-globin tetramers) ranging from 0.01% to 30% in erythrocytes demonstrated in most individuals with *ATRX* mutations.
    3. Hemoglobin electrophoresis: demonstration of Hb H (not highly sensitive).
    4. Red blood cell indices: microcytic hypochromic anemia.
    5. Considerable variation in the hematologic manifestations associated with ATRX mutations.
3. Brain CT/MRI (Wada et al. 2013).
    1. Nonspecific brain atrophy (63%)
    2. White matter abnormalities, especially around the trigones (41%)
    3. Widespread and scattered white matter abnormalities (4%)
    4. Delayed myelination (15%)
    5. Severe and rapidly progressive cortical brain atrophy (4%)
    6. Multiple symmetric deep and subcortical lesions with high signal intensities on T2 and fluid-attenuated inversion recovery images (Lee et al. 2015)
4. Molecular genetic testing (Stevenson 2014).
    1. Sequence analysis and mutation scanning of select exons.
    2. Sequence analysis and mutation scanning of all exons and splice junctions.
    3. Deletion/duplication analysis.
    4. X-chromosome inactivation studies: the finding of nonrandom X-chromosome inactivation is not unique to ATRX syndrome and is therefore not diagnostic.
5. Whole-exome sequencing (Lee et al. 2015).
    1. Male patients with developmental delay and widespread white matter changes, even without distinctive facial dysmorphism and hematologic abnormalities, should be suspected having ATRX syndrome.
    2. Clinical utility of whole-exome sequencing: particularly in ultrarare neurological diseases and nonspecific developmental disabilities and atypical presentation.
6. Carrier testing in at-risk females possible when the disease-causing mutation in the family is known.

Genetic Counseling

1. Recurrence risk (Stevenson 2014)
    1. Patient's sib.
        1. Carrier mother
            1. A 50% chance of transmitting the *ATRX* mutation.
            2. Offspring with a 46,XY karyotype who inherit the *ATRX* mutation will be affected.
            3. Offspring with a 46,XX karyotype who inherit the mutation are unaffected female carriers.
        2. Sibs of proband with de novo gene mutation: at increased risk of inheriting the disease-causing mutation because of possible germline mosaicism in the mother (Bachoo and Gibbons 1999)
    2. Patient's offspring: affected individual does not reproduce.
2. Prenatal diagnosis and preimplantation genetic diagnosis: possible for pregnancies at increased risk for ATRX syndrome when the disease-causing mutation in the family is known (Fichera et al. 2001; Stevenson 2014)
3. Management
    1. Multidisciplinary interventions
        1. Infant stimulation
        2. Early intervention
        3. Special education
    2. Management of feeding and gastrointestinal problems
        1. Gavage feeding for difficulty in sucking.
        2. Fundoplication and feeding gastrostomy may be required for gastroesophageal reflux.
        3. Surgical correction of pseudovolvulus.
        4. Prevention of constipation.

5. Consider biopsy to rule out Hirschsprung's disease and colonic hypoganglionosis.
6. Control of severe drooling.
    1. Anticholinergics
    2. Botulinum toxin type A injection of the salivary glands
    3. Surgical redirecting of the submandibular ducts
3. Seizure control
4. Genitourinary problems
    1. Orchiopexy for cryptorchidism
    2. Treat recurrent urinary tract infections
5. Orthopedic management for musculoskeletal anomalies
6. Hearing loss management
7. Alpha thalassemia
    1. No treatment required for the mild anemia
    2. Iron not required unless iron stores are shown to be low

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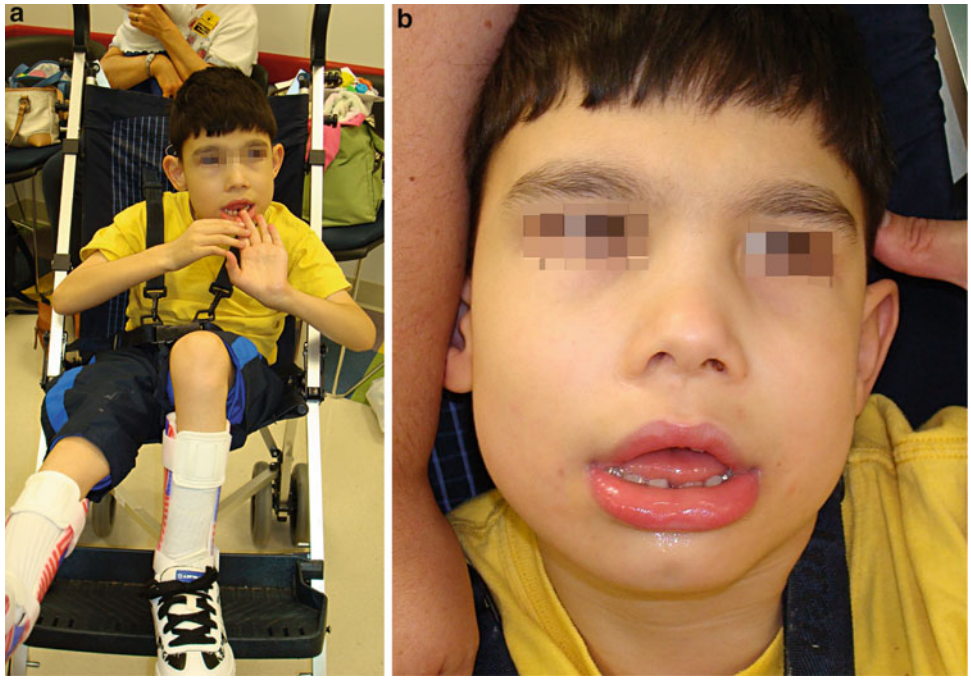

Fig. 1 (**a**, **b**) A 7-year-old boy with global developmental delay and the characteristic facial appearance of ATRX syndrome: upswept frontal hairline, ocular hypertelorism, epicanthal folds, a small triangular upturned nose, open mouth, tented upper lip, prominent everted lower lip, and hypotonic appearing face. He has mild microcytic, hypochromic anemia (mean cell volume 74.8 FL (76–90), MCH 23.6 pg (27–31), MCHC 31.5 g/dl (32–36)). Sequence analysis showed a C > T change at nucleotide 736 in the *XNP* gene (c.736C > T). This change results in the substitution of a cysteine for an arginine at amino acid 246 (R246C). This change is consistent with the diagnosis of ATRX syndrome. His mother has the same *XNP* gene mutation

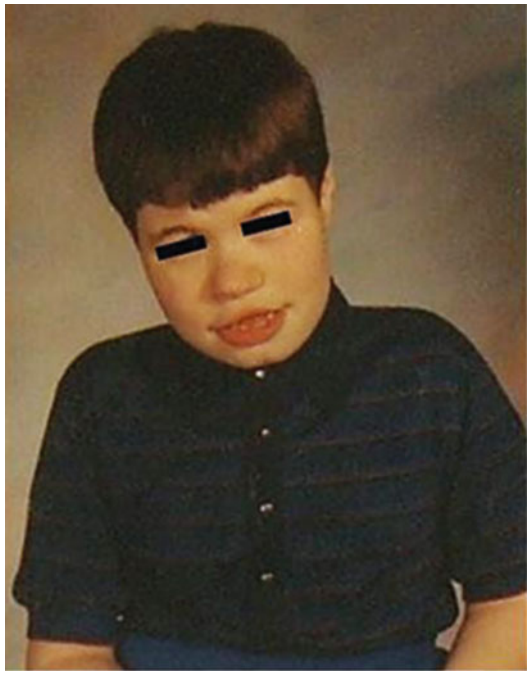

Fig. 2 A maternal uncle was similarly affected (similar characteristic facial features) with recurrent pneumonias, anemia, and mental retardation

Ambiguous Genitalia

Contents

Most cases of ambiguous genitalia are discovered at birth, occurring approximately once in every 1,000 live births. Genital ambiguity usually is due to virilization of genetic females or undervirilization of genetic males who have normal gonads. Less common are disorders of sexual differentiation that involve gonadal dysgenesis (Chi et al. 2008). In females, congenital adrenal hyperplasia (CAH), specifically 21-hydroxylase deficiency, is the most common condition leading to inappropriate virilization. In males, defects in testosterone production, metabolism, or peripheral action can lead to ambiguous genitalia. Later presentations of ambiguous genitalia often include previously unrecognized genital ambiguity, inguinal hernia in a girl (e.g., complete androgen insensitivity), delayed or incomplete puberty, primary amenorrhea or virilization in a girl, breast development in a boy, and gross or cyclic hematuria in a boy (unrecognized virilized 46,XX with CAH) (Lee et al. 2006).

Synonyms and Related Disorders

Disorder of sex development (DSD); Female pseudohermaphroditism; Genetic disorders of sexual differentiation (gonadal dysgenesis, true hermaphroditism, sex reversal); Male pseudohermaphroditism; Testicular feminization syndrome; Undervirilization of male infant; Virilization of female infant

Genetics/Basic Defects

1. Normal development of the human reproductive system (Chi et al. 2008):
    1. Sexual differentiation of the fetus begins at 6–7 weeks of gestation.
    2. During embryogenesis, the fetus contains both female (Müllerian) and male (Wolffian) genital ducts:
        1. Müllerian ducts develop into fallopian tubes, uterus, and the upper one third of the vagina.
        2. Wolffian ducts develop into the vas deferens, epididymis, and seminal vesicles.
    3. "Default" pathway of the bipotential gonad and internal structures: female.
    4. The presence of the sex-determining region Y gene (SRY) in males activates a cascade of events that culminates in differentiation of the gonad as a testis which produces the following two key hormones:

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DOI 10.1007/978-1-4939-2401-1_10

1. Testosterone:
    1. Function: stimulates Wolffian duct differentiation.
    2. Production: initially driven by placental human chorionic gonadotropin (hCG) which subsequently replaced by fetal pituitary gonadotropins after the first trimester, both acting through the luteinizing hormone (LH) receptor.
    3. Local conversion of testosterone to dihydrotestosterone (DHT) by the enzyme 5α-reductase leads to fusion of the labioscrotal folds and formation of the scrotum and penis, both critical events occurring in the first trimester.
2. Müllerian-inhibiting substance (MIS) or anti-Müllerian hormone (AMH): stimulates Müllerian duct regression
5. The absence of testosterone and MIS in females leads to:
    1. Involution of the Wolffian ducts.
    2. Differentiation of the Müllerian ducts into female internal genitalia
    3. Needs both X chromosomes to develop normally differentiated and functional ovaries; females with X chromosome deletion (Turner syndrome) have abnormal gonadal differentiation and oocytes loss, leading to streak gonads.

2. Broad categories of ambiguous genitalia
    1. XX baby with virilization:
        1. In the virilized XX baby, the gonads are ovaries and the internal genitalia are female.
        2. The external genitalia are masculinized by circulating androgens to a variable degree, ranging from subtle clitoromegaly to complete labial fusion with urethral tubularization to the tip of the enlarged phallus.
        3. If exposure occurred late, clitoromegaly without labial fusion is seen. The gonads are not palpable.
        4. The commonest cause of virilization in the XX "female" is congenital adrenal hyperplasia. This autosomal recessive condition results from an enzymatic defect in adrenal steroidogenesis, leading to accumulation of steroids proximal to the block, which are converted to androgens. The commonest of these is 21-hydroxylase deficiency, followed by 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase deficiency. The serum and urinary steroid profile will help to confirm the diagnosis. Other possible causes include exposure to exogenous androgens, such as from maternal androgens or progestin ingestion or, rarely, maternal androgen-producing tumors.
        5. The majority of true hermaphrodites also have a 46,XX chromosomal makeup, but these form a distinct group.
    2. The XY baby with undervirilization:
        1. The undervirilized XY baby presents with a small phallus with severe chordee, posterior hypospadias, and poorly formed bifid scrotum with or without testicular maldescent. Inadequate testosterone production, either as a result of testicular dysgenesis or autosomal recessive enzymatic defects, is rare.
        2. The commonest cause is a group of disorders known as androgen insensitivity syndrome (AIS), previously also known as testicular feminization syndrome. This is an X-linked disorder resulting from peripheral resistance to androgen action, either from mutations in the androgen receptor gene or elsewhere in the molecular pathway.
        3. Whether AIS may, in fact, be due to a defect in the conversion of dihydrotestosterone to 5α-androstanediol remains to be seen.
        4. 5α-reductase deficiency, an autosomal recessive defect resulting in deficient dihydrotestosterone necessary in the virilization of the external genitalia in early embryogenesis, is another cause of undervirilization.
    3. True hermaphroditism:
        1. In the true hermaphrodite, both testicular and ovarian tissues coexist.
        2. The gonads are usually ovary-testis or ovary-ovotestis.

3. The genotype is usually 46,XX (Damiani et al. 1997), although 46,XY or mosaicism can occur (Hadjiathanasiou et al. 1994).
4. Asymmetry of the gonads, internal and external genitalia, is a feature in true hermaphroditism. The right side is more commonly the "masculine" side, while the left side is often more "feminine."

4. Mixed gonadal dysgenesis:
   1. In mixed gonadal dysgenesis, there is a testis on one side (more commonly the right side) and a streak gonad on the other.
   2. The testis may be dysgenetic or initially normal, and the streak gonad histologically is composed of whorls of ovarian stroma without oocytes.
   3. The karyotype is most commonly 45,X/46,XY, but other mosaic patterns have been described.
   4. As with true hermaphrodites, asymmetry is a feature in mixed gonadal dysgenesis.

3. XX true hermaphroditism:
   1. Mechanisms:
      1. Hidden mosaicism with a Y-bearing cell line.
      2. Translocation of Y-material including SRY from paternal Y to X chromosome.
      3. An autosomal (Berkovitz et al. 1992) or X-linked mutation permits testis differentiation in the absence of SRY.
   2. An unusual cause of ambiguous genitalia:
      1. Both ovarian and testicular tissues present either in the same or in a contralateral gonad
      2. Predominantly 46,XX karyotype
   3. Several familial forms reported although the great majority of cases are sporadic:
      1. Occurring with a higher frequency in South African blacks suggesting a genetic origin
      2. Several families in which 46,XX males coexist with 46,XX true hermaphrodites strongly suggest that both disorders are alternative manifestations of the same genetic defect.
      4. SRY-negative true hermaphroditism could be the result of genetic defects at an unknown X-linked or autosomal sex-determining locus.
      5. Mutations in SRY originated ovotestes development described in 46,XY patients.
      6. The absence of SRY in gonadal tissue reported in cases of 46,XX true hermaphroditism.
      7. Possible underestimate of gonadal hidden mosaicism for SRY in XX true hermaphrodites suggesting that true hermaphroditism is a genetically heterogeneous condition.

4. Causes of ambiguous genitalia (Chi et al. 2008):
   1. Virilization of female infant:
      1. Excessive androgen production – congenital adrenal hyperplasia:
         1. 21α-hydroxylase deficiency
         2. 11β-hydroxylase deficiency
         3. 3β-hydroxysteroid dehydrogenase deficiency
      2. Defects in androgen metabolism: placental aromatase deficiency
      3. Maternal hyperandrogenism:
         1. Maternal androgen production (luteoma of pregnancy, adrenal tumor, untreated CAH)
         2. Progestational agents
   2. Undervirilization of male infant:
      1. Defects in testosterone production:
         1. Leydig cell hypoplasia/agenesis
         2. Defects in testicular and adrenal steroidogenesis (steroid acute regulatory (StAR) protein deficiency, 3β-hydroxysteroid dehydrogenase deficiency, 17α-hydroxylase/17,20 lyase deficiency, 17α-hydroxysteroid dehydrogenase (ketosteroid reductase) deficiency)
      2. Defects in testosterone metabolism: 5α-reductase deficiency
      3. Defects in testosterone action: androgen insensitivity syndrome
      4. Exogenous estrogen/progestin exposure
   3. Genetic disorders of sexual differentiation:
      1. Gonadal dysgenesis:
         1. 45,X (streak ovaries)
         2. 46,XX gonadal dysgenesis

3. 46,XY complete and partial gonadal dysgenesis
4. 45,X/46,XY mixed gonadal dysgenesis
5. 47,XXY (seminiferous tubular dysgenesis)

2. True hermaphroditism
3. Sex reversal:
   1. XX males (SRY±)
   2. XY female (SRY±)
   3. Smith-Lemli-Opitz syndrome (SLOS)
   4. *DAX1* mutations
   5. *WT1* mutations

5. 46,XY DSD, testicular development disorders: causative genes and phenotypes (Ono and Harley 2013):
   1. *ARX* (Xp22.13, testicular factor (TF)): dysgenetic testis, no Müllerian structures, ambiguous external genitalia, lissencephaly, epilepsy, and temperature instability
   2. *ATRX* (Xq13.3, chromatin-remodeling protein): dysgenetic testis, no Müllerian structures, female-like or ambiguous or male-like external genitalia, α-thalassemia, mental retardation, and dysmorphic face
   3. *CBX2* (17q25, polycomb protein): normal ovaries, Müllerian structures present, and female-like external genitalia
   4. *DHH* (12q13.1, signaling molecule): dysgenetic testis, Müllerian structures present, female-like external genitalia, and minifascicular neuropathy
   5. *DMRT1* (9p24.3, TF): dysgenetic testis or ovotestis +/− Müllerian structures, female-like or ambiguous or male-like external genitalia, facial abnormality, mental retardation, and microcephaly
   6. GATA4 (8p23.1-p22, TF): dysgenetic testis, Müllerian structures absent, ambiguous or male-like external genitalia, and congenital heart disease
   7. *MAMLD1* (Xq28, transcriptional co-activator): normal function of sex organs, no Müllerian structures, and hypospadias
   8. *MAP3K1* (5q11.2, kinase): dysgenetic testis, Müllerian structures may be present, and female-like or ambiguous or male-like external genitalia
   9. *NROB1* (Xp21.3, nuclear receptor (NR)/TF): dysgenetic testis or ovary +/− Müllerian structures, female-like or ambiguous or male-like external genitalia, cleft palate, and mental retardation
   10. *NR5A1* (9q33, NR/TF): dysgenetic testis +/− Müllerian structures, female-like or ambiguous or male-like external genitalia, and +/− adrenal insufficiency
   11. SOX9 (17q24-q25, TF): dysgenetic testis or ovotestis, +/− Müllerian structures, female-like or ambiguous external genitalia, and campomelic dysplasia
   12. *SRY* (Yp11.3, TF): dysgenetic testis or ovotestis, +/− Müllerian structures, and female-like or ambiguous external genitalia
   13. *WNT4* (1p35, signaling molecule): dysgenetic testis, Müllerian structures present, ambiguous external genitalia, cleft lips and palate, tetralogy of Fallot, intrauterine growth retardation, microcephaly, and mental retardation
   14. *WT1* (11p13, TF): dysgenetic testis +/− Müllerian structures, female-like or ambiguous external genitalia, Wilms tumor, renal abnormalities, and gonadal tumors (WAGR, Denys-Drash, and Frasier syndromes)
   15. *WWOX* (16q23.3-q24.1, oxidoreductase): dysgenetic testis, no Müllerian structures, and female-like external genitalia
6. 46,XX DSD, ovarian development disorders – causative genes (locus, protein) and phenotypes (Ono and Harley 2013):
   1. *MAMLD1* (Xq28, transcriptional co-activator?): streak or dysgenetic gonads, Müllerian structures present, and ambiguous external genitalia
   2. *NR5A1* (9q33, NR/TF): dysgenetic gonads (primary ovarian failure), Müllerian structures present, and female-like external genitalia
   3. *RSPO1* (1p34.3, signaling molecule): testis or ovotestis, no Müllerian structures, male-like or ambiguous external genitalia, palmoplantar hyperkeratosis, and squamous cell carcinoma of the skin

4. *SOX3* (Xq27.1, TF): gonadal histological phenotype (atrophic change in testis with loss of normal spermatogenesis), Müllerian structures not determined, male-like or ambiguous external genitalia, microcephaly, developmental delay, and growth retardation
5. *SOX9* (17q24-q25, TF): gonadal histological phenotype not determined, no Müllerian structures, and male-like or ambiguous external genitalia
6. *SRY* (Yp11.3, TF): testis or ovotestis, no Müllerian structures, and male-like or ambiguous external genitalia
7. *WNT4* (1q35, signaling molecule): ovary or testis or ovotestis, no Müllerian structures, female-like or ambiguous or male-like external genitalia, Mayer-Rokitansky-Küster-Hauser syndrome (autosomal dominant), and SERKAL syndrome (autosomal recessive)

Clinical Features

1. Physical features suggestive of ambiguous genitalia (Lee et al. 2006):
    1. Overt genital ambiguity (e.g., cloacal exstrophy)
    2. Apparent female genitalia with enlarged clitoris and posterior labial fusion (e.g., CAH)
    3. Apparent male genitalia with undescended testes, hypospadias, or micropenis
2. Rules of thumb and clinical significance of internal genitalia (the gonads and the genital ducts) (Low et al. 2003):
    1. Testes descend, while ovaries do not: the presence of a palpable gonad implies the presence of testicular tissue on the same side, which implies the presence of the *SRY* gene somewhere in the genome.
    2. Testicular descent – directly linked to Müllerian duct regression:
        1. The presence of two palpable gonads means there is no uterus.
        2. With asymmetrical gonadal descent, similar ductal asymmetry internally can be predicted.
        3. On the side of the descended gonad, there will be Wolffian duct derivatives but no Müllerian structures. Correspondingly, the contralateral hemi-uterus is likely to be present.
        4. When there are no palpable gonads, the gonadal and ductal status is unknown.
    3. The presence of a uterus (digitally palpated or ultrasonically detected) means no Müllerian-inhibiting substance/anti-Müllerian hormone (MIS/AMH) action during the "sensitive" period in early gestation. This implies either no testes, dysgenetic nonfunctional testes, or defects in production or action of MIS/AMH as occurs in the rare syndrome of persistent Müllerian duct syndrome (PMDS).
    4. Testosterone, as well as MIS/AMH, functions as a locally acting exocrine hormone in the development of the internal genital ducts:
        1. Gonadal asymmetry as occurs in true hermaphrodites, and mixed gonadal dysgenesis results in corresponding duct asymmetry.
        2. Circulating androgens in over-androgenized XX babies are insufficient to allow development of male internal genitalia.
3. Rules of thumb and clinical significance of external genitalia (Low et al. 2003):
    1. External virilization, of any degree, is due to the effect of androgens:
        1. "Clitoromegaly" in an otherwise phenotypic female is always abnormal, indicating abnormal exposure to androgens.
        2. The genotype may be "XX" with virilization or "XY" with undervirilization.
    2. The degree of external virilization proportionally predicts the degree of lower vaginal development:
        1. A baby who is incompletely virilized externally, an incomplete vaginal remnant, is likely to be retained.
        2. In a 46,XX "female" baby, the greater the external virilization, the smaller the vaginal remnant and the higher its opening into the posterior urethra.

3. With the exception of the phallus, circulating androgens masculinize the external genitalia only during a critical period (8th–12th weeks):
    1. Scrotal fusion indicates the presence of early circulating androgens, while an unfused scrotum means deficient early androgen effect.
    2. An enlarged phallus without urethral/scrotal fusion means there has been a delayed androgen effect (beyond 12 weeks).
    3. Enlargement of the phallus to normal penile size means continued presence of an androgen effect throughout later gestation (12 weeks to term).
4. Female pseudohermaphroditism (Anhalt et al. 1996):
    1. Congenital adrenal hyperplasia (please see the chapter):
        1. 21-hydroxylase deficiency
        2. 11α-hydroxylase deficiency
        3. 3β-hydroxysteroid dehydrogenase deficiency
    2. Maternal androgens
5. Male pseudohermaphroditism (Anhalt et al. 1996):
    1. Dysmorphic syndromes
    2. Defects in testosterone biosynthesis:
        1. Cholesterol desmolase deficiency (20,22-desmolase)
        2. 17α-hydroxylase deficiency
        3. 3β-hydroxysteroid dehydrogenase deficiency
        4. 17,20 lyase (desmolase) deficiency
        5. 17β-hydroxysteroid oxidoreductase (ketoreductase) deficiency
        6. Leydig cell hypoplasia or hCG resistance
    3. Defects in androgen target tissues:
        1. 5α-reductase deficiency
        2. Androgen insensitivity (testicular feminization)
        3. Incomplete resistance
    4. Persistent Müllerian duct syndrome
    5. Gonadal dysgenesis
    6. Vanishing testes
6. True hermaphroditism contains both ovarian and testicular gonadal tissue separately or, more commonly, together as ovotestis:
    1. During intrauterine life: the presence of ovarian and testicular tissue with variability in hormonal production results in abnormal differentiation of internal and external genitalia.
    2. At birth:
        1. Variable degrees of genital ambiguity present in nearly all patients.
        2. The presence of labioscrotal folds, normally developed labia majora in most affected individuals.
        3. A hemiscrotum or even a normal scrotum in a minority of cases.
        4. A phallus of variable length with chordee and urethra generally opens as a urogenital sinus in majority of cases while less severe hypospadias in some cases.
        5. Ovaries generally locate in ovarian position, while testes locate in the scrotum generally, inguinal canal, or even intra-abdominally.
        6. Location of ovotestis depends on the amount of testicular or ovarian tissue present.
        7. Development of internal genitalia – variable depending on the neighboring gonad:
            1. The presence of Müllerian derivatives: an ovary is present and ovotestes in most cases.
            2. Wolffian structures: observed in association with testes.
        8. A unicornuate uterus is usually found.
    3. At puberty:
        1. Relative production rate of sex hormones varies depending on the composition of the gonads.
        2. Secondary sex characteristics depend on the type of predominant steroid hormone production.
        3. Breast development frequent after puberty.
        4. Menstruation occurring in approximately 50% of patients.
        5. Ovulation common.
        6. Pregnancy reported in a few cases.

4. Pregnancy in true hermaphrodites:
    1. Complications with preterm labor, neonatal death, or the delivery process itself.
    2. Recommendation to remove the remaining gonad(s) due to an increased risk of germ cell malignancies after thorough discussion of the risks, benefits, alternatives, and implications of future sterility and hormone deprivation.
    3. Pregnancy can occur in true hermaphrodites spontaneously. To date all offspring are males (Schultz et al. 2009).
7. Recently proposed revised nomenclature (Lee et al. 2006; Hughes 2008):
    1. Disorders of sex development (DSD) replacing "intersex"
    2. 46,XY DSD replacing "male pseudohermaphrodite, undervirilization of an XY male, and undermasculization of an XY male"
    3. 46,XX DSD replacing "female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female"
    4. Ovotesticular DSD replacing "true hermaphrodite"
    5. 46,XX testicular DSD replacing "XX male or XX sex reversal"
    6. 46,XY complete gonadal dysgenesis replacing "XY sex reversal"
8. Recently proposed classification of causes of disorders of sex development (DSDs) (Hughes et al. 2006; Hughes 2008):
    1. Sex chromosome DSD:
        1. 47,XXY (Klinefelter syndrome and variants)
        2. 45,X (Turner syndrome and variants)
        3. 45,X/46,XY (mixed gonadal dysgenesis)
        4. 46,XX/46,XY (chimerism)
    2. 46,XY DSD (Mendonca et al. 2009):
        1. Disorders of gonadal (testicular) development: complete or partial gonadal dysgenesis (e.g., SRY, SOX9, SFI, WTI, DHH), ovotesticular DSD, and testis regression
        2. Disorders in androgen synthesis or action: disorders of androgen synthesis (e.g., LH receptor mutations, Smith-Lemli-Opitz syndrome) and disorders of androgen action (androgen insensitivity syndrome, drugs, and environmental modulators)
        3. Others: syndromic associations of male genital development (e.g., cloacal anomalies, Robinow, Aarskog, hand-foot-genital, popliteal pterygium), persistent Müllerian duct syndrome, vanishing testis syndrome, isolated hypospadias, congenital hypogonadotropic hypogonadism, cryptorchidism, and environmental influences
    3. 46,XX DSD:
        1. Disorders of gonadal (ovarian) development: gonadal dysgenesis, ovotesticular DSD, and testicular DSD (e.g., SRY+, dup SOX9, RSP01)
        2. Androgen excess: fetal (21 hydroxylase, 11β-hydroxylase), fetoplacental (aromatase deficiency, oxidoreductase deficiency), and maternal (maternal virilizing tumors such as luteomas, androgenic drugs)
        3. Others: syndromic associations (e.g., cloacal anomalies), Müllerian agenesis/hypoplasia (e.g., MURCS), uterine abnormalities (e.g., MODYS), vaginal atresia (e.g., McKusick-Kaufman), and labial adhesions

Diagnostic Investigations

1. Approach to the baby with ambiguous genitalia (Chen 1986; Low et al. 2003):
    1. History:
        1. Careful history taking indispensable to an accurate diagnosis:
            1. Maternal steroid ingestion.
            2. Antenatal diagnosis of an androgen-producing tumor.

3. A positive family history of a known intersex disorder will give important clues to the underlying disorder.
4. Majority of cases, however, will not yield a positive history.

2. Steps in the evaluation of a baby with ambiguous genitalia:
   1. Document the degree of external virilization: The greater the degree of virilization, the greater the amount of early androgen exposure (between 8 and 12 weeks) and the greater the extent of vaginal regression.
   2. Examine the urogenital sinus carefully by pulling it open. If skin tags with a slight bluish hue are seen, then the hymen and therefore the vagina is confirmed present.
   3. Determine the presence and location of gonads:
      1. Palpable gonads predict the presence of SRY, testicular development, and Müllerian regression on the ipsilateral side.
      2. The degree of testicular descent correlates with the degree of androgen exposure in the second half of pregnancy.
   4. Three possible clinical scenarios:
      1. Both gonads palpable and symmetrical: Palpable gonads are almost always testes, and the implication, in general, is that the baby is an inadequately virilized male and Müllerian duct structures are absent. The differential diagnoses include inadequate testosterone production, receptor deficiency, 5α-reductase deficiency, and minor testicular dysplasia (an exception is the occurrence of bilateral symmetrical ovotestes in a true hermaphrodite).
      2. Gonadal asymmetry with only one gonad palpable: This implies that at least one testis is present. The other may be an ovary, an ovotestis, or a streak gonad.
      3. When gonadal asymmetry is encountered, always consider true hermaphroditism or mixed gonadal dysgenesis.
   5. Impalpable gonads:
      1. Gonadal and duct status: unknown.
      2. Additional clues may be obtained by careful examination to determine if the external inguinal rings are open, which are felt as inverted V-shaped defects superior and medial to the pubic tubercle. Open external rings indicate a high likelihood of an undescended canalicular testis, while a closed external ring is consistent with the presence of ovaries or extremely dysplastic testes with minimal testosterone production. Per rectal examination is also useful in this circumstance. A gentle examination with the little finger will easily palpate the cervix and confirm the presence of the uterus.
      3. Look for other clues in the general physical examination, such as facial dysmorphism or developmental abnormalities that may be part of a sex chromosome abnormality. Hyperpigmentation may occur in congenital adrenal hyperplasia.
2. Clinical assessment strategy in the newborn with ambiguous genitalia (Wunsch 2007):
   1. Ultrasound of the inguinal region and the lower abdomen: used to detect the presence of a uterus, as well as the presence and position of intra-abdominal gonads. However, visualization may be difficult in the small neonate.
   2. Laparoscopy if gonads are not localized.
   3. MRI: suitable for older cooperative children, but imaging of small and developmentally disrupted gonads is frequently unsuccessful.
3. Urogenital sinogram to confirm the presence of and delineate the anatomy of the lower vagina

4. MRI (Choi et al. 1998):
    1. Female pseudohermaphroditism: shows normal internal female genitalia with masculinized external genitalia
    2. Male pseudohermaphroditism: shows normal or mildly defective testes with incompletely masculinized external genitalia
    3. Gonadal dysgenesis: shows combinations of normal, dysgenetic, and streak gonads; no gonads are evident in gonadal agenesis
    4. True hermaphroditism: shows both testicular and ovarian tissue
5. Hormonal investigations:
    1. Serum analysis of 17-hydroxyprogesterone.
    2. Serum profile of adrenal steroids, gonadal androgens, and its precursors.
    3. Human chorionic gonadotropin stimulation tests may be needed to confirm the normal rise of gonadal hormones with stimulation, while testosterone/dihydrotestosterone ratios reflect 5α-reductase activity.
6. Chromosomal analysis to identify the genotype of the affected baby, either as XX, XY, or a mosaic pattern
7. FISH analysis with SRY probes to identify the presence of Y sequences on the X chromosome in cases of 46,XX hermaphroditism and ambiguous genitalia
8. Biopsy of the genital skin for androgen receptor assay
9. Panendoscopy and/or laparoscopy to delineate the internal genitalia
10. Gonadal biopsies on occasion
11. Diagnostic evaluation and potential diagnoses based upon symmetry of genitalia (Mieszczak et al. 2009):
    1. Symmetrical external genitalia:
        1. Palpable gonad: gene testing of *SF1*
        2. Nonpalpable gonad – ultrasound:
            1. Uterus (lack of MIH): hormonal assessment (17-α-hydroxyprogesterone, androstenedione, testosterone, plasma renin activity) for congenital adrenal hyperplasia and in utero androgen exposure
            2. No uterus (presence of MIH): hormonal assessment (MIH, LH, testosterone, FSH (follicle-stimulating hormone), inhibin B, androstenedione) for Leydig cell hypoplasia, 3β-HSD, 17β-HSD (hydroxysteroid dehydrogenase), androgen insensitivity, 5α-reductase deficiency, and testicular regression
    2. Asymmetric external genitalia (virilization of labia different on each side) – assessment includes:
        1. Fluorescence in situ hybridization for SRY (sex-determining region Y)
        2. Hormonal assessment:
            1. MIH
            2. LH
            3. Testosterone
            4. FSH
        3. Inhibin B: androstenedione
        4. Gene testing:
            1. *SOX9* (17q24) – male gonadal dysgenesis, campomelic dysplasia, or XY sex reversal
            2. *WT1* (11p13) – XX male (SRY+), Frasier syndrome, or Denys-Drash syndrome with Wilms's tumor
            3. *DAX1* (Xp21.3) – mixed gonadal dysgenesis, XY female (SRY-), or congenital adrenal hypoplasia
            4. *WNT4* – XO/XY
            5. *DHH* – ovotesticular DSD
            6. *ATRX* – α-thalassemia X-linked mental retardation syndrome
            7. *SLOS* – Smith-Lemli-Opitz syndrome
        5. Imaging: ultrasound
12. Genetic testing (Wherrett 2015):
    1. Molecular analysis: available in many forms of DSD, particularly CAH and complete androgen insensitivity
    2. Microarray analysis for infants with syndromic forms of DSD: to detect chromosomal deletions
    3. Whole genome and exome sequencing: promising (Baxter and Vilain 2013; Tobias and McElreavey 2014)

4. Molecular techniques used to identify genetic causes of DSDs (Achermann et al. 2015):
    1. Array-CGH. SNP array-CGH:
        1. CNVs (copy number variants)
        2. Mosaicism
        3. Uniparental disomy
        4. LOH
    2. Sanger sequencing:
        1. SNVs
        2. Small insertions and deletions
        3. Microsatellite analysis
    3. qPCR:
        1. CNVs
        2. SNPs
        3. Gene expression
    4. MLPA:
        1. CNVs
        2. SNPs methylation defects
    5. Targeted capture array:
        1. SNVs
        2. CNVs
13. Online information on DSD: available for patients, parents and professionals (Ahmed and Rodie 2010)

Genetic Counseling

1. Recurrence risk depends on the inheritance pattern of the disorder (e.g., autosomal recessive disorders (congenital adrenal hyperplasia, testosterone biosynthetic defects, Leydig cell hypoplasia); autosomal dominant disorders (campomelic dysplasia, Denys-Drash syndrome, Frasier syndrome); X-linked recessive disorders (androgen insensitivity syndrome, male pseudohermaphroditism due to testicular 17,20-desmolase deficiency)):
    1. Patient's sib:
        1. Autosomal recessive: 25%
        2. Autosomal dominant: not increased unless a parent is affected or having gonadal mosaicism
        3. X-linked recessive: 50% of male sibs affected if the mother is a carrier
    2. Patient's offspring:
        1. Autosomal recessive: not increased unless the spouse is also a carrier.
        2. Autosomal dominant: 50%.
        3. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
2. Prenatal diagnosis:
    1. Prenatal ultrasonography. Pitfalls in sonographic fetal sex determination (Odeh et al. 2009) include:
        1. Fetuses with malformations of the external genitalia represent a diagnostic challenge.
        2. Clues to the presence of congenital malformations of the external genitalia include:
            1. Nonvisualization of the fetal bladder (Wilcox and Chitty 2001).
            2. Diagnosis of female genitalia at early gestation based on caudal orientation of the genital tubercle, followed at a later time by observation of male genitalia (Borneshtien et al. 1995).
            3. Marked phallic size discrepancy for gestational age, curvature of the phallus, and scrotal-phallus malpositions.
            4. Nondescended testis in the third trimester.
            5. The absence of phallic, labial, or scrotal structures (Mandell et al. 1995).
            6. Abnormalities of the genitalia should also be suspected whenever a mismatch is found between the sonographic fetal sex and the karyotypic fetal sex (Stephens 1984; Cheikhelard et al. 2000).
    2. Prenatal diagnosis of DSDs (Achermann et al. 2015):
        1. Fetal karyotyping from cells cultured from chorionic villi (at 11–14 weeks of gestation) or amniotic fluid (at about 16 weeks of gestation).
        2. Prenatal detection of ambiguous genitalia by ultrasonography or genotype-phenotype discordance.
        3. Identification of circulating cell-free fetal DNA (cfDNA) in maternal blood: provides an important alternative

approach for noninvasive prenatal diagnosis. Currently, PCR amplification of cfDNA is the gold standard method to define fetal sex early in pregnancy without any risk of spontaneous abortion.

3. Prenatal diagnosis is possible for pregnancies at increased risk for various genetic syndromes when the disease-causing mutation in the family is known.

3. Management:
   1. Ambiguous genitalia: likely the most devastating condition to face any parent of a newborn.
   2. Gender identity: dealing with emotional, psychosocial, cultural, diagnostic, and treatment issues (Byne 2006).
   3. Factors to consider when discussing sex assignment with families (Lee et al. 2006):
      1. Diagnosis
      2. Genital appearance
      3. Potential for fertility
      4. Surgical options
      5. Long-term hormone replacement therapy
      6. Family views
      7. Cultural practices
   4. Challenge facing clinicians – come to an accurate and expeditious diagnosis and then to a rational sex assignment:
      1. The condition is rare.
      2. Clinical diagnosis frequently difficult.
      3. Understanding of normal sexual differentiation is crucial to understanding these disorders.
   5. Hormone replacement therapy is often required to induce and sustain puberty and optimize bone mineral accrual and psychosexual development in individuals with ambiguous genitalia (Warne et al. 2005; Drobac et al. 2006; Nabhan and Lee 2007):
      1. Intramuscular injections of either testosterone cypionate or ethanate are used for pubertal induction for hypogonadal boys. Other testosterone preparations such as gels and patches are available, but there is limited experience of their use for the induction of puberty (Rogol 2005).
      2. Estrogen replacement orally or injection to induce secondary sexual characteristic development and menses for girls with hypogonadism. A progestin is usually added after breakthrough bleeding or after 1–2 years of continuous estrogen. In women without a uterus, there is no evidence that the addition of cyclic progesterone is beneficial.
   6. Surgical care:
      1. Feminizing genitoplasty, including vaginoplasty and clitoroplasty, in a virilized female.
      2. Surgical reconstruction in undervirilized males who typically have hypospadias: gender reassignment may be considered in patients with male pseudohermaphroditism and genital inadequacy.
      3. Testes in individuals with 46,XY gonadal dysgenesis or fragments of Y-chromosome material raised female should be removed to prevent testicular malignancy.

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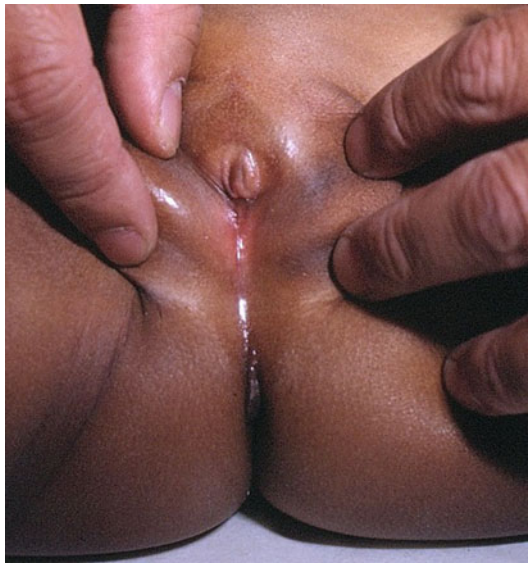

Fig. 1 Vaginal labia agglutination (adhesion) in a female infant

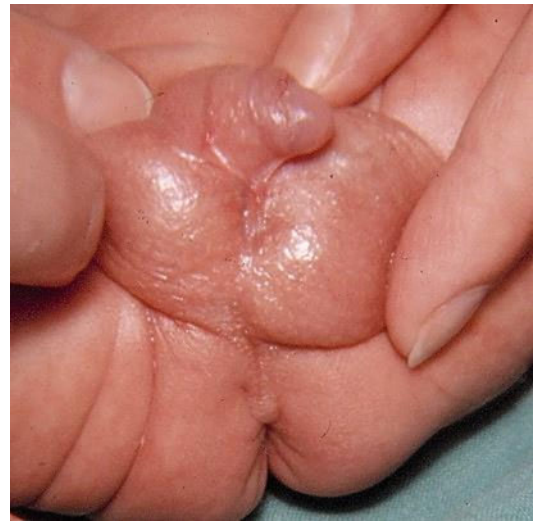

Fig. 3 Penoscrotal hypospadias with a chordee in a male infant

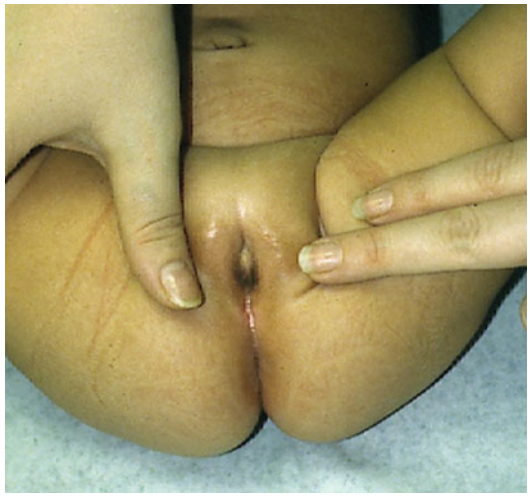

Fig. 2 Vaginal atresia in a female newborn

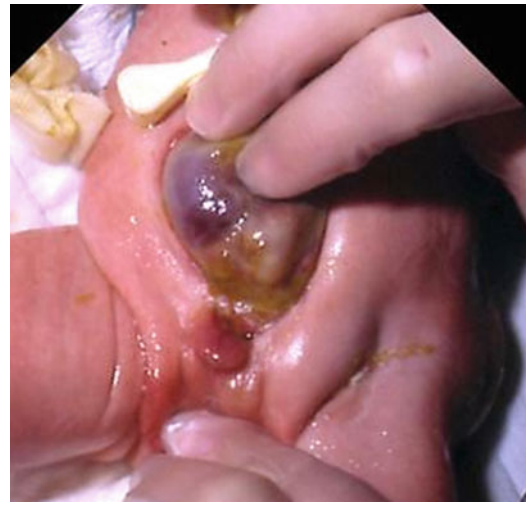

Fig. 4 Cloacal exstrophy with ambiguous genitalia in an infant

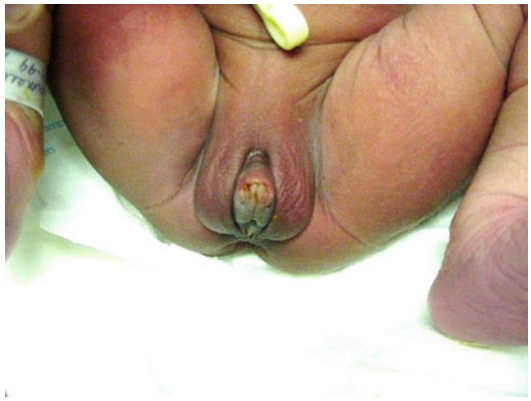

Fig. 5 Ambiguous genitalia with clitoromegaly in a female infant

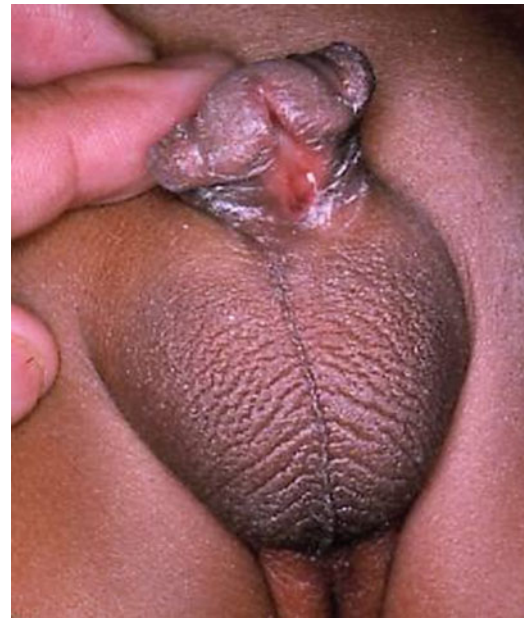

Fig. 7 Penoscrotal hypospadias in Smith-Lemli-Opitz syndrome

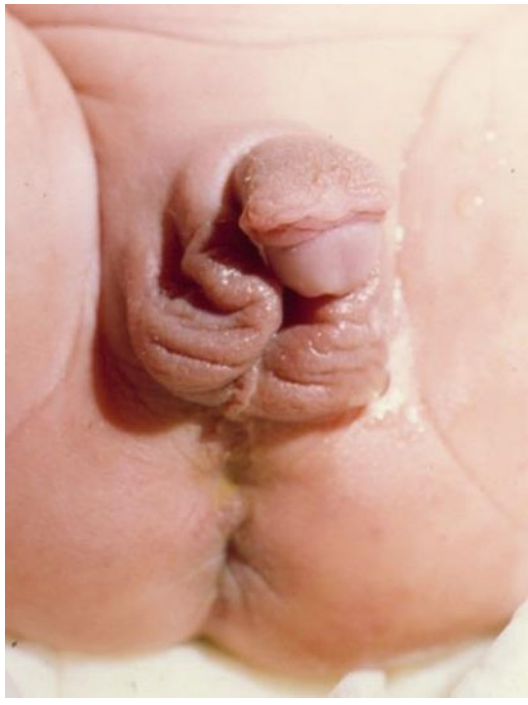

Fig. 6 Ambiguous genitalia in a female infant with congenital adrenal hyperplasia

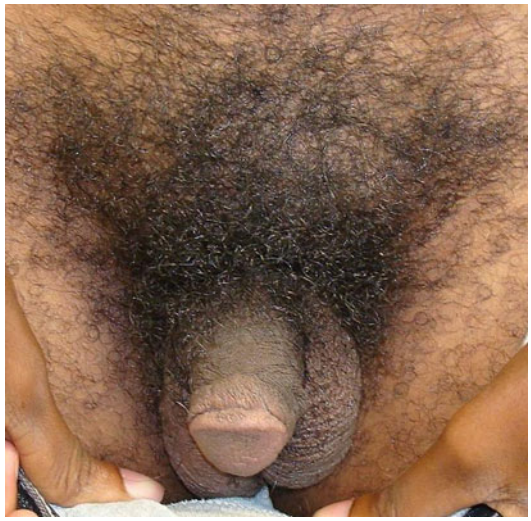

Fig. 8 A 17-year-old male was followed for 46,XX true hermaphroditism. He was born with low shaft hypospadias and *left* inguinal hernia. He underwent *left* groin exploration and *left* inguinal hernia repair. At operation, the patient was noted to have an odd testicle which looked like a typical ovotestis. Two biopsied specimens were obtained: one revealed immature ovary containing numerous follicles and other a fragment of immature testicle containing seminiferous tubules. He was followed at age of 11. He had Tanner III gynecomastia, Tanner III–IV pubic hair, and Prader 5–8 cm^3 volume testes that were somewhat irregular in size and firm. The LH and FSH were 3.2 and 21 μ/ml (both were normal pubertal levels), respectively. A beta HCG was <3 mIU/ml, and testosterone level 351 ng/dl (normal pubertal levels), estrone 1.3 ng/dl, and estradiol 0.8 ng/dl (normal male levels). His bone age was between 12 and 12.5 years of age

Amniotic Deformity, Adhesions, Mutilations (ADAM) Complex

Contents

ADAM complex occurs in 1 of every 5,000–15,000 births and had been demonstrated in 1–2% of malformed infants (Heifetz 1984). The birth prevalence rate was estimated at 1.16 per 10,000 live births (Garza et al. 1988).

Synonyms and Related Disorders

Amniotic band disruption complex; Amniotic band syndrome; Amniotic constriction band; Congenital ring constrictions; Constriction ring syndrome; The Early Amnion Rupture Spectrum (TEARS)

Genetics/Basic Defects

1. Streeter intrinsic theory (Streeter 1930; Wiedrich 1998)
    1. An intrinsic defect of the subcutaneous germplasm causes soft tissue to slough. The resulting external healing leads to the constriction ring.
    2. Significant rate of associated anomalies as indirect proof of existence of some genetic force at work to cause the syndrome.
2. Torpin extrinsic theory (Torpin 1965; Torpin and Fauklner 1966) (currently most popular theory)
    1. Early amniotic rupture leading to the formation of mesodermal fibrous strands that entangle limbs and appendages
    2. Amnion rupture without injury to the chorion resulting in amniotic bands
    3. Oligohydramnios playing a major role in the development of the constricting bands
    4. Higher incidence of clubfeet possibly resulting from continuous pressure on the feet from the undersized uterus
    5. Amniotic bands essentially encircling the affected part resulting in constricting rings
    6. Supporting evidence
        1. Constriction rings often occurring in a straight line across multiple digits as if one external band affects multiple adjacent digits
        2. Frequent involvement of the central digits
        3. Occasional attachment of amnion in the constricting ring
        4. Facial clefting which does not follow developmental planes

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Other theory: simultaneous occurrence of both extrinsic and intrinsic factors in the development of constriction band syndrome
4. Other factors/mechanisms implicated in the etiology of amniotic band syndrome: the cause of amniotic band syndrome remains elusive and controversial (Bagatin et al. 1997; Ossipoff and Hall 1977).
    1. Simple oligohydramnios
    2. Fetal hypertension
    3. Venous stasis
    4. Localized fetal ischemia caused by uterine contractions
    5. Intrauterine hemorrhage as the precipitating event
    6. Vascular compromise (lack of distal blood flow demonstrated in association with forearm amputation defects)
    7. Cocaine drug abuse: cocaine acting as a teratogen by inducing fetal hypoxemia through impaired uteroplacental fetal blood flow and directly through its vasoconstrictive properties on the fetal vasculature
    8. Incompetent cervix
    9. Amniocentesis implicated. An increased incidence of anomalies related to amniotic band syndrome in association with prenatal amniocentesis in animal models (Kino 1975; Cignini et al. 2012)
    10. Familial occurrences reported despite no evidence for a genetic predisposition to amniotic band syndrome (Lubinsky et al. 1983)

Clinical Features

1. The nature and severity of deformities: related to the timing and initiating event of amniotic rupture (Heifetz 1984)
2. Triad of amniotic band syndrome
    1. Amnion-denuded placenta
    2. Fetal attachment or entanglement by amniotic remnants
    3. Fetal deformation, malformation, and/or disruption (Goldfarb et al. 2009)
        1. Fetal deformation
            1. Fetal compression secondary to oligohydramnios (talipes equinovarus, scoliosis, and various joint contractures)
            2. Fetal entanglement by amniotic bands
        2. Fetal malformation resulting from amniotic band interfering with the normal sequence of embryologic development. Classic malformations include:
            1. Body wall defects, internal organ abnormalities
            2. Craniofacial abnormalities
        3. Fetal disruption secondary to cleavage of structures that have already developed normally. Classic disruptive findings are:
            1. Constriction bands
            2. Amputations
            3. Acrosyndactyly
3. Craniofacial disruptions (up to one-third of cases) (Bagatin et al. 1997; Eppley et al. 1998)
    1. Facial clefting
        1. Most likely associated with swallowing of band at about 5 months of gestation
        2. Unusual extensions with asymmetric locations, such as oblique facial clefting (Mishima et al. 1996)
    2. Orbital defects
        1. Anophthalmos
        2. Microphthalmos
        3. Enophthalmos
        4. Hypertelorism
    3. Corneal abnormalities
        1. Anomalous eyelid configuration
        2. Ineffective eye closure
    4. Other ocular abnormalities
        1. Strabismus due to defects in extraocular muscles
        2. Epiphora related to either lachrymal system involvement or eyelid abnormalities
        3. Orbital clefts, lid anomalies (colobomas, ptosis, ectropia), lacrimal outflow obstruction, and globe involvement (Hollsten and Katowitz 1990)

5. CNS involvement: usually associated with amniotic band rupture before 45 days of gestation
    1. Neural tube defects (cranioschisis, atypical or asymmetrical meningocele, myelomeningocele, encephalocele, or anencephaly)
    2. Ventriculomegaly
    3. Pressure defects of the parenchyma
6. Calvarial defects
7. Cleft lip/palate

4. Limb abnormalities (Keller et al. 1978; Bourne and Klassen 1987; Askins and Ger 1988; de Pablo et al. 1995; Walter et al. 1998)
    1. Limb reduction defects/limb length discrepancies
    2. Intrauterine amputations (Baker and Rudolph 1971; Light and Ogden 1993; Al-Qattan 2000)
    3. Ring constrictions with or without distal lymphedema, clubbing, or syndactyly
        1. Deeper rings
        2. Circumferential rings
    4. Club feet
    5. Digital anomalies: frequently involved
        1. Syndactyly
        2. Acrosyndactyly
        3. Digital hypoplasia
        4. Symphalangism
        5. Symbrachydactyly
        6. Camptodactyly
    6. Significant neurovascular impairment distal to the constricting band
5. Umbilical cord strangulation by amniotic bands
    1. Common occurrence (10%)
    2. Cord strangulation
    3. Severe strangulation of the umbilical cord at times resulting in fetal death
    4. Stillbirths observed in about 97% of umbilical cord strangulation by amniotic bands
6. Associated anomalies
    1. Hemangiomas
    2. Cardiac defect
    3. Limb/body wall defects (Moerman et al. 1992)
    4. Thoracoabdominal wall defects
        1. Thoracoschisis
        2. Extrathoracic heart
        3. Omphalocele
        4. Gastroschisis
    5. Aplasia cutis
    6. Short umbilical cord
    7. Oligohydramnios sequence
7. Patterson's classification system of congenital ring constriction based on the severity of the syndrome (Patterson 1961)
    1. Simple constriction rings
    2. Constriction rings associated with deformity of the distal part, with or without lymphedema
    3. Constriction rings associated with soft tissue fusions of distal parts (acrosyndactyly)
    4. Intrauterine amputation
8. Hall's classification system for amniotic band syndrome
    1. Mild constriction without lymphedema
    2. Moderate constriction with lymphedema
    3. Severe constriction with amputation
9. Weinzweig's classification system for amniotic band syndrome (Weinzweig 1995)
    1. Mild constriction without lymphedema
    2. Moderate constriction with distal deformity, syndactyly, or discontinuous neurovascular or musculotendinous structures without vascular compromise
        1. Without lymphedema
        2. With lymphedema
    3. Severe constriction with progressive lymphaticovenous or arterial compromise
        1. Without soft tissue loss
        2. With soft tissue loss
    4. Intrauterine amputation
10. Lockwood's classification of fetal anomalies in amniotic band syndrome according to their presumed mechanism (Lockwood et al. 1989)
    1. Anomalies caused by interruption of embryonic morphogenesis
        1. Cleft lip and palate
        2. Omphalocele
        3. Cardiac anomalies
        4. Renal agenesis or dysplasia
        5. Bladder exstrophy
        6. Imperforate anus

2. Anomalies caused by fetal vascular compromise
    1. Gastroschisis
    2. Gallbladder agenesis
    3. Single umbilical artery
3. Anomalies caused by intrauterine constraint
    1. Club foot
    2. Clubbed hands
    3. Abnormal facies
    4. Valgus-varus deformities
    5. Kyphoscoliosis
4. Anomalies caused by disruption of normally developed structures
    1. Severe central nervous system or calvarial defect
    2. Acrosyndactyly
    3. Amputations
    4. Constriction bands
    5. Facial clefts (anatomically inappropriate)
    6. Aplasia cutis

11. Proposed prenatal classification in stages of amniotic band syndrome involving extremities (modified postnatal classification by Weinzweig 1995; Hüsler et al. 2009)
    1. Amniotic bands without signs of constriction
    2. Constriction without vascular compromise (normal vascular Doppler studies, when compared to opposite side) may have distal deformity
        1. Without or only mild lymphedema
        2. With severe lymphedema
    3. Severe constriction with progressive arterial compromise. The flow has to be measured proximally, at and distally to the constriction band.
        1. Abnormal distal Doppler studies when compared to contralateral extremity
        2. No vascular flow to extremity
    4. Bowing or fracture of long bones at constriction site
    5. Intrauterine amputation
12. Prognosis
    1. Early amniotic rupture results in spontaneous abortion or stillbirth, whereas late rupture results primarily in limb involvement (Higginbottom et al. 1979).
    2. Prenatally diagnosed amniotic adhesion with a grim prognosis.
    3. Most cases of cranial and body wall defects incompatible with extrauterine life.
    4. Infants born with limited limb abnormalities: better prognosis with good results after surgical repair of the constrictions or syndactyly.

Diagnostic Investigations

1. Radiography
    1. Syndactyly with amputation of distal parts
    2. Intrauterine amputation of limbs and digits
2. MRI (Laor et al. 1996)
    1. Delineate the depth of the constriction band.
    2. Delineate the extent of the resultant lymphedema.
    3. Delineate the integrity of the musculature.
    4. Define the vascular anatomy, which may be anomalous; may help to prevent injury to the vessels during surgery.
3. Histology (Day-Salvatore et al. 1995)
    1. Absence of amniotic membrane on the fetal surface of the chorionic sac, including the placental sac.
    2. Presence of amnion remnant as a cuff of thick membrane at the base of the umbilical cord at its insertion site.
    3. Amniotic squames and cellular debris are frequently embedded in the superficial soft tissue of the chorion indicating chronic amniotic rupture.
    4. Constricting bands encircling digits.
4. Placentas with early amnion rupture (Yang 1990)
    1. Absence of amniotic epithelium on the fetal surface.
    2. Presence of a slightly fibrotic small amniotic band (remnant) attaching to the umbilical cord at the placental end.

3. Presence of degenerated vernix squamous cells in the fibrous stroma of chorion and amnion.
4. The findings support Torpin's hypothesis that ADAM sequence is a complication of early amnion rupture.

Genetic Counseling

1. Recurrence risk (Levy 1998)
    1. Patient's sib: minimal risk
    2. Patient's offspring: minimal risk
2. Prenatal diagnosis (Mahony et al. 1985; Chen and Gonzalez 1987; Yamaguchi et al. 1988; Burton and Filly 1991; Laberge et al. 1995; Hüsler et al. 2009)
    1. Possible by ultrasonography during the second and third trimesters.
    2. Possible as early as the first trimester in certain cases (Nishi and Nakano 1994).
    3. Degree of deformity depends on the severity and location of the band formation and the gestational age at amniotic rupture.
    4. Visualization of amniotic sheets or bands attached to the fetus. The diagnosis of amniotic band syndrome should not be made solely on the basis of a membrane observed in the uterine cavity.
    5. Restricted fetal movement.
    6. Characteristic asymmetric fetal anomalies.
    7. Constriction bands around the limbs.
    8. Prenatal natural history of amniotic band sequence without body wall defect.
        1. Prematurity
        2. Preterm rupture of membranes
        3. Low birth weight (<2,500 g)
        4. May lead to compromised blood supply to the constricted body parts
        5. Constriction bands may spontaneously resolve (Pedersen and Thomsen 2001)
        6. Fetal death associated with amniotic band strangulation of the umbilical cord reported (Heifetz 1984; Lurie et al. 2008)
    9. Prenatal surgical intervention (Quintero et al. 1997): amniotic band was surgically interrupted to avoid spontaneous amputation of the extremity. Adequate blood flow distal to the obstruction was preserved with significant functional improvement of the extremity.
3. Management (Hall et al. 1982; Walter et al. 1998)
    1. Surgery not needed for shallow constriction bands that are not circumferential and without distal swelling.
    2. Distal edema or impairment of neurovascular function requiring staged constriction band excision, Z-plasty, or W-plasty.
    3. Digital amputation may be required for a ring so constrictive that distal edema is massive.
    4. Multiple plastic surgical procedures required for corrections of the complex craniofacial abnormalities.
    5. Procedures for the upper extremity deformities (Foulkes and Reinker 1994).
        1. Band release, Z- or W-plasty
        2. Syndactyly/web space release
        3. Skin graft
        4. Stump revision
        5. Osteotomy/osteoclasis
        6. Hardware removal
        7. Ray resection/transposition
        8. Distraction osteogenesis
        9. Pollicization/osteocutaneous transfer
        10. Tendon transfer
        11. Excision supernumerary digit
        12. Amputation
    6. Procedures for the lower extremity deformities (Foulkes and Reinker 1994).
        1. Band release, Z- or W-plasty
        2. Syndactyly release
        3. Simple revision
        4. Amputation/excision toe
        5. Clubfoot procedure
        6. Hip procedure
        7. Tibial derotation
        8. Removal of skin tag
    7. Surgical management of abdominopelvic constriction rings in amniotic band syndrome (Capone et al. 2015).
        1. Anterior sheath Y-V plasty.

2. Pteruges release of the Scarpa fascia.
3. Limited Z-plasty closure may minimize the need for serrated scar patterns.

8. Intrauterine release of extremity amniotic band should be indicated in severe cases with risk of intrauterine amputations or irreversible deformities when no other severe disorders are associated (Soldado et al. 2009). The most relevant risks that have to be assumed are premature rupture of membranes and complications related to prematurity.
9. In utero surgical intervention proposed to avoid amputation or permanent damage to the extremity of the fetus, provided the maternal and fetal risks of surgery are small.
10. Fetoscopic amniotic band release (Javadian et al. 2013; Derderian et al. 2014).
    1. A safe procedure.
    2. When umbilical cord involvement is present, it should be treated to reduce the risk of fetal demise.
    3. May allow preservation of life and/or limb function.

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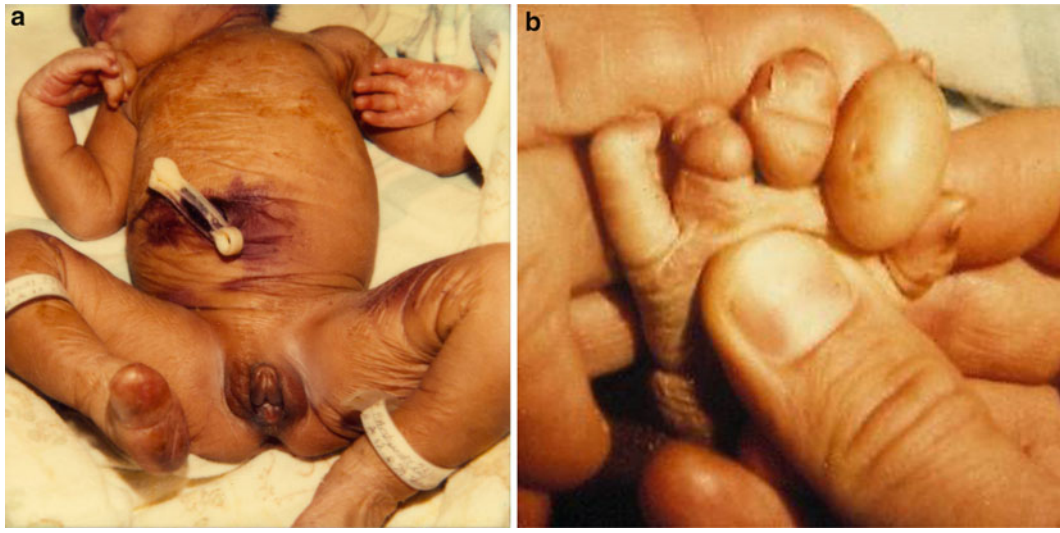

Fig. 1 (**a**, **b**) An infant with club left hand with a missing finger, constricting rings with marked distal lymphedema of the right index finger, and pseudosyndactyly of the right foot

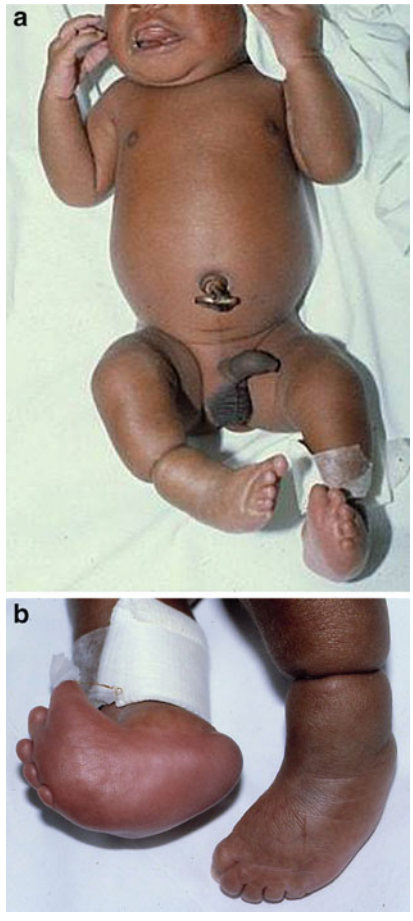

Fig. 2 (**a**, **b**) An infant with deep constricting groove around the lower one-third of both legs. The patient also had terminal amputation and constriction rings of fingers with a small amniotic band still attached to the constricting ring of the second finger (not shown)

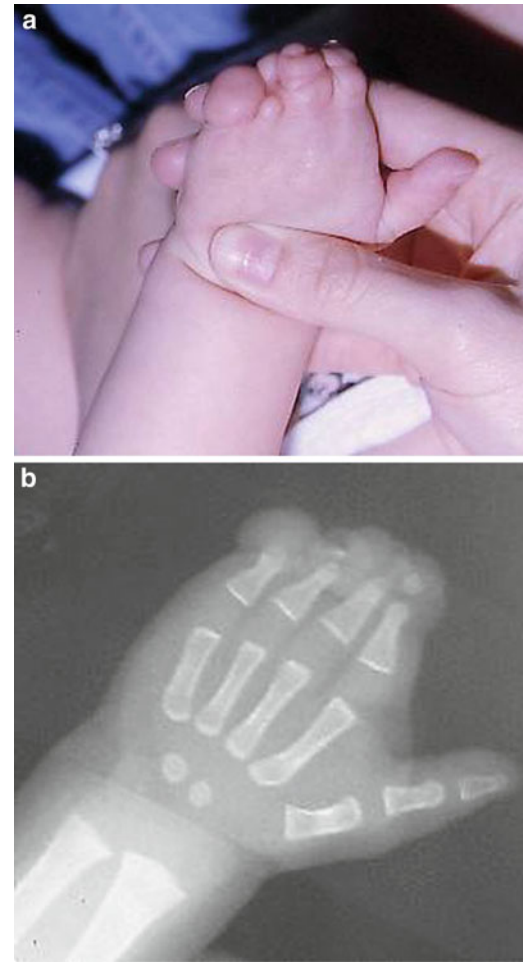

Fig. 3 (**a**, **b**) A hand of an infant with constriction bands of the fingers with amputations, shown by the radiograph

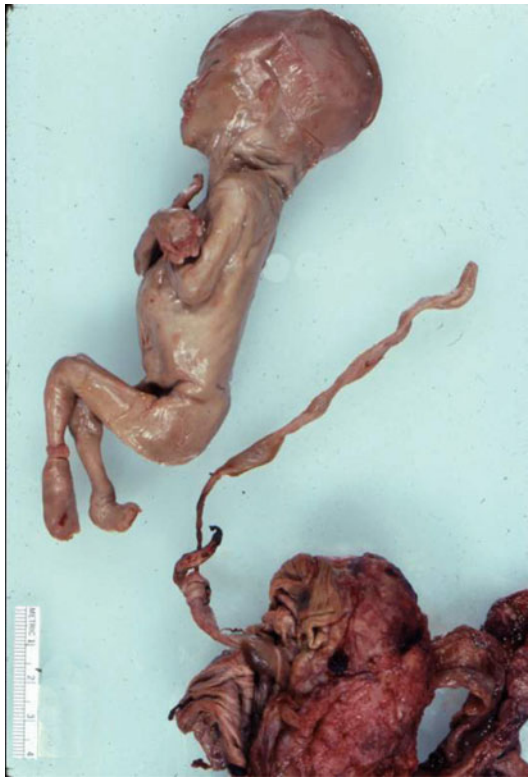

Fig. 4 A small stillborn fetus (110 g) showing amniotic constriction band at left ankle. Amputation and pseudosyndactyly of fingers and toes are present (Courtesy of Dr. Samuel Yang)

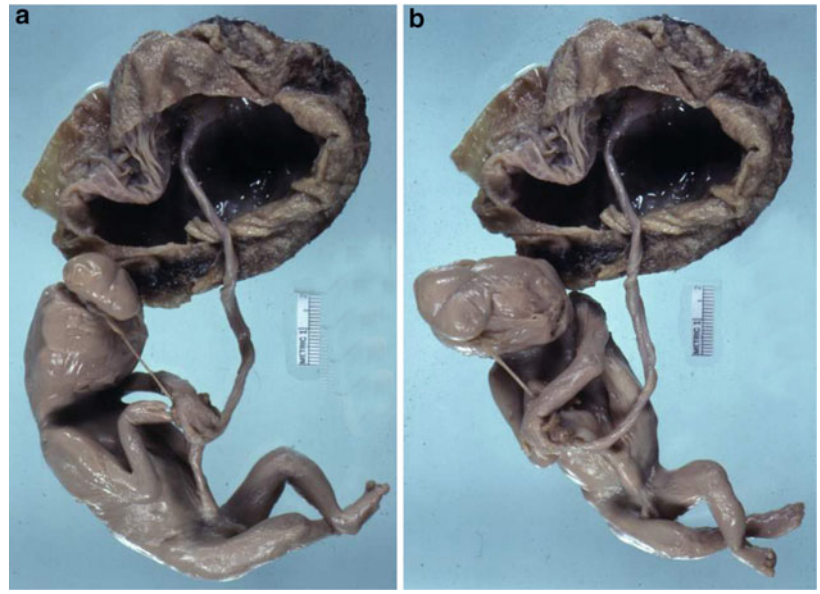

Fig. 5 (**a**, **b**) A small stillborn fetus (60 g) with a fibrous amniotic band constricting a portion of the head and facial cleft (Courtesy of Dr. Samuel Yang)

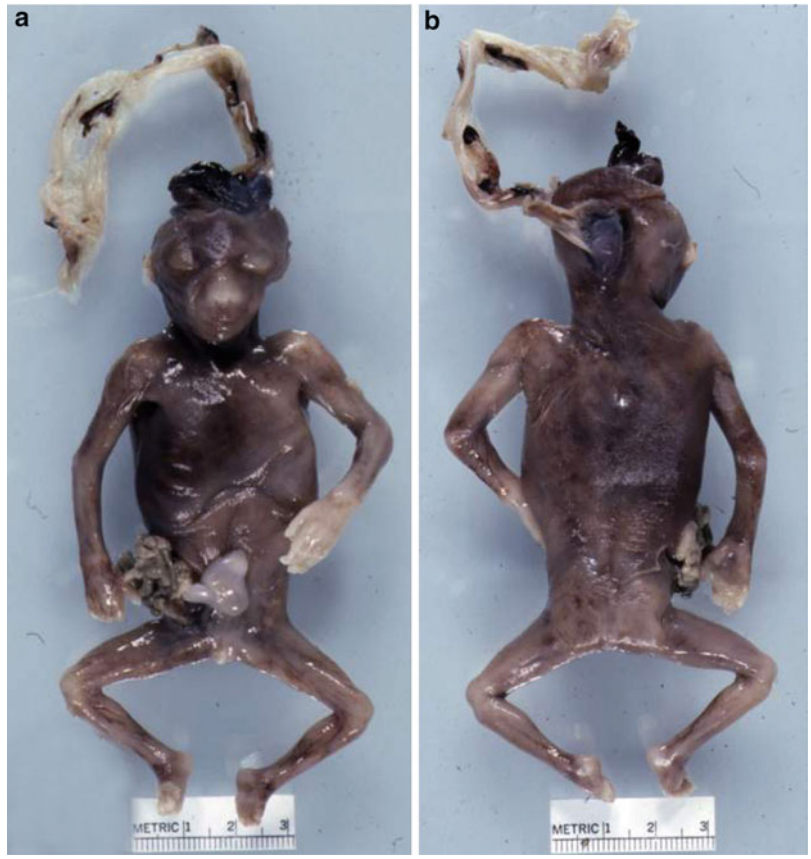

Fig. 6 (**a**, **b**) A small fetus with a large amniotic band which caused anencephaly (Courtesy of Dr. Samuel Yang)

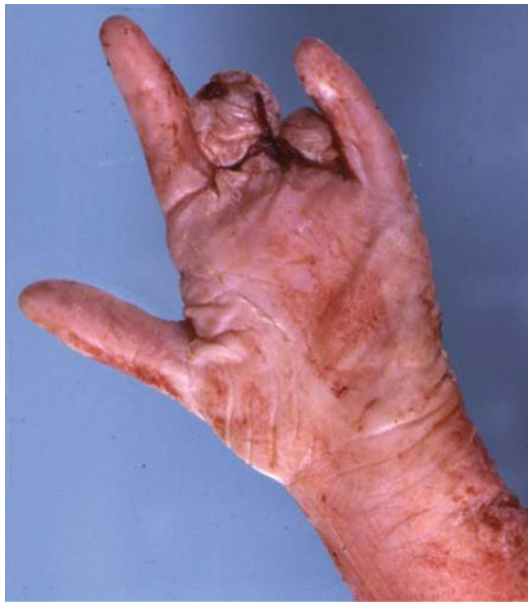

Fig. 7 The left hand of a 1,100 g fetus showing in utero amputation of the third and fourth fingers

Fig. 8 A placenta with a long strand of amniotic band which was pulled out of the mouth of the premature neonate at birth. The baby did not have amniotic band syndrome (Courtesy of Dr. Samuel Yang)

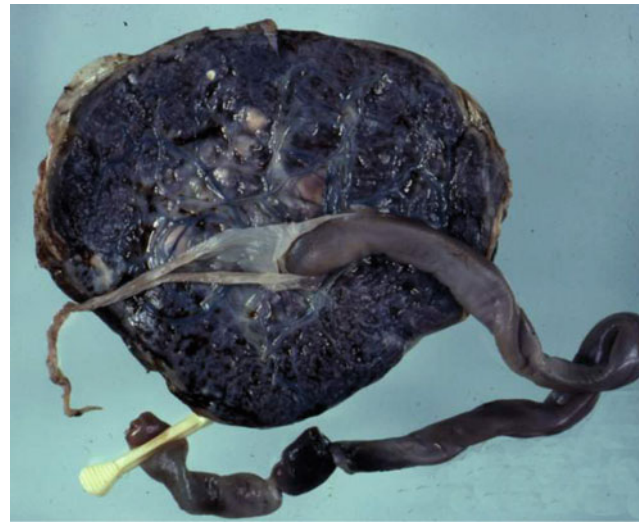

Fig. 9 Cord strangulation by amniotic band (Courtesy of Dr. Samuel Yang)

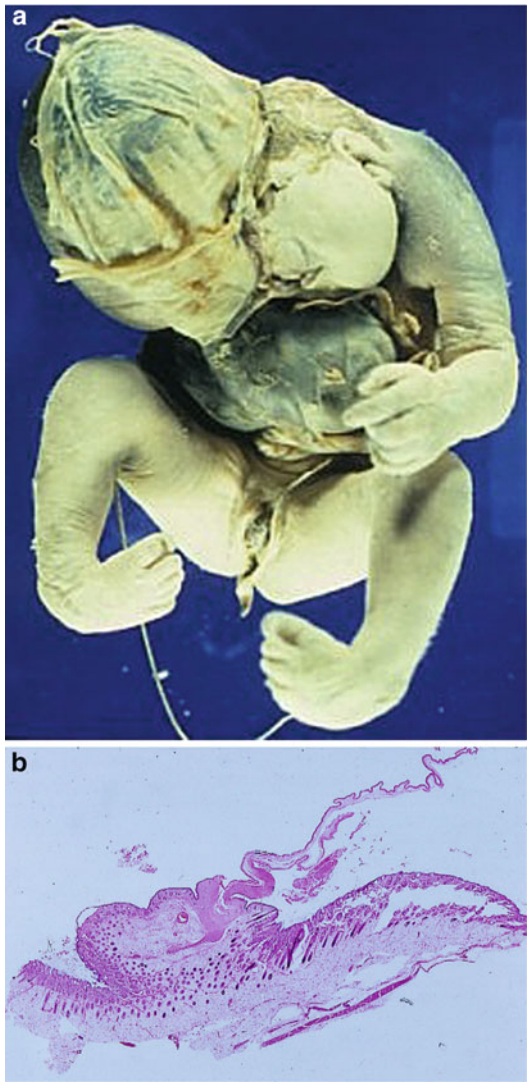

Fig. 10 (**a**, **b**) A fetus with a large meningoencephalocele and an amniotic band attaching to its base. Facial defects, a large gastroschisis, and talipes equinovarus were also present. Histology of the scalp shows an amniotic band fused with the soft tissue of the upper dermis. The amniotic epithelium of the band is visible as a darker line on the surface. The epidermis of the scalp is denuded at the site of band attachment (Chen and Gonzalez 1987)

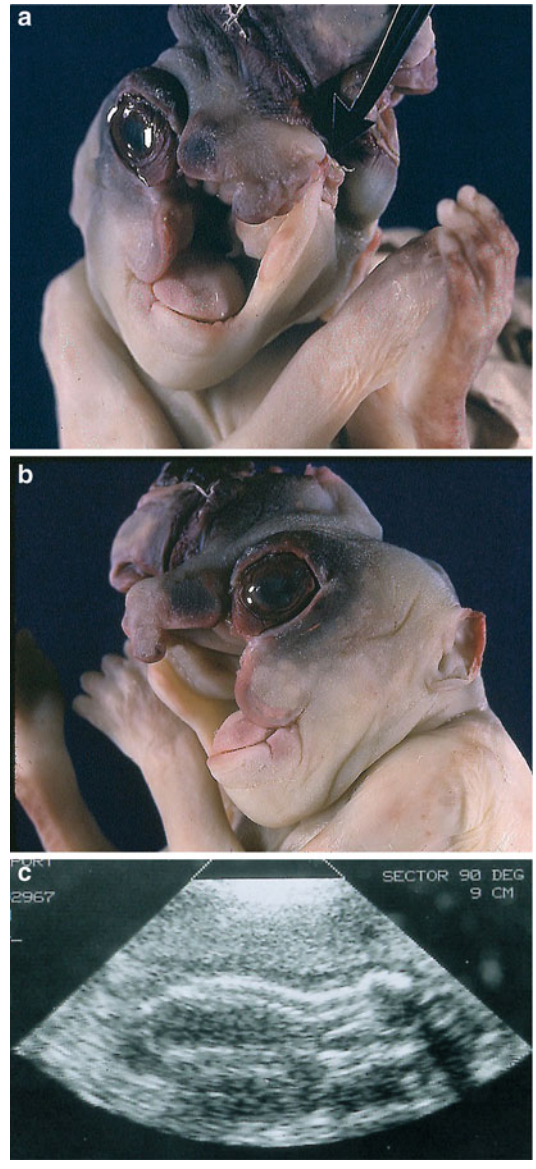

Fig. 11 (**a**–**c**) A fetus with marked craniofacial defects and the site of amniotic band attachment at the base of the skull. The fetus also had amputation of the distal left great toe (not shown). Prenatal ultrasonography showed a complex structure arising from the top and front of the craniofacial region

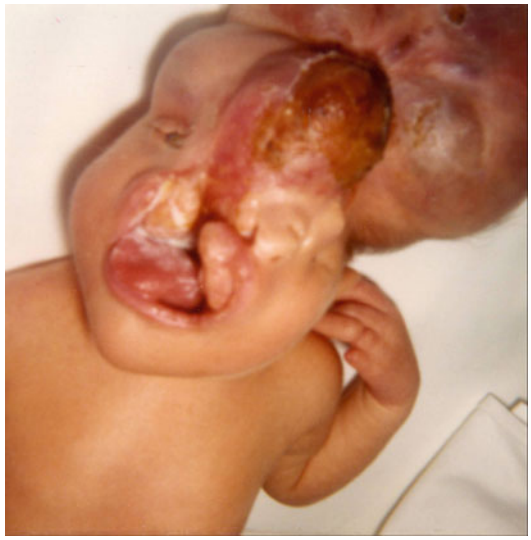

Fig. 12 An infant with marked craniofacial anomalies, a constricting ring of a finger with distal lymphedema, and an amputation of the fifth finger

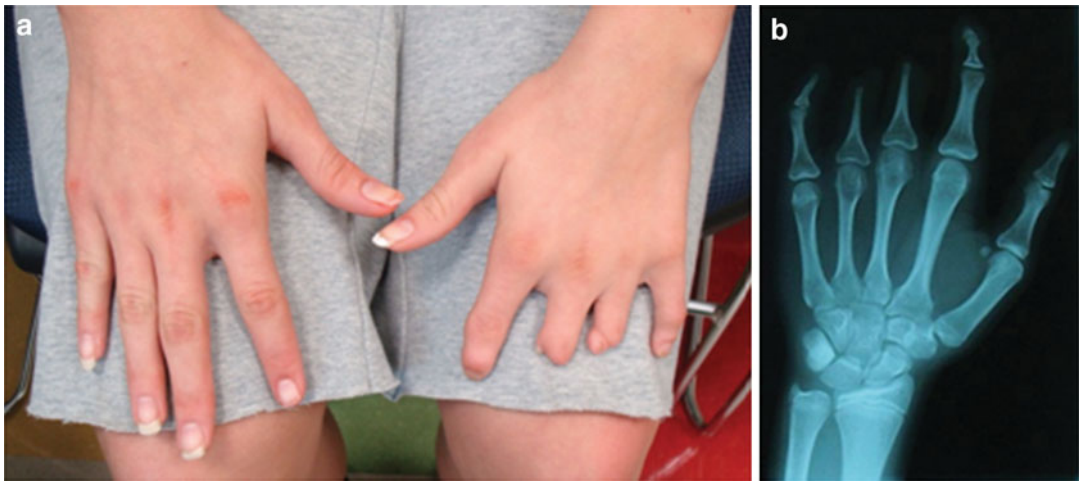

Fig. 13 (**a, b**) This 14-year-old Caucasian female was evaluated for amniotic band syndrome. The left hand was small and characterized by brachydactyly with characteristic preservation of nails (**a**). The radiograph of the left hand (**b**) showed poorly developed proximal phalanges, especially distal ends of 3rd–5th fingers, poorly developed middle phalanx of the 2nd and 5th fingers, missing middle phalanx of the 3rd and 4th fingers, and absence of distal phalanx of the 2nd-5th fingers. The right hand and fingers were normal

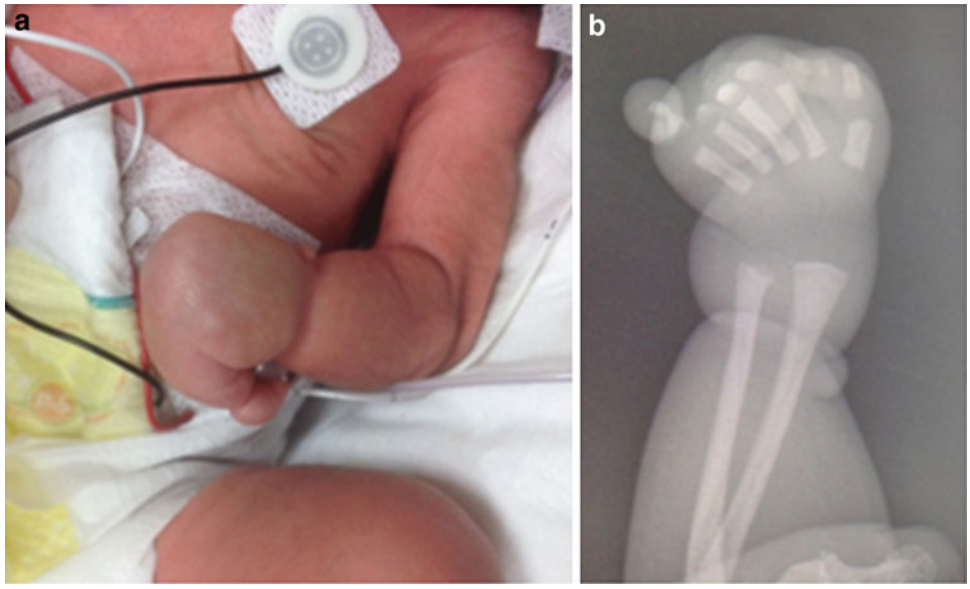

Fig. 14 (**a, b**) This newborn girl (**a**) was evaluated for amniotic band syndrome. The left hand was held in flexed position at the wrist with a constriction ring above. There was a fibrous strand extending from constriction ring area to the fingers. The 2nd and 4th fingers were partially amputated. There were constriction rings on the 3rd and 5th fingers with distal lymphedema, especially worst on the 5th. Radiograph of the left hand (**b**) showed the wrist in flexion position with absence of the mid- and distal phalanx of the 4th and 2nd fingers (Courtesy of Dr. Bharti Manchandia)

Androgen Insensitivity Syndrome

Contents

In 1953, Morris (Morris 1953) described the clinical phenotype of "testicular feminization" after reviewing 82 cases. Morris's phenotype included a female body habitus with normal breast development, minimal pubic and axillary hair, and typically absent or rudimentary vagina or absent uterus. The term "testicular feminization syndrome" was based on the observation of the complete absence of signs of virilization in phenotypic females with testes and a 46,XY karyotype. The change in nomenclature from testicular feminization to androgen insensitivity syndrome (AIS) was prompted by the finding of normal urinary 17-ketosteroid levels, an androgen metabolite, as well as by the absence of treatment effect when 46,XY women were treated with methyl testosterone, suggesting androgen resistance rather than a deficiency (Wilkins 1950; Speroff and Fritz 2005; Oakes et al. 2008).

AIS probably represents the most common cause of male pseudohermaphroditism (Holterhus et al. 1997). It is an X-linked recessive disorder in 46,XY individuals with normal androgen production and metabolism. The prevalence of AIS is estimated to be 1 in 20,000–1 in 99,000 genetic males (Bangsboll et al. 1992; Boehmer et al. 2001). The prevalence of phenotypic females with inguinal hernias is estimated to be 0.8–2.4% (Gans and Rubin 1962; Nielsen and Bulow 1976).

Synonyms and Related Disorders

Androgen receptor deficiency; Dihydrotestosterone receptor deficiency; Testicular feminization syndrome

Genetics/Basic Defects

1. Inheritance:
   1. X-linked recessive inheritance:
      1. Affected XY individuals
      2. Carrier XX females
   2. Manifesting carrier females (about 10% of carrier females)
2. Caused by mutations of androgen receptor (*AR*) gene (mapped to chromosomal locus Xq11–q12) (Lubahn et al. 1988):
   1. Mutations of androgen receptor: responsible for a variable degree of impaired androgen action
   2. De novo mutations:

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_12

1. De novo mutation rate close to 30%
2. Somatic or germ-line mosaicism observed for "de novo" mutations in which the mutation is present in some of the cells in one of the clinically unaffected parents (Boehmer et al. 1997)

3. Type of mutations (Gottlieb et al. 1999a, b)
   1. Point mutations
   2. Complete and partial gene deletions
   3. Small insertion deletions
4. Variable expressivity of a particular point mutation attributable to somatic mosaicism for the mutation (Holterhus et al. 1997)

3. Pathogenesis:
   1. Androgen insensitivity syndrome:
      1. Target tissue resistance to the androgen testosterone and its 5α-reduced product dihydrotestosterone leads to androgen insensitivity syndrome (Hughes and Deeb 2006).
      2. Normal production of testosterone and normal conversion to dihydrotestosterone (DHT) by the normal testes in affected individuals, differentiating this condition from 5α-reductase deficiency.
      3. Absence of fallopian tubes, uterus, or proximal (upper) vagina in affected individuals because testes produce normal amounts of müllerian-inhibiting factor (MIF).
   2. Complete androgen insensitivity syndrome (CAIS):
      1. Most severe form
      2. Complete resistance to all actions of testosterone and dihydrotestosterone
   3. Incomplete androgen insensitivity syndrome (IAIS) (Reifenstein syndrome):
      1. Partial resistance to the action of testosterone and dihydrotestosterone.
      2. Phenotypic variation in two siblings with partial androgen insensitivity syndrome with a point mutation of the androgen receptor gene (Evans et al. 1997): One sibling had clitoromegaly and labial fusion and was raised as a girl, whereas the other sibling had micropenis and penoscrotal hypospadias and was raised as a boy. The phenotypic variation in this family is thus dependent on factors other than abnormalities of the androgen receptor gene alone.
      4. Mild androgen insensitivity syndrome (MAIS): resistance to the action of androgen varies in different tissues
   4. Causes of a partial androgen insensitivity syndrome (Hughes et al. 2012):
      1. Defects in androgen production:
         1. Partial gonadal dysgenesis: mutations in *SRY*, *NR5A1*, and *WT1*
         2. Mutations of the luteinizing hormone receptor
         3. Biosynthetic enzyme deficiencies: 17,20-lyase deficiency, P450 oxidoreductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency type 3, and 5α-reductase deficiency type 2
      2. Genetic:
         1. Klinefelter syndrome
         2. Smith-Lemli-Opitz syndrome
         3. Denys-Drash syndrome
         4. Frasier syndrome
      3. Partial androgen insensitivity syndrome:
         1. Mutations of the androgen receptor gene
         2. Normal androgen receptor gene with fetal growth restriction

Clinical Features

1. Variable phenotypic expression allowing the classification of AIS into complete and partial forms and a rare group of phenotypically normal men with azoospermia
2. Complete androgen insensitivity syndrome:
   1. Presumptive diagnosis of CAIS (Gottlieb et al. 2014):
      1. Absence of extragenital abnormalities
      2. Two nondysplastic testes
      3. Absent or rudimentary müllerian structures (absence of fallopian tubes, uterus, or cervix)
      4. A short vagina
      5. Under-masculinization of the external genitalia at birth

6. Impaired spermatogenesis (sterility) and/or somatic virilization at puberty
2. External phenotype:
   1. Invariably presenting as a normal female external appearance (female habitus)
   2. Female external genitalia ("testicular feminization," Tfm)
   3. Underdeveloped, short blind-ending vagina
   4. Normal breast and female adiposity development
   5. Unaffected sexual identity and orientation
   6. Scant or absent pubic and/or axillary hair
3. Urogenital tract:
   1. Absent or rudimentary Wolffian duct derivatives (epididymitis and/or vas deferens)
   2. Inguinal or labial masses subsequently identified as testes in a phenotypic female infant or child
   3. Inguinal hernia: the commonest presentation of CAIS in childhood (Deeb and Hughes 2005)
   4. 1.1% incidence rate of CAIS in a child with a premenarcheal inguinal hernia while 80–90% of girls with CAIS eventually develop an inguinal hernia (Gans and Rubin 1962; Viner et al. 1997; Sarpel 2005)
4. Other features:
   1. Primary amenorrhea in a phenotypic female adolescent: most typical presentation.
   2. Complete androgen insensitivity syndrome almost always runs true in families (i.e., affected XY relatives usually have normal female external genitalia and seldom have any sign of external genital masculinization, such as clitoromegaly or posterior labial fusion).

3. Partial androgen insensitivity syndrome (PAIS):
   1. Predominantly female external genitalia (incomplete androgen insensitivity syndrome):
      1. Signs of external genital masculinization:
         1. Clitoromegaly
         2. Partial fusion of the labioscrotal folds
      2. Female habitus and breast development
      3. Normal axillary and pubic hair
      4. Inguinal or labial testes as in CAIS
      5. Wolffian duct derivatives emptying into the vagina
      6. Distinct urethral and vaginal openings or a urogenital sinus
      7. No müllerian duct derivatives
   2. Ambiguous external genitalia (Reifenstein syndrome):
      1. Microphallus (<1 cm) with clitoris-like underdeveloped glans
      2. Labia majora-like bifid scrotum
      3. Descended or undescended testes
      4. Perineoscrotal hypospadias or urogenital sinus
      5. Gynecomastia in puberty
   3. Predominantly male external genitalia (Reifenstein syndrome):
      1. Simple (glandular or penile) or severe (perineal) "isolated" hypospadias with a normal-sized penis and descended testes or severe hypospadias with micropenis
      2. Bifid scrotum
      3. Either descended or undescended testes
      4. Gynecomastia in puberty
4. Mild androgen insensitivity syndrome:
   1. Two phenotypic forms at puberty:
      1. Impaired spermatogenesis and fertility
      2. Normal or sufficient spermatogenesis to preserve fertility
   2. Clinical features common to both forms:
      1. Male external genitalia ("undervirilized male syndrome")
      2. Gynecomastia in puberty
      3. High-pitched voice
      4. Sparse sex hair
      5. Impotence
5. Manifesting carrier females:
   1. Asymmetric distribution and sparse or delayed growth of pubic or axillary hair
   2. A history of late (15 years) or delayed (16 years or older) menarche
6. Classification of causes of disorders of sex development (please see the chapter of "► Ambiguous Genitalia")

7. Differential diagnosis (Oakes et al. 2008; Mendoza and Motos 2013):
    1. 5α-reductase deficiency:
        1. Internal male genitalia (testosterone dependent)
        2. No external genitalia (DHT dependent)
        3. Ambiguous or female genitalia at birth
    2. Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome (müllerian agenesis):
        1. A more common cause of primary amenorrhea: an incidence rate of 1 in 5,000 (Aittomaki et al. 2001)
        2. Lack a uterus and a vagina due to the absence of müllerian duct development
        3. Normal breast development
        4. Normal axillary and pubic hair (Speroff and Fritz 2005)
        5. A 46,XX karyotype
    3. Swyer syndrome (XY gonadal dysgenesis) (Nunes et al. 2014):
        1. There is complete gonadal dysgenesis and the lack of secretion of antimüllerian hormone leads to normal development of müllerian structures.
        2. Lack of breast development.
        3. Short stature.
        4. Localize testes and to rule out testicular tumors by ultrasound and MRI.

Diagnostic Investigations

1. Diagnostic workup:
    1. Diagnosis of CAIS usually based on:
        1. Clinical findings.
        2. Laboratory evaluation: hormone resistance is diagnosed when serum hormone concentrations are normal or high but the clinical effect is subnormal (Jääskeläinen 2012).
        3. Imaging studies including transabdominal pelvic ultrasound and MRI: to document internal anatomy.
    2. Diagnosis of PAIS and MAIS based on:
        1. Clinical findings
        2. Laboratory evaluation
        3. Family history consistent with X-linked recessive inheritance
2. Laboratory investigations:
    1. AIS:
        1. Chromosome analysis: 46,XY karyotype
        2. Evidence of normal or increased synthesis of testosterone by the testes
        3. Evidence of normal conversion of testosterone to 5α-dihydrotestosterone
        4. Evidence of normal or increased luteinizing hormone production by the pituitary gland
        5. Evidence of deficient or defective androgen-binding activity of genital skin fibroblasts
    2. CAIS, IAIS, Reifenstein syndrome, and MAIS:
        1. Chromosome analysis: 46,XY karyotype
        2. Testosterone: normal or high male plasma levels and production rates
        3. Estrogen: plasma levels and production rates higher than in normal men
        4. Gonadotropin: elevated plasma LH levels (may be normal in MAIS)
    3. Additional findings of sporadic cases of predominantly male phenotype of PAIS:
        1. Impaired development of the prostate and of the Wolffian duct derivatives demonstrated by ultrasonography or genitourography
        2. Less than normal decline of sex hormone-binding globulin in response to a standard dose of the anabolic androgen, stanozolol
        3. Higher than normal levels of antimüllerian hormone during the first year of life or at the beginning of puberty
3. Histologic investigations:
    1. CAIS:
        1. Testes: apparently normal in early life but begin to lose their germ cell population in late childhood
        2. Development of testicular hamartomas (composed of Sertoli and Leydig cells (Rutgers and Scully 1991), spindle cells, stroma, and germ cells in varying proportion) and benign and malignant tumors beginning in the postpubertal period

3. Germinal cell tumors, usually seminomas, in approximately 8% of CAIS cases
2. IAIS:
   1. Histologic appearance of the gonads similar to that of CAIS
   2. Cryptorchidic testes, usually containing spermatocytes and rare observation of spermatozoa in a minority of patients
3. MAIS with oligospermia or azoospermia in phenotypically normal males with testicular biopsy showing:
   1. Presence of Sertoli cell only
   2. Arrest of spermatogenesis at the spermatid stage

4. Detection of known mutations of the androgen receptor gene clinically available by sequence analysis and (multi)exonic or whole-gene deletion/duplication Gottlieb et al. 2014):
   1. CAIS: detected in 65–95% of patients
   2. PAIS: detected in <50% of patients
   3. MAIS: proportion of patients with detected mutations unknown

Genetic Counseling

1. Recurrence risk: genetic counseling according to X-linked recessive inheritance (Gottlieb et al. 2014):
   1. Patient's sib:
      1. Recurrence risk: low but greater than that of the general population because the possibility of germ-line mosaicism (Boehmer et al. 1997) exists provided the mother is not a carrier
      2. Fifty percent of sibs inheriting the mutation from the carrier mother:
         1. Sibs with a 46,XY karyotype who inherit the mutation will be affected.
         2. Sibs with a 46,XX karyotype who inherit the mutation will be carriers.
      3. Risk for another child with AIS is low if somatic mosaicism is present in the index patient (Holterhus et al. 1997).
   2. Patient's offspring:
      1. 46,XY individuals with AIS (i.e., CAIS, PAIS, MAIS): almost always infertile
      2. Manifesting carrier females: 50% risk of transmitting the AR gene mutation in each pregnancy
   3. Offspring of a known *AR* mutation carrier female:
      1. Twenty-five percent of 46,XY children: affected
      2. Twenty-five percent of 46,XY children: unaffected
      3. Twenty-five percent of 46,XX children: carrier
      4. Twenty-five percent of 46,XX children: not a carrier
      5. A wide range of phenotypes observed for the same mutation in different families making genetic counseling more difficult
2. Carrier detection:
   1. Family pedigree
   2. Clinical features:
      1. Asymmetric distribution and sparse or delayed growth of pubic or axillary hair in manifesting carriers (10% of carriers), resulting from skew X chromosome inactivation.
      2. Normal pubic and axillary hair do not rule out the 46,XX carrier state.
   3. Deficient or defective androgen-binding activity of single-cell clones from a genital skin fibroblast line, provided an affected 46, XY family member is known to have deficient or defective androgen-binding activity in a genital skin fibroblast cell line
   4. Molecular genetic testing (Davies et al. 1995; Hiort et al. 1998):
      1. A complete screening strategy of the entire androgen receptor gene needed to find the mutation in a new case of androgen insensitivity syndrome. Once the mutation is identified in the proband, carrier detection of other family members is possible.
      2. Intragenic polyglutamine and polyglycine trinucleotide repeats in the

N-terminal region of the androgen receptor may be used as polymorphisms to follow the affected X chromosome through the family and used for carrier status determination.

3. Prenatal diagnosis:
    1. Request for prenatal diagnosis uncommon.
    2. Finding of discordance between chromosomal and phenotypic sex by ultrasonographic and cytogenetic analysis (Bianca et al. 2009).
    3. 3D and 4D ultrasonography and surface rendering of external genitalia demonstrate the power in the detection of external and internal genital malformations (Mazza et al. 2013).
    4. Cell-free fetal DNA (cfDNA) testing (Zilberman et al. 2015).
    5. Molecular prenatal diagnosis of partial androgen insensitivity syndrome bases on the Hind III polymorphism of the androgen receptor gene (Hughes and Patterson 1994).
    6. Prenatal diagnosis by mutation analysis: clinically available in families in which the disease-causing allele has been identified in an affected family member.
    7. Fetal sex determination by amniocentesis or CVS:
        1. XX fetus: additional testing not warranted
        2. XY fetus: extract DNA for mutation analysis
    8. Sequencing of the androgen receptor, SRY, and 5α-reductase when the fetal genotype is male and fetal phenotype is female sonographically (Zilberman et al. 2015).
    9. Preimplantation and prenatal genetic diagnosis made using androgen receptor mutational analysis (deletion/insertion mutation) (Yu et al. 2012).
4. Management (Gottlieb et al. 2014):
    1. Psychological support:
        1. Probably the most important aspect of medical care
        2. Psychologist or psychiatrist consultations to help adjust to child's condition, including support on how to inform the child, over time and in an age-appropriate manner
        3. Androgen Insensitivity Syndrome Support Group (http://www.medhelp.org/www/ais)
    2. CAIS:
        1. Gender assignment and sex of rearing: uniformly female (Hughes and Deeb 2006).
        2. Inguinal hernia repair.
        3. Remove testes (gonadectomy) as soon as the diagnosis is made: current recommendation, however, is for removal of gonads after puberty (Oakes et al. 2008).
        4. The rationale for postpubertal gonadectomy: testicular malignancy seldom occurs before puberty unlike that of usual crypt orchid testes.
        5. Estrogen replacement therapy necessary to initiate puberty, maintain feminization, and avoid osteoporosis.
        6. Dilatation of short vaginal length (vaginoplasty) to avoid dyspareunia.
        7. Systemic disclosure of the condition to parents and patients in an empathic setting.
    3. PAIS with predominantly female genitalia:
        1. Management issues similar to CAIS.
        2. Prepubertal gonadectomy helps avoid discomfort of increasing clitoromegaly at the time of puberty.
    4. PAIS with ambiguous genitalia or predominantly male genitalia:
        1. Sex of rearing based on the genital phenotype, genital reconstructive surgery, and hormone therapy.
        2. Sex assignment in infants with ambiguous genitalia requires delicate decision-making by parents and health-care personnel and should be resolved as early as is feasible.
        3. A male sex of rearing demands a therapeutic trial with pharmacologic doses of androgen to predict potential androgen responsiveness at puberty and to facilitate reconstructive surgery.
        4. Reduction mammoplasty for gynecomastia developing in puberty.

5. MAIS:
    1. Reduction mammoplasty often required for gynecomastia
    2. A trial of androgen pharmacotherapy to improve virilization

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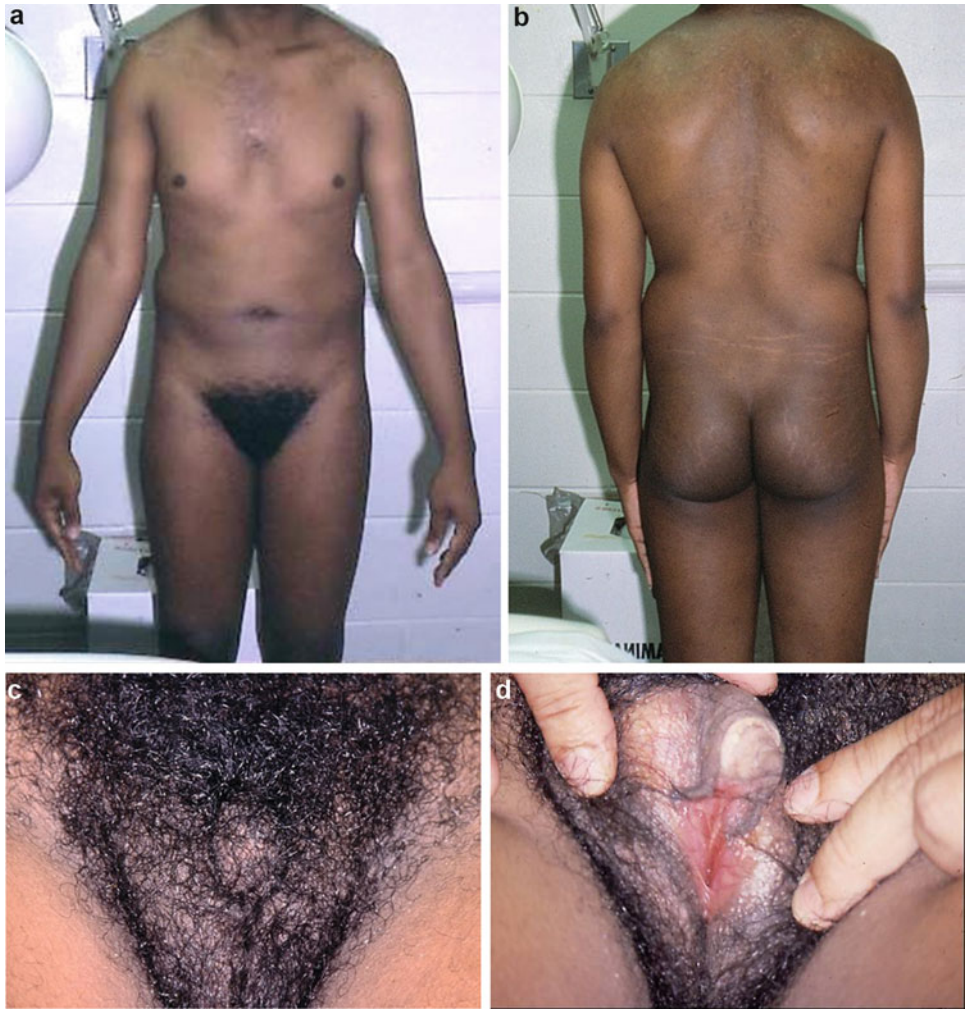

Fig. 1 (**a**–**d**) A 24-year-old 46,XY individual with incomplete androgen insensitivity syndrome showing female habitus, normal axillary and pubic hair, and clitoromegaly

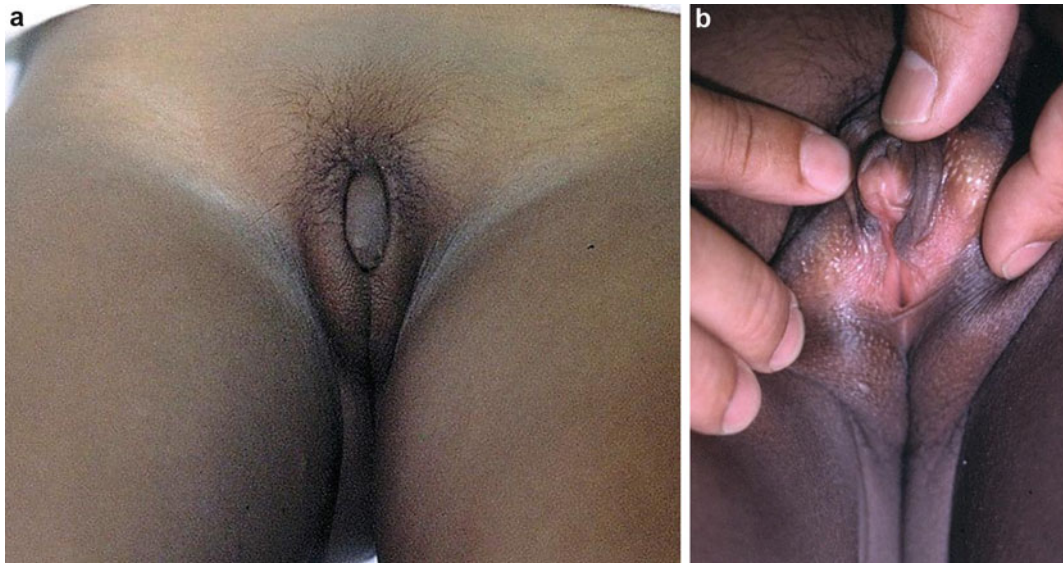

Fig. 2 (**a**, **b**) A 14-year-old sibling (46,XY) with incomplete androgen insensitivity syndrome showing the same phenotype

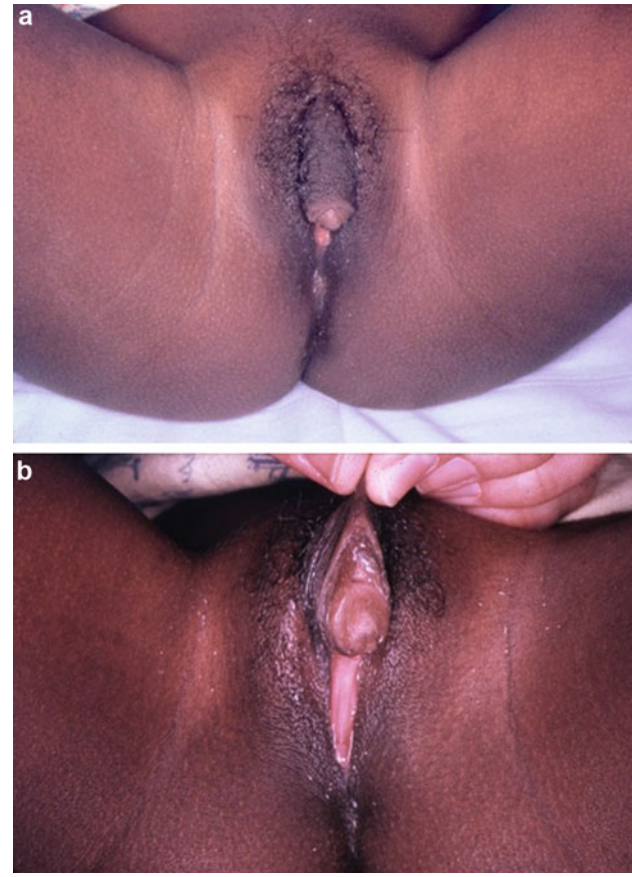

Fig. 3 (**a**, **b**) Appearance of external genitalia of another patient with androgen insensitivity syndrome

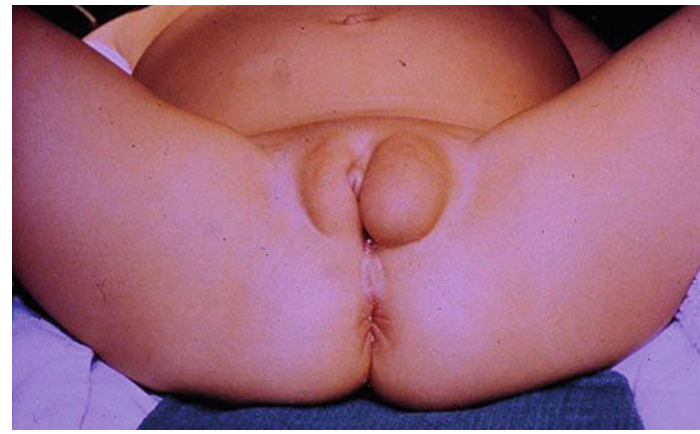

Fig. 4 A neonate with androgen insensitivity syndrome showing a mass in the left labioscrotal fold which proved to be a testis

Angelman Syndrome

Contents

In 1965, Angelman (Angelman 1965) reported three children with a similar pattern of severe learning disability, seizures, ataxic jerky movements, easily provoked laughter, absent speech, and dysmorphic facial features. The syndrome, which bears his name, was originally called the "happy puppet" syndrome. The incidence is estimated to be 1 in 12,000 to 1 in 20,000 (Clayton-Smith and Pembrey 1992; Petersen et al. 1995; Steffenburg et al. 1996).

Synonyms and Related Disorders

Happy puppet syndrome

Genetics/Basic Defects

1. Inheritance (Chan et al. 1993)
    1. Sporadic in most cases
    2. Rare familial transmission (always transmitted through maternal lineage)
2. Caused by deficiency of gene expression from abnormality on the maternally derived chromosome 15 because of genomic imprinting
    1. The relevant region on chromosome 15q
        1. Normally expressed on the maternally derived chromosome
        2. Normally imprinted on the paternally derived chromosome
    2. Inability of the imprinted paternal allele to produce functional protein since the normally expressed maternal copy is often deleted in Angelman syndrome
3. Genetic mechanisms responsible for the disorder (Malzac et al. 1998; Buiting 2010; Bird 2014)
    1. Chromosome deletions and translocations
        1. Deletion (de novo) of the maternally derived chromosome region 15q11-q13 (about 70%): affects several imprinted genes including *UBE3A* (E6AP-3A ubiquitin-protein ligase gene) (Kishino et al. 1997) and *SNRPN* (small nuclear ribonucleoprotein polypeptide N)
        2. Maternal somatic and germline mosaicism for 15q11-q13 deletion: reported as the cause for AS (Sanchez et al. 2014)
        3. Rare families with deletion due to unique chromosome 15 rearrangement within 15q11-q13 (<1%)

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4. Diagnostic tests
    1. Abnormal methylation analysis with presence of paternal band only
    2. Other diagnostic tests: high-resolution cytogenetics or FISH analysis
2. *UBE3A* and other presumed single-gene mutations (20–25%)
    1. Imprinting of the *UBE3A* gene with paternal silencing in human brain (Rougeulle et al. 1997)
    2. Inability to degrade unwanted proteins
    3. Compromise cellular functions secondary to absence of *UBE3A*
    4. Result in abnormal cortical functioning with severe mental retardation
    5. Diagnostic tests for mutations
        1. Normal methylation analysis with presence of both maternal and paternal bands
        2. Other diagnostic tests: screening of *UBE3A* for mutations
3. Paternal uniparental disomy (UPD) (both copies of a chromosome come from the father) of the chromosome 15 (Fridman and Koiffmann 2000) (1–2%)
    1. Paternal UPD is isodisomic in almost all cases.
    2. Most likely origin of paternal UPD: maternal nondisjunction producing a monosomy 15 conception, with postzygotic rescue by duplication of the paternal chromosome 15 (Mutirangura et al. 1993).
    3. Chromosomal nondisjunction events in Angelman syndrome: mainly due to mitotic errors, but paternal meiosis II nondisjunction (Gyftodimou et al. 1999) can occur and give origin to an AS UPD15 individual by two different mechanisms (rescue of a trisomic fetus or fertilization of a nullisomic egg with the disomic sperm) (Fridman and Koiffmann 2000).
    4. Affected individuals having two alleles of all genes (both derived from the father) but remain silenced with no production of functional protein.
    5. Milder phenotypic manifestations (lower incidence of seizures).
    6. Diagnostic tests
        1. Abnormal methylation analysis with presence of paternal band only
        2. Other diagnostic tests: RFLP analysis
4. Imprinting defects (2–4%)
    1. A mutation within the "imprinting center," located within 15q11-q13 on chromosome 15, renders the imprinting center unable to function properly (2%). Normally, imprinting center regulates which segments of DNA are imprinted.
        1. Abnormal methylation analysis with presence of paternal band only
        2. Positive screening for imprinting center for mutation
    2. Imprinting defect without imprinting center mutation (2%).
        1. Abnormal methylation analysis with presence of paternal band only
        2. Negative screening for imprinting center for mutation
    3. Mosaic imprinting defect (frequency unknown).
        1. Abnormal methylation analysis with presence of faint maternal band
        2. Usually negative screening for imprinting center for mutation
    4. Microdeletions reported in the imprinting center.
5. No genetic abnormality identified: Patients with clinical features of Angelman syndrome but no demonstrable cytogenetic or molecular abnormality of chromosome 15q11-q13

Clinical Features

1. Consistent cardinal features (100%) (Williams et al. 1995a, b, 2006; Cassidy 2000; Clayton-Smith and Laan 2003; Bird 2014)
    1. Normal newborn phenotype
        1. Normal prenatal and birth history
        2. Normal head circumference
        3. Absence of major birth defects

2. Developmental delay
    1. Starting around 6 months of age
    2. Eventually classified as severe developmental delay and/or severe intellectual disability
3. Profound speech impairment
    1. Absent or minimal use of words
    2. Receptive and nonverbal communication skills better than verbal capability
4. Jerky movement (Van Lierde et al. 1990) or balance disorder
    1. Abnormal ataxic gait
    2. Puppet-like jerky movements of limbs
    3. Hand-flapping movement
5. Typical behavioral pattern
    1. An easily excitable personality, often with hand-flapping movements
    2. Short attention span
    3. A happy, sociable disposition
    4. Inappropriately happy affect
    5. Bouts of inappropriate laughter
    6. Hypermotoric behavior

2. Frequent features (>80%)
    1. Delayed, disproportionate growth in head circumference, usually resulting in microcephaly by age 2
    2. Seizures (80%)
        1. Onset usually before 3 years of age (1–5 years)
        2. Variety of seizures (tonic-clonic, atypical absences, complex partial, myoclonic, atonic, tonic seizures to status epilepticus)
    3. Characteristic EEG with large-amplitude slow spike waves and triphasic waves
3. Associated features (20–80%)
    1. Hypotonia at birth
    2. Characteristic craniofacial appearance
        1. Microcephaly
        2. Flat occiput
        3. Occipital groove
        4. Strabismus
        5. Tongue thrusting
        6. Prognathia
        7. Wide mouth
        8. Widely spaced teeth
        9. Frequent drooling
        10. Excessive chewing/mouthing behaviors
    3. Gastrointestinal difficulties
        1. Swallowing disorder
        2. Feeding problems during infancy
        3. Gastroesophageal reflux
        4. Constipation
    4. Hypopigmented skin
    5. Light hair and eye color, compared to other family members, seen only in deletion cases
    6. Refractive and alignment errors
    7. Hyperactive lower limb deep tendon reflexes
    8. Uplifted, flexed arm position especially during ambulation
    9. Increased sensitivity to heat
    10. Sleep disturbance
    11. Fascination with water or crinkly items
    12. Mouthing behavior
    13. Ankle pronation
4. Adolescent and adult phenotype (Smith 2001)
    1. More striking facial features
        1. Marked mandibular prognathism
        2. Pointed chin
        3. Macrostomia
        4. Prominent lower lip
        5. Deeply set eyes
        6. Keratoconus secondary to eye rubbing
    2. Scoliosis and joint contractures increasing with age
    3. Improved hyperactivity and concentration
    4. Persistent sociable disposition
    5. A good quality of life maintained despite the above problems
    6. Life span not greatly reduced
5. Phenotype-genotype correlations (Lossie et al. 2001; Bird 2014)
    1. Patients with chromosome 15 deletions: in general, the most severely affected
        1. Higher incidence of seizures, microcephaly, and hypopigmentation. Severe epilepsy seen in these patients is considered to be the result of the absence of one copy of the *GABA* receptor genes.
        2. Greater delay in motor milestones.
        3. Absent speech.
        4. Shorter and lighter than the general population.

5. Severe clinical features thought to be the result of haploinsufficiency for a number of genes within the 15q11-q13 region.
2. Phenotype in the non-deletion cases: milder than in the deletion cases
3. Phenotype in the paternal UPD: milder than that of the deletion cases
    1. A low incidence of seizures, microcephaly, and hypopigmentation
    2. Able to say a few words in many patients
    3. Better growth parameters
    4. Less obvious dysmorphic features
    5. Typical behavioral pattern
4. Imprinting defects
    1. Less likely to have microcephaly, hypopigmentation, or seizures
    2. More able than the deletion group with less delay in motor milestones and better communication skills
    3. Growth better than the deletion patients
    4. Obesity relatively common within this group
5. Milder phenotype associated with incomplete imprinting defect or cellular mosaicism (displayed as Angelman syndrome methylation pattern) (Fairbrother et al. 2015)
6. Point mutations in the *UBE3A*
    1. Phenotype between the deletion group and the UPD group
    2. Frequently with mild or absence of ataxia, epilepsy, and microcephaly
    3. Not hypopigmented
    4. Better motor and communication skills than the deletion group

6. Differential diagnosis (Williams et al. 2001, 2010a; Dagli et al. 2015)
    1. Nonspecific psychomotor delay and/or seizures including cerebral palsy, static encephalopathy, and mitochondrial encephalomyopathy: tremulousness and jerky limb movements seen in most infants with Angelman syndrome are not seen in these conditions.
    2. Mowat-Wilson syndrome (Please see the chapter of Mowat-Wilson syndrome)
        1. Findings suggesting Angelman syndrome
            1. Happy affect
            2. Prominent mandible
            3. Diminished speech
            4. Microcephaly
            5. Constipation
        2. Typically results from heterozygous mutations in *ZEB2*
    3. Christianson syndrome (Christianson et al. 1999; Gilfillan et al. 2008)
        1. An X-linked disorder
        2. Caused by mutations in the *SLC9A6* gene
        3. Clinical features
            1. Apparently happy disposition.
            2. Severe cognitive delays.
            3. Ataxia.
            4. Microcephaly.
            5. Seizure disorder.
            6. A rapid (10–14 Hz) background frequency EEG, compared to a generalized high-amplitude, slow spike-wave (1.5–3 Hz) pattern seen in patients with *SLC9A6* mutations.
            7. Cerebellar and brain stem atrophy in some cases.
            8. Individuals with *SLC9A6* disorder may have thinner body appearance and may lose ambulation beyond 10 years of age.
    4. Adenylosuccinate lyase deficiency (Spiegel et al. 2006; Gitiaux et al. 2009)
        1. Results in accumulation of succinylpurines leading to:
            1. Psychomotor retardation
            2. Autistic features
            3. Hypotonia
            4. Seizures
        2. The following behavior profile may mimic Angelman syndrome:
            1. Motor apraxia
            2. Severe speech deficits
            3. Excessive laughter
            4. A very happy disposition
            5. Hyperactivity
            6. A short attention span
            7. Mouthing of objects
            8. Tantrums
            9. Stereotyped movements

5. Pitt-Hopkins syndrome
    1. Characteristic features
        1. Mental retardation.
        2. Distinctive facial features including wide mouth.
        3. Intermittent hyperventilation followed by apnea (Zweier et al. 2007). Diurnal hyperventilation is a salient feature in some and occurs after 3 years of age (Peippo et al. 2006).
    2. Mutation and deletion screening for the *TCF4* gene: available
6. Rett syndrome (Please see the chapter.)
    1. Seizures and severe speech impairment of Rett syndrome: resemble infant girls with Angelman syndrome, but children with Angelman syndrome do not have a regressive course and do not lose purposeful use of their hands, as do girls with Rett syndrome.
    2. Testing for mutations of *MECP2*: clinically available.
7. Prader-Willi syndrome (Please see the chapter): Prader-Willi and Angelman syndromes shared a common chromosome 15 deletion but differ in parental origin of the deletion (Knoll et al. 1989). Infants with Angelman syndrome who present with feeding difficulties and muscle hypotonia may be misdiagnosed as having Prader-Willi syndrome because the 15q11.2-q13 deletion, detected by comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH), was not proven by DNA methylation analysis to be of maternal origin.
8. Other microdeletion syndromes
    1. Microdeletion of 22q13.3 deletion (Phelan-McDermid) syndrome (Precht et al. 1998)
        1. Nondysmorphic facial features
        2. Absent or minimal speech
        3. Moderate to severe developmental delay
        4. Behavioral features in the autism spectrum
    2. Microdeletions of the 2q23.1 region (van Bon et al. 2010; Williams et al. 2010b)
        1. Severe speech delay.
        2. Seizures.
        3. Behavioral disorders.
        4. Microcephaly. Some individuals present with an AS-like phenotype.
    3. Other new microdeletion disorders, detected by CGH, may be associated with some features of Angelman syndrome (Brunetti-Pierri et al. 2008; Sharkey et al. 2009).

Diagnostic Investigations

1. Normal metabolic, hematologic, and chemical laboratory profiles
2. Normal brain imagings (MRI, CT) with occasional mild cortical atrophy and dysmyelination
3. Abnormal EEG
    1. High-amplitude slow spike-wave activities (most common)
    2. Hypsarrhythmia (infantile spasm)
4. Cytogenetic studies
    1. To detect visible chromosome rearrangement (<1%)
        1. Translocation
        2. Inversion
    2. High-resolution chromosome studies to demonstrate large del(15)(q11-q13)
    3. Fluorescence in situ hybridization (FISH) to identify 15q11-q13 microdeletions, using D15S10 and/or *SNRPN* probes: detects about 70% of patients
5. DNA methylation studies: to demonstrate characteristic DNA methylation pattern (i.e., paternal imprint only) of 15q11-q13 cloned DNA sequences using methylation-sensitive restriction endonucleases
    1. Diagnose about 80% of classic Angelman syndrome including patients with a deletion, uniparental disomy, or an imprinting defect (Glenn et al. 2000).
    2. Certain maternally inherited genes are extensively methylated and thus inactivated while the paternal alleles are unmethylated and active in normal individuals.
    3. Unmethylated *SNRPN* alleles in patients with Angelman syndrome, caused by:

1. Uniparental disomy
2. Imprinting center defects
3. Typical 15q11-q13 deletion

4. Inability to distinguish the molecular classes (15q11-q13 deletion, uniparental disomy, or imprinting center defect).

6. *UBE3A* mutation analysis
   1. Detect mutations in the E6-AP ubiquitin-protein ligase gene.
   2. Detect additional 11% of patients.
   3. Invaluable in clinically typical Angelman syndrome patients with a normal methylation analysis (Fang et al. 1999).
   4. Intragenic *UBE3A* mutations include (Malzac et al. 1998; Fang et al. 1999):
      1. Insertion
      2. Deletion
      3. Nonsense mutation
      4. Missense mutation
      5. Splice mutation
7. DNA polymorphisms to demonstrate absence of maternal alleles at 15q11-q13 loci, which may result either from maternal deletion or from paternal uniparental disomy
   1. Determined by analysis of simple sequence repeats (microsatellites) in the parents and affected individual.
   2. Determine parental origin of 15q11-q13 and the rest of chromosome 15.
   3. Detect patients with deletions and uniparental disomy but not the *UBE3A* mutation class of patients.
   4. Detect biparental inheritance of 15q11-q13 with abnormal DNA methylation in patients with imprinting center defects.
8. Simple algorithm for genetic testing in patients with clinical suspicion of Angelman syndrome (Clayton-Smith and Laan 2003; Williams et al. 2010a)
   1. Abnormal methylation analysis
      1. FISH analysis or array CGH if methylation analysis is abnormal
         1. Presence of del(15)(q11.3-q13) (5–7 Mb deletion)
         2. Absence of del(15)(q11-q13)
      2. RFLP analysis if FISH analysis is negative
         1. Presence of UPD
         2. Absence of UPD
      3. Angelman syndrome imprinting center deletion analysis (2–200 kb deletions) if UPD is absent
   2. Normal methylation analysis
      1. Screen *UBE3A* mutation (sequence analysis for sequence variants and gene or intragenic deletion study for partial or whole-gene deletions) in clinically typical patients
         1. If positive, check parents.
         2. If negative, keep on reviewing patient's findings; for patients with an AS phenotype, consider an alternative diagnosis such as Pitt-Hopkins syndrome, Mowat-Wilson syndrome, Kleefstra syndrome, Phelan-McDermid syndrome, Koolen-de Vries syndrome, Christianson syndrome, and MBD5 haploinsufficiency (Williams et al. 2001; Tan et al. 2014).
      2. No further testing required for clinical normal patients (not Angelman syndrome)
9. Currently, about 10% of patients with classic phenotypic features of Angelman syndrome are not amenable to diagnostic testing due to presently unidentified genetic mechanisms.
10. Consensus criteria for the diagnosis of Angelman syndrome by laboratory findings and genetic test abnormalities (Williams et al. 2006)
    1. Normal metabolic, hematologic, and chemical laboratory profiles.
    2. Structurally normal brain using MRI or CT (may have mild cortical atrophy or dysmyelination).
    3. Characteristic Angelman syndrome pattern of DNA methylation of the *SNURF-SNRPN* exon 1/promoter. Detects cases due to 15q11.2-q13 deletion, UPD, and imprinting defects (may have mosaic methylation pattern in non-deletion imprinting defects).
    4. Abnormal FISH indicates a deletion of 15q11.2-q13 DNA sequences within the common Angelman syndrome deletion overlap region.

1. Use of a pericentromeric FISH probe enhances the ability to detect subtle translocation.
2. Array CGH can be used to detect the deletion but confirmation by FISH is currently required.
3. Class I and II deletions can be distinguished by array CGH or FISH using appropriate clones.

5. DNA polymorphism analysis within 15q11.2-q13 showing paternal UPD.
6. Deletion in the imprinting center, demonstrated by real-time PCR, single-copy FISH, or other analysis methods of the Angelman syndrome imprinting center smallest region of overlap (SRO).
7. Pathogenic DNA sequence change in the *UBE3A* gene.

11. Diagnostic approach (van Buggenhout and Fryns 2009; Williams et al. 2010a)
    1. Cytogenetic study: large deletion/translocation/duplication: Rare (<1%)
    2. DNA methylation test
        1. Abnormal
            1. FISH and CGH: to demonstrate 5–7 Mb deletion of 15q11.2-q13 (about 68% of the patients)
            2. UPD study to demonstrate paternal UPD (about 7% of the patients)
            3. Imprinting center deletion study to demonstrate: imprinting center defect (about 3% of the patients)
        2. Normal
            1. Sequence analysis of the *UBE3A* gene detects mutations in about 11% of the patients.
            2. Gene or intragenic deletion study of *UBE3A* gene detects partial or whole-gene deletions (rare).

Genetic Counseling

1. Recurrence risks: depending on the genetic mechanism involved and on whether the mother is shown to carry genetic abnormalities of 15q11-q13 (Khan and Wood 1999; Laan 1999; Buiting 2010; Williams et al. 2010a; Dagli et al. 2015)
    1. Reasons of difficulty in providing recurrence risk estimation:
        1. Causal heterogeneity of Angelman syndrome
        2. Maternal germ cell mosaicism (Stalker et al. 1998)
    2. Patient's sib (Ramsden et al. 2010)
        1. Most cases (70–75%) of Angelman syndrome (resulting from de novo deletion of 15q11-q13 on the maternal chromosome) have a recurrence risk of <1% (Stalker and Williams 1998).
        2. For proband with a large deletion: <1% risk to sibs. However, germline mosaicism for these large deletions has been reported (Kokkonen and Leisti 2000).
        3. For proband with an inherited small interstitial deletion or an unbalanced chromosome translocation: The risk to sibs depends on whether the rearrangement is inherited or de novo (Horsthemke et al. 1996; Stalker and Williams 1998), possibly as high as 50%.
        4. For proband with paternal UPD of chromosome 15 (3–7% of cases) (in families in which Angelman syndrome is the result of paternal UPD and in which no Robertsonian chromosomal translocation is identified): The risk to sibs of having Angelman syndrome is <1% (the risk figure is based on the lack of recurrence among all known cases of UPD in Angelman syndrome with normal chromosomes).
        5. For proband with paternal UPD and with predisposing parental translocation: approaching 100% if father has a 15;15 Robertsonian translocation.
        6. For proband with imprinting defect:
            1. With an imprinting center deletion excluded (2–3% of cases): <1%
            2. With inherited imprinting center deletion (about 10–15% of patients with an imprinting defect): up to 50% (if present in the mother)

7. For proband with *UBE3A* mutation (about 10% of cases):
    1. De novo mutation: <1%
    2. With inherited mutation from mother: 50%
8. For families with familial structural chromosomal rearrangements, recurrence risk varies, depending upon the chromosomes that are involved (Yesodharan et al. 2014):
    1. Reported rare occurrence of two siblings with AS.
    2. Their karyotypes revealed monosomy of chromosome 15 and a derivative chromosome 1 leading to AS.
    3. Their mother was a balanced translocation carrier involving chromosomes 1p and 15p.
9. For proband without identifiable molecular abnormality (about 10% of cases): undetermined risk (up to 50%)

3. Patient's offspring: To date, only one individual with Angelman syndrome reported to have reproduced (Lossie and Driscoll 1999)
    1. Females with Angelman syndrome are fully capable of reproduction: The mother and fetus inherited large deletions of maternal 15q11-13.
    2. Demonstrated paternal-only DNA methylation imprints along 15q11-13.
    3. *UBE3A* was paternally expressed (not imprinted) in eye tissue from the fetus with Angelman syndrome.

2. Prenatal diagnosis
    1. Possible when the underlying genetic mechanism is as follows:
        1. A deletion
        2. Uniparental disomy
        3. An imprinting defect
        4. A *UBE3A* mutation
        5. A chromosome rearrangement
    2. Combined use of methylation analysis, chromosomal/FISH analysis, and DNA marker studies through analysis of fetal cells obtained by CVS or amniocentesis: to identify the common ~4-Mb deletion, paternal UPD, or imprinting mutation in about 70–80% of cases with Angelman syndrome.
    3. Mutation analysis for *UBE3A* (Tsai et al. 1998).
    4. Readily accomplished if a disease-causing mutation is identified and is present in the mother.
    5. Dilemmas associated with the molecular characterization of a fetus (Gilbert et al. 1997): DNA prepared from a 21-week fetal blood sample detected a fetus with normal maternal and paternal DNA methylation patterns but inherited the same maternal chromosome 15q11-q13 as the affected sibs. This is probably a result of germline mosaicism in the mother.
    6. Preimplantation genetic diagnosis:
        1. Available for families in which the underlying mechanism has been identified in the proband to be UBE3A mutations or imprinting center deletions.
        2. The relative hypomethylation of the early embryo makes PGD problematic for DNA methylation testing.

3. Management (Williams 2001)
    1. Routine management
        1. Feeding difficulties
        2. Constipation
        3. Gastroesophageal reflux
        4. Strabismus
    2. Seizure control difficult with antiepileptic drugs, especially in childhood
        1. Sodium valproate as monotherapy or in combination with clonazepam or other benzodiazepines
        2. Experience with the newer antiepileptic drugs: very limited
        3. Vagal stimulation needed for seizures refractory to pharmacological intervention (Thibert et al. 2009)
    3. Physical therapy for unstable or nonambulatory children
    4. Occupational therapy for improving fine motor and oral-motor control
    5. Speech and communication therapy

    1. Augmentative communication aids, such as picture cards or communication boards
    2. Sign language
6. Consistent behavioral modifications
7. Orthopedic management
    1. Subluxed or pronated ankles
    2. Tight Achilles tendons
    3. Scoliosis
8. Primary areas of clinical management in adults (Larson et al. 2015)
    1. Seizures
    2. Sleep
    3. Aspiration risk
    4. Gastroesophageal reflux disease
    5. Constipation
    6. Dental care
    7. Vision
    8. Obesity
    9. Scoliosis
    10. Bone density
    11. Mobility
    12. Communication
    13. Behavior
    14. Anxiety

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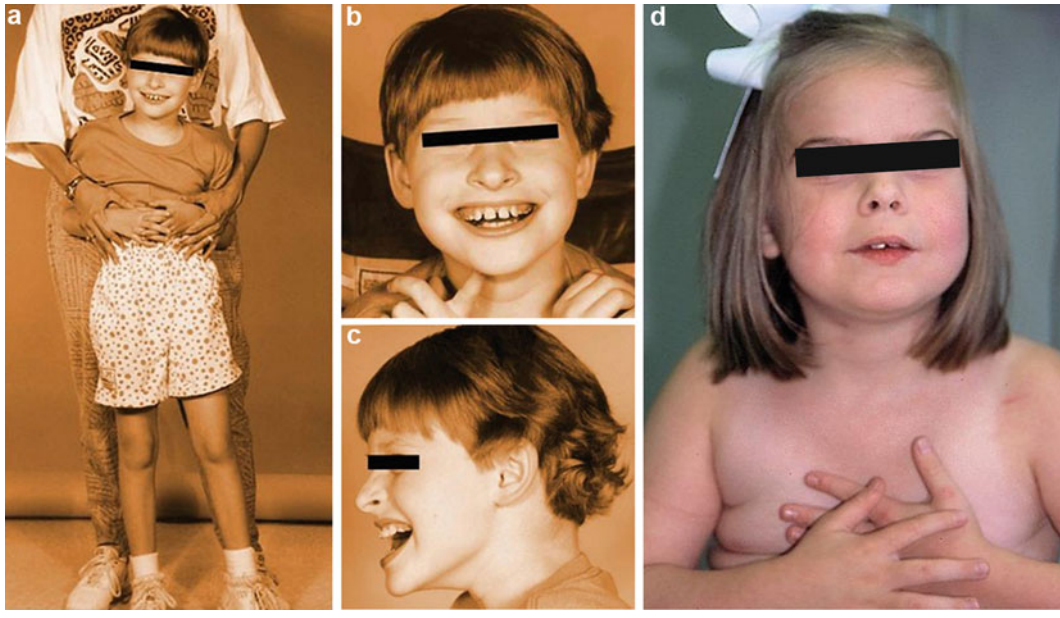

Fig. 1 (**a**–**d**) Two children with Angelman syndrome showing happy disposition, an open mouth expression, widely spaced teeth, and a pronounced mandible. The diagnoses were confirmed cytogenetically [del(15)(q11-13)]

Apert Syndrome

Contents

Apert syndrome is named after the French physician who described the syndrome acrocephalosyndactylia in 1906. Apert syndrome is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet. It probably is the most familiar and best-described type of acrocephalosyndactyly. Prevalence is estimated at 1 in 65,000 (approximately 15.5 in 1,000,000) live births (Cohen et al. 1992; Cohen and Kreiborg 1992, 1993a). Apert syndrome accounts for 4.5% of all cases of craniosynostosis.

Synonyms and Related Disorders

Acrocephalosyndactyly types 1 and 2; Apert-Crouzon disease; Vogt cephalodactyly

Genetics/Basic Defects

1. Inheritance
   1. Autosomal dominant.
   2. Sporadic in majority (>98%) of cases, resulting from new mutations with a paternal age effect (Moloney et al. 1996).
   3. Rarity of familial cases can be explained by reduced genetic fitness of individuals because of severe malformations and the presence of mental retardation in many cases.
   4. Two sisters born to normal unrelated parents: the 1st known example of germinal mosaicism in Apert syndrome (Allanson 1986).
2. Cause
   1. Caused by specific missense substitution mutations, involving adjacent amino acids (i.e., Ser252Trp or Pro253Arg) in the linker between the second and third extracellular immunoglobulins domains of *FGFR2*, which maps to chromosome bands 10q25-q26 (more than 98% of cases with Apert syndrome).
   2. Remaining cases are caused by Alu-element insertion mutations in or near exon 9 of *FGFR2* (Oldridge et al. 1999).
3. Pathogenesis (Kreiborg and Cohen 1990; Chen 2014)
   1. Unique fibroblast growth factor receptor 2 (*FGFR2*) mutations (Lomri et al. 1998)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Leading to an increase in the number of precursor cells that enter the osteogenic pathway
2. Ultimately leading to increased subperiosteal bone matrix formation and premature calvaria ossification during fetal development

2. Fusion of the cranial sutures
   1. The order and rate of suture fusion determine the degree of deformity and disability.
   2. Once a suture becomes fused, growth perpendicular to that suture becomes restricted, and the fused bones act as a single bony structure.
   3. Compensatory growth occurs at the remaining open sutures to allow continued brain growth.
   4. Complex, multiple sutural synostosis frequently extends to premature fusion of the sutures at the base of the skull, causing midfacial hypoplasia, shallow orbits, a foreshortened nasal dorsum, maxillary hypoplasia, and occasional upper airway obstruction.
3. Syndactyly of Apert syndrome
   1. A keratinocyte growth factor receptor (KGFR)-mediated effect, provided by the observation of the correlation between KGFR expression in fibroblasts and severity of syndactyly.
   2. Different phenotypic expressions in patients with Ser252Trp and those with Pro253Arg. The syndactyly is more severe with Pro253Arg mutation (Lajeunie et al. 1999) for both hands and feet, whereas cleft palate is significantly more common with Ser252Try mutation (Slaney et al. 1996).
4. During early infancy (younger than 3 months of age)
   1. Premature closure of the coronal suture area, evident by a bony condensation line beginning at the cranial base and extending upward with a characteristic posterior convexity.
   2. Widely patent anterior and posterior fontanelles.
   3. Presence of a gaping defect of the midline of the calvaria, extending from the glabellar area to the posterior fontanelle via the metopic suture area, anterior fontanelle, and sagittal suture area. The skull with gaping midline defect appears to permit adequate accommodation of the growing brain.
   4. Normal lambdoidal sutures in all cases.
5. During the first 2–4 years of life
   1. Obliteration of the midline defect by coalescence of the enlarging bony islands without evidence of any proper formation of sutures.
   2. Very early onset in fetal life of growth inhibition in the sphenofrontal and coronal suture area, suggested by an extremely short squama and orbital part of the frontal bone together with the posterior convexity of the coronal bone condensation line.

Clinical Features

1. History (Chen 2014)
   1. Headache and vomiting: signs of acute increase of intracranial pressure, especially in cases of multiple suture involvement.
   2. Stridor and sleep apnea indicate upper airway problems, due to craniosynostosis of the base of the skull.
   3. Visual disturbance due to exposure keratitis and conjunctivitis.
   4. Mental retardation in many patients, though patients with normal intelligence have been reported (Patton et al. 1988; Renier et al. 1996).
2. Skull
   1. Craniosynostosis
   2. Coronal sutures most commonly involved, resulting in acrocephaly, brachycephaly, turribrachycephaly, flat occiput, and high prominent forehead
   3. Large late-closing fontanels
   4. Gaping midline defect

5. Rare cloverleaf skull anomaly in approximately 4% of infants

3. Facial features (Cohen and Kreiborg 1996)
   1. Horizontal grooves above the supraorbital ridges that disappear with age
   2. A break in the continuity of the eyebrows
   3. A trapezoid-shaped mouth at rest
   4. Flattened, often asymmetric face
   5. Maxillary hypoplasia with retruded midface
   6. Eyes (Buncic 1991)
      1. Down-slanting palpebral fissures
      2. Hypertelorism
      3. Shallow orbits
      4. Proptosis
      5. Exophthalmos
      6. Lateral ptosis
      7. Widened palpebral fissures
      8. Tearing secondary to exposure keratitis
      9. Prolonged corneal exposure resulting in corneal scars and opacification
      10. Partially open eye during sleep
      11. Strabismus
      12. Amblyopia
      13. Optic atrophy
      14. Keratoconus
      15. Ectopic lentis
      16. Congenital glaucoma
      17. Lack of pigment in the fundi with occasional papilledema
      18. Rare luxation of the eye globes as an extreme complication of severe exorbitism, producing possible strangulation of the circulation of the globe and blindness
   7. Mouth: characteristic trapezoidal shape (Kreiborg and Cohen 1992)
      1. A prominent mandible
      2. Down-turned corners
      3. High arched palate
      4. Bifid uvula
      5. Cleft palate
      6. Crowded upper teeth
      7. Malocclusion
      8. Delayed dentition
      9. Ectopic eruption
      10. Shovel-shaped incisors
      11. Supernumerary teeth
      12. V-shaped maxillary dental arch
      13. Bulging alveolar ridges
   8. Ears (Gould and Caldarelli 1982)
      1. Apparent low-set ears
      2. Occasional conductive hearing loss
      3. Congenital fixation of stapedial footplate
4. Extremities and digits
   1. The upper limbs affected more severely than lower limbs.
   2. Coalition of distal phalanges and synonychia of the hands (never present in the feet).
   3. The glenohumeral joint and proximal humerus affected more severely than the pelvic girdle and femur.
   4. The elbow involved much less severely than the proximal portion of the upper limb.
   5. Syndactyly of the hands and feet with partial-to-complete fusion of the digits, often involving second, third, and fourth digits. These often are termed mitten hands and socked feet. In severe cases, all digits are fused, with the palm deeply concave or cup shaped and the sole supinated.
   6. Hitchhiker posture or radial deviation of short or broad thumbs resulting from abnormal proximal phalanx.
   7. Brachydactyly.
   8. Contiguous nail beds (synonychia).
   9. Subacromial dimples and elbow dimples during infancy.
   10. Limited mobility at the glenohumeral joint with progressive limitation in abduction, forward flexion, and external rotation.
   11. Limited elbow mobility common with decreased elbow extension, flexion, pronation, and supination.
   12. Short humeri, a constant finding beyond infancy.
   13. Limited genu valga present in many cases.
5. Other skeletal and cartilaginous segmentation defects
   1. Congenital cervical spinal fusion (68%), especially C5–C6 (Kreiborg et al. 1992)

2. Aplasia or ankylosis of shoulder, elbow, and hip joints
3. Tracheal cartilage anomalies
4. Rhizomelia (Cohen and Kreiborg 1993c)

6. CNS
   1. Intelligence varying from normal to mental deficiency, though a significant number of patients are mentally retarded. Malformations of the CNS may be responsible for most cases.
   2. Common CNS malformations (Cohen and Kreiborg 1990).
      1. Megalencephaly.
      2. Agenesis of the corpus callosum.
      3. Malformed limbic structures.
      4. Variable ventriculomegaly. Progressive hydrocephalus is uncommon.
      5. Encephalocele.
      6. Gyral abnormalities.
      7. Hypoplastic cerebral white matter.
      8. Pyramidal tract abnormalities.
      9. Heterotopic gray matter.
      10. Papilledema and optic atrophy with loss of vision in cases with insidious intracranial pressure increase.
7. Cardiovascular (10%) (Cohen and Kreiborg 1993b)
   1. Atrial septal defect
   2. Patent ductus arteriosus
   3. Ventricular septal defect
   4. Pulmonary stenosis
   5. Overriding aorta
   6. Coarctation of aorta
   7. Dextrocardia
   8. Tetralogy of Fallot
   9. Endocardial fibroelastosis
8. Genitourinary (9.6%) (Cohen and Kreiborg 1993b)
   1. Polycystic kidneys
   2. Duplication of renal pelvis
   3. Hydronephrosis
   4. Stenosis of bladder neck
   5. Bicornuate uterus
   6. Vaginal atresia
   7. Protuberant labia majora
   8. Clitoromegaly
   9. Cryptorchidism
9. Gastrointestinal (1.5%) (Cohen and Kreiborg 1993b)
   1. Pyloric stenosis
   2. Esophageal atresia and tracheoesophageal fistula
   3. Ectopic or imperforate anus
   4. Partial biliary atresia with agenesis of gallbladder
10. Respiratory (1.5%) (Cohen and Kreiborg 1993b)
    1. Anomalous tracheal cartilage
    2. Tracheoesophageal fistula
    3. Pulmonary aplasia
    4. Absence of right middle lobe of the lung
    5. Absence of interlobular lung fissures
11. Skin (Cohen and Kreiborg 1995b)
    1. Hyperhidrosis (common)
    2. Acneiform lesions frequent after adolescence
    3. Interruption of the eyebrows
    4. Hypopigmentation
    5. Hyperkeratosis in the plantar surface
    6. Paronychial infections more commonly affected in feet than hands and observed more commonly in institutionalized patients
    7. Excessive skin wrinkling of forehead
    8. Skin dimples at knuckles, shoulders, and elbows
12. At risk for complications resulting from elevated intracranial pressure despite surgical attempts to increase cranial capacity in infancy
13. Early death
    1. Upper airway compromise
       1. Reduction in nasophrynx size
       2. Choanal patency
       3. Obstructive sleep apnea
       4. Cor pulmonale
    2. Lower airway compromise due to anomalies of the tracheal cartilage
14. Differential diagnosis (Cohen 1977, 1988; Chen 2014; Jabs 1998)
    1. Beare-Stevenson syndrome
       1. Mental retardation
       2. Associated cutaneous disorders
          1. Cutis gyrata
          2. Acanthosis nigricans (hands and feet)
       3. Caused by *FGFR2* mutations

2. Carpenter syndrome (see the chapter)
    1. An autosomal recessive disorder
    2. A peculiar face
    3. Preaxial polydactyly of hands, feet, or both
    4. Absence of osseous fusion of hand bones
3. *FGFR3*-associated coronal synostosis syndrome
    1. Variable clinical presentation overlapping with Pfeiffer, Jackson-Weiss, or Saethre-Chotzen syndrome phenotypes.
    2. Some individuals with a disease-causing mutation may have no clinical problems.
4. Jackson-Weiss syndrome
    1. Caused by *FGFR2* mutations
    2. Enlarged or broad great toes with varus deviation
    3. Tarsal or metatarsal fusion
    4. Lack of thumb abnormalities
    5. Midface hypoplasia
5. Pfeiffer syndrome
    1. Identifiable mutations in *FGFR1* and *FGFR2* (∼67% of patients)
    2. Hand and foot abnormalities
        1. Broad thumbs and halluces
        2. Occasional cutaneous syndactyly
    3. Lack of osseous fusion of the phalanges
    4. Craniofacial features
        1. Turribrachycephaly
        2. Occasional cloverleaf skull
        3. Ocular hypertelorism
        4. Shallow orbits
        5. Sown-slanting palpebral fissures
        6. Proptosis
        7. Strabismus
        8. Low nasal bridge
        9. Small nose
        10. Maxillary hypoplasia
        11. Mandibular prognathism
6. Saethre-Chotzen syndrome (see the chapter)
    1. Characteristic facies
    2. Relatively mild cranial deformity
    3. Lack of osseous fusion of the hand bones
    4. Identifiable mutations in the *TWIST* gene (∼75% of patients).

Diagnostic Investigations

1. Psychometric evaluation
2. Hearing assessment
3. Imaging studies
    1. Skull radiography to evaluate craniostenosis, which usually involves coronal sutures and maxillary hypoplasia
        1. Sclerosis of suture line
        2. Bony bridging and beaking along the suture line
        3. An indistinct suture line
        4. Turribrachycephaly
        5. Shallow orbits
        6. Hypoplastic maxillae
    2. Spine radiography (Thompson et al. 1996)
        1. Spinal fusions, most commonly at the levels of C3–4 and C5–6, appearing to be progressive and occurring at the site of subtle congenital anomalies
        2. Small-sized vertebral body and reduced intervertebral disk space: indicators of subsequent bony fusion
    3. Limb radiography (Cohen and Kreiborg 1995a)
        1. Multiple epiphyseal dysplasia (Cohen and Kreiborg 1993d).
        2. Short humeri.
        3. Glenoid dysplasia.
        4. Cutaneous and osseous syndactyly.
        5. Complete syndactyly involving the second and fifth digits (mitten hands).
        6. Multiple progressive synostosis involves distal phalanges, proximal fourth and fifth metacarpals, capitate, and hamate.
        7. Progressive symphalangism of interphalangeal joints.
        8. Shortened and radial deviation of distal phalanx.
        9. Delta-shaped deformity of proximal phalanx of the thumbs.
        10. Complete syndactyly involving the second and fifth toes (socked feet).

11. Fusion of tarsal bones, metatarsophalangeal and interphalangeal joints, and adjacent metatarsals.
12. Delta-shaped proximal phalanx of the first toes.
13. Occasional partial or complete duplication of the proximal phalanx of the great toes and first metatarsals.

4. Computed tomography
    1. CT scan with comparative 3-dimensional reconstruction analysis of the calvaria and cranial bases: the most useful radiological examination in identifying skull shape and presence or absence of involved sutures
    2. Precise definition of the pathological anatomy, permitting specific operative planning
5. Magnetic resonance imaging
    1. Demonstration of the anatomy of the soft tissue structures and associated brain abnormalities
    2. Visualization of the spatial arrangement of the bones

4. Molecular analysis
    1. Exquisitely specific molecular mechanism with a narrow mutational spectrum
    2. More than 98% of cases: caused by specific missense substitution mutations, involving adjacent amino acids (Ser252Trp, Ser252Phe, or Pro253Arg) in exon 7 of *FGFR2*
    3. The remaining cases: due to Alu-element insertion mutations in or near exon 9.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib.
        1. A negligible recurrence risk for patient's sib when parents are not affected except in the case of germinal mosaicism in which the risk for future sibs depends on the proportion of germ cells bearing the mutant allele.
        2. 50% risk, if a parent is also affected
    2. Patient's offspring: a 50% recurrence risk for an affected individual to have an affected offspring.
    3. Advanced paternal age effect in new mutations has been shown clinically and demonstrated conclusively at the molecular level.
2. Prenatal diagnosis (Hill et al. 1987; Kaufmann et al. 1997; Ferreira et al. 1999; Skidmore et al. 2003; Quintero-Rivera et al. 2006)
    1. Prenatal ultrasonography in low-risk pregnancies with finding of abnormal fetal skull shape
        1. Prenatal diagnosis of Apert syndrome suspected with findings of fetal "mitten hands" associated with abnormal skull shape and midfacial hypoplasia and confirmed by molecular diagnosis. Craniosynostosis is usually not detected until the third trimester.
        2. Low yield for testing mutations in the *FGFR2* gene.
        3. Mutation identification not helpful in determining the prognosis of a fetus, which is largely determined by the clinical diagnosis and not by the molecular diagnosis.
    2. Prenatal MRI: a useful and sometimes indispensable, additional diagnostic tool (Weber et al. 2010)
    3. Fetoscopy (Leonard et al. 1982) to visualize fetal anomalies comparable to Apert syndrome in a pregnancy at risk: an invasive procedure not used currently
    4. Molecular genetic analysis
        1. An affected parent with identified mutation of *FGFR2* gene: prenatal diagnosis available on fetal DNA obtained through amniocentesis or chorionic villus sampling
        2. An affected parent without identified mutation of *FGFR2* gene: linkage analysis available to an informative family with at least two affected family members based on an accurate clinical diagnosis and an accurate understanding of genetic relationships in the family
3. Management
    1. Treatment goals (Fearon and Podner 2013)

1. Prevention of avoidable developmental delays from raised intracranial pressure and sleep apnea.
2. Reducing operative interventions may potentially improve developmental outcomes.

2. Protection of the cornea
   1. Instill lubricating bland ointments in the eyes at bedtime to protect corneas from desiccation
   2. Artificial teardrops during the day
   3. Lateral or medial tarsorrhaphy in severe cases to narrow the palpebral fissure cosmetically and protect the corneas and the vision
3. Upper airway obstruction during the neonatal period
   1. Remove excessive nasal secretions
   2. Treat upper airway infection
   3. Humidification with added oxygen
   4. Judicious use of topic nasal decongestants
   5. Rarely requires orotracheal intubation
4. Sleep apnea
   1. Polysomography (a sleep recording of multiple physiologic variables), currently the most reliable method for determining the presence of sleep apnea
   2. Continuous positive pressure
   3. Tracheostomy indicated in severely affected children
5. Chronic middle ear effusion associated with bilateral conductive hearing deficit
   1. Antimicrobial therapy
   2. Bilateral myringotomy and placement of ventilation tubes: the most effective treatment
6. Craniofacial surgery (Marsh et al. 1991)
   1. Cranium
      1. Removes synostotic sutures
      2. Reshapes the calvaria
      3. Allows more normal cranial development to proceed with respect to shape, volume, and bone quality
      4. Relieves increased intracranial pressure
   2. Orbits
      1. Correction of ocular proptosis: the primary objective of orbital surgery
      2. Reduction of increased interorbital distance (hypertelorism)
      3. Correction of increased interior malrotation
   3. Nose
      1. Infants and child: nasal reconstruction focusing on correction of the excessively obtuse nasofrontal angle, flat nasal dorsum, and ptotic nasal tip
      2. Teenager and adult: reduction of the nasal tip bulk
   4. Midface
      1. Normalization of midface appearance
      2. Expansion of the inferior orbit
      3. Volumetric expansion of the nasal and nasopharyngeal airways
      4. Establishment of a normal dentoskeletal relationship
   5. Mandible: mandibular osteotomies to improve dentoskeletal relations for masticatory and esthetic benefit
7. Surgical reconstruction of syndactyly angiographic planning of a single-stage, 5-digit release for all classes of deformity (Harvey et al. 2012)
8. Psychological and social challenges confronted by individuals with Apert syndrome (Campis 1991)
   1. Emotional adjustment
   2. Body image development
   3. Impact of surgery and hospitalization on children with Apert syndrome.

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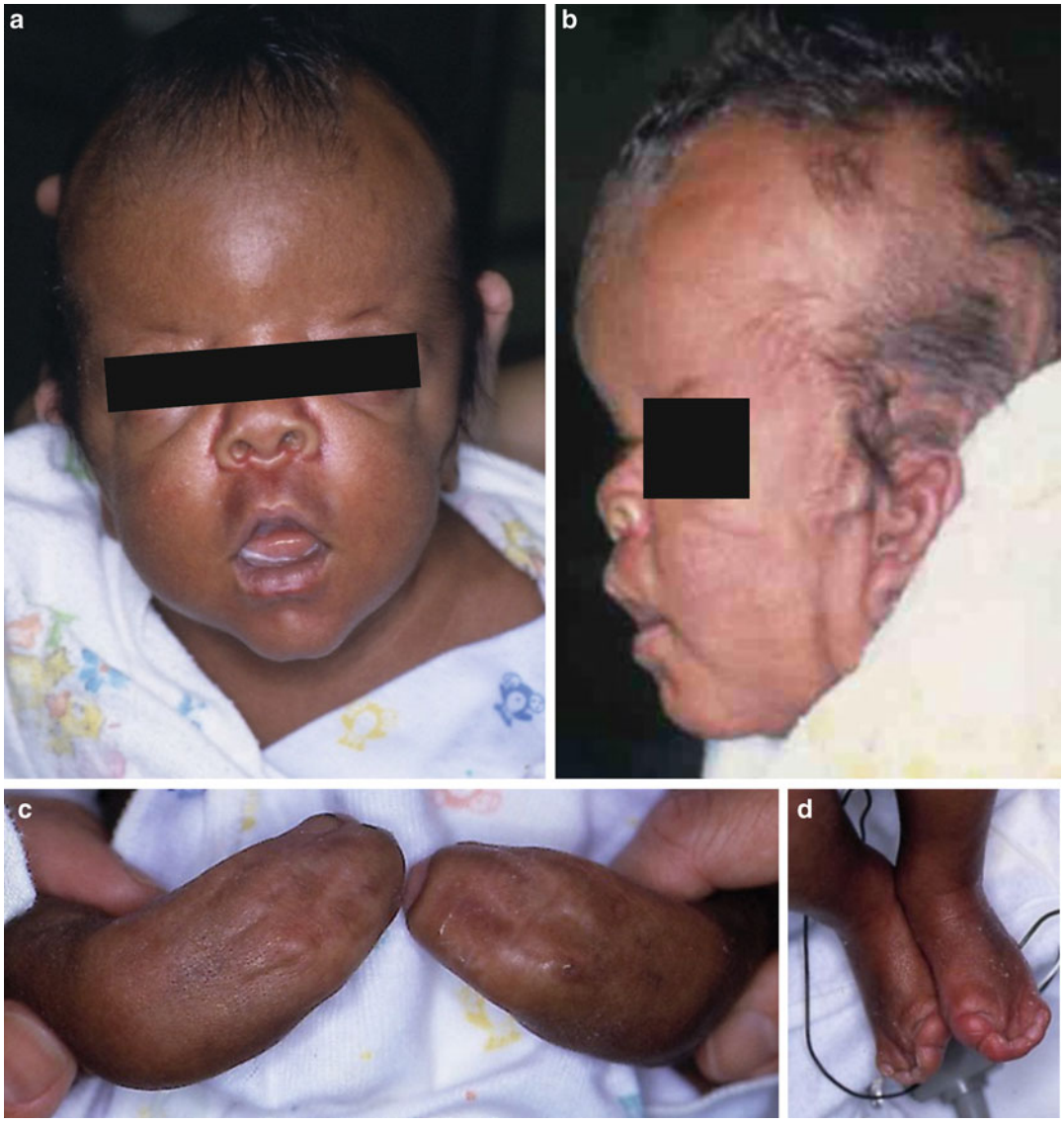

Fig. 1 (**a**–**d**) An infant with Apert syndrome showing characteristic facial appearance and typical mitten hands and socked feet

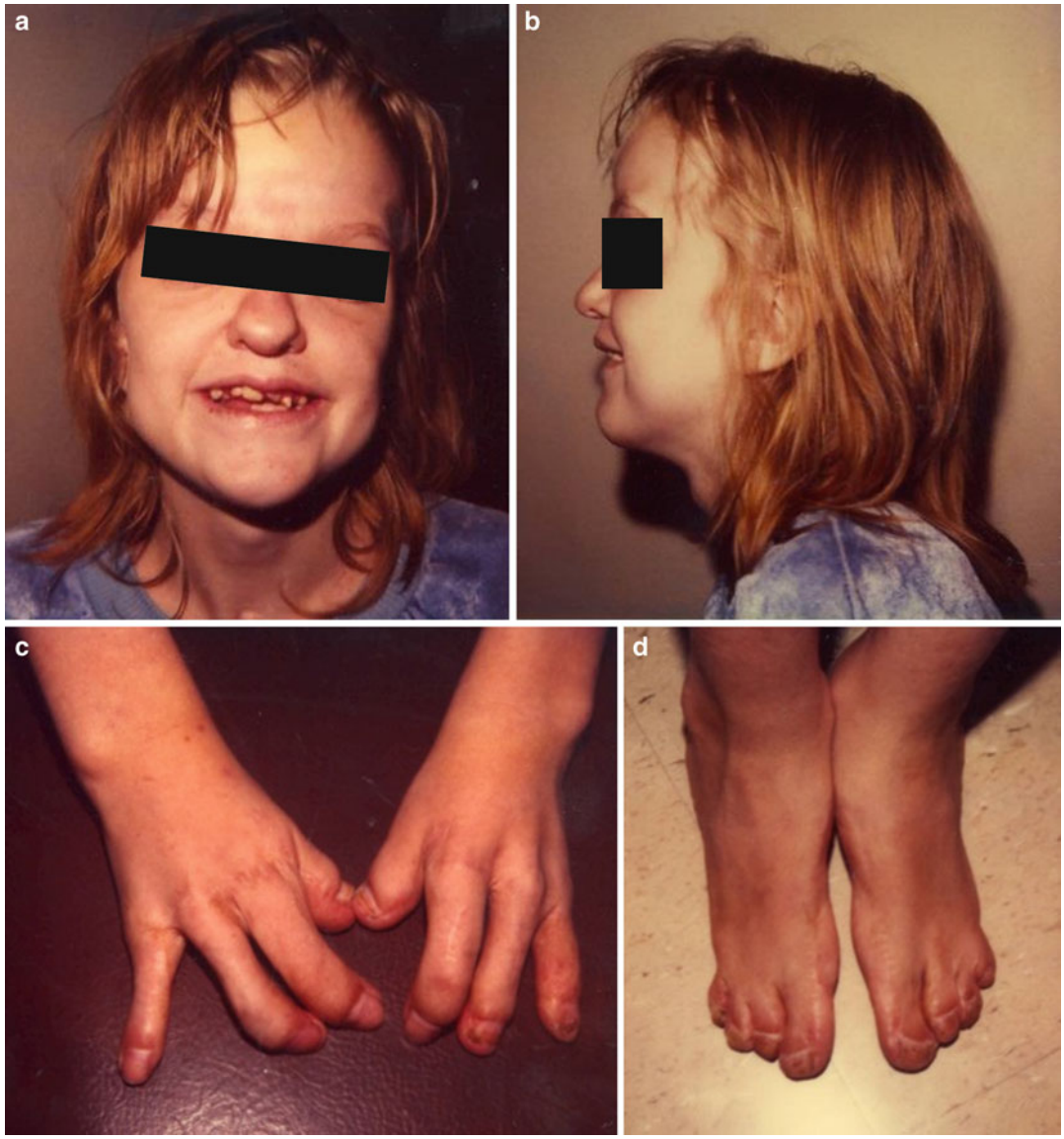

Fig. 2 (**a**–**d**) A 13-year-old girl with Apert syndrome showing characteristic facial appearance and postoperative status of the fingers and toes

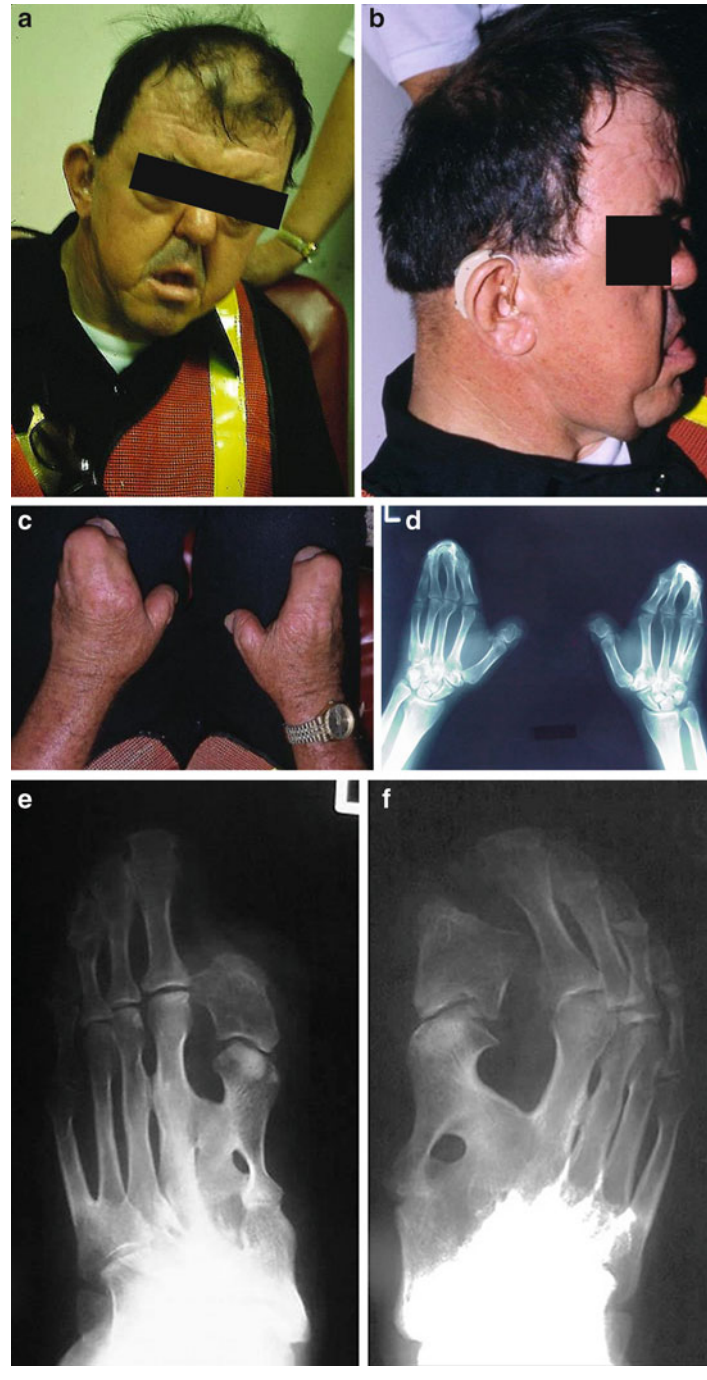

Fig. 3 (**a**–**f**) An adult with Apert syndrome showing typical craniofacial appearance, hearing loss (wearing hearing aids), and mitten hands. Radiographs showed cutaneous and osseous syndactyly, complete syndactyly involving the second through fifth digits (mitten hands), symphalangism of interphalangeal joints, delta-shaped proximal phalanx of the thumbs, complete syndactyly involving the second through fifth digits (socked feet), and partial duplication of the proximal phalanx of the great toes and first metatarsals

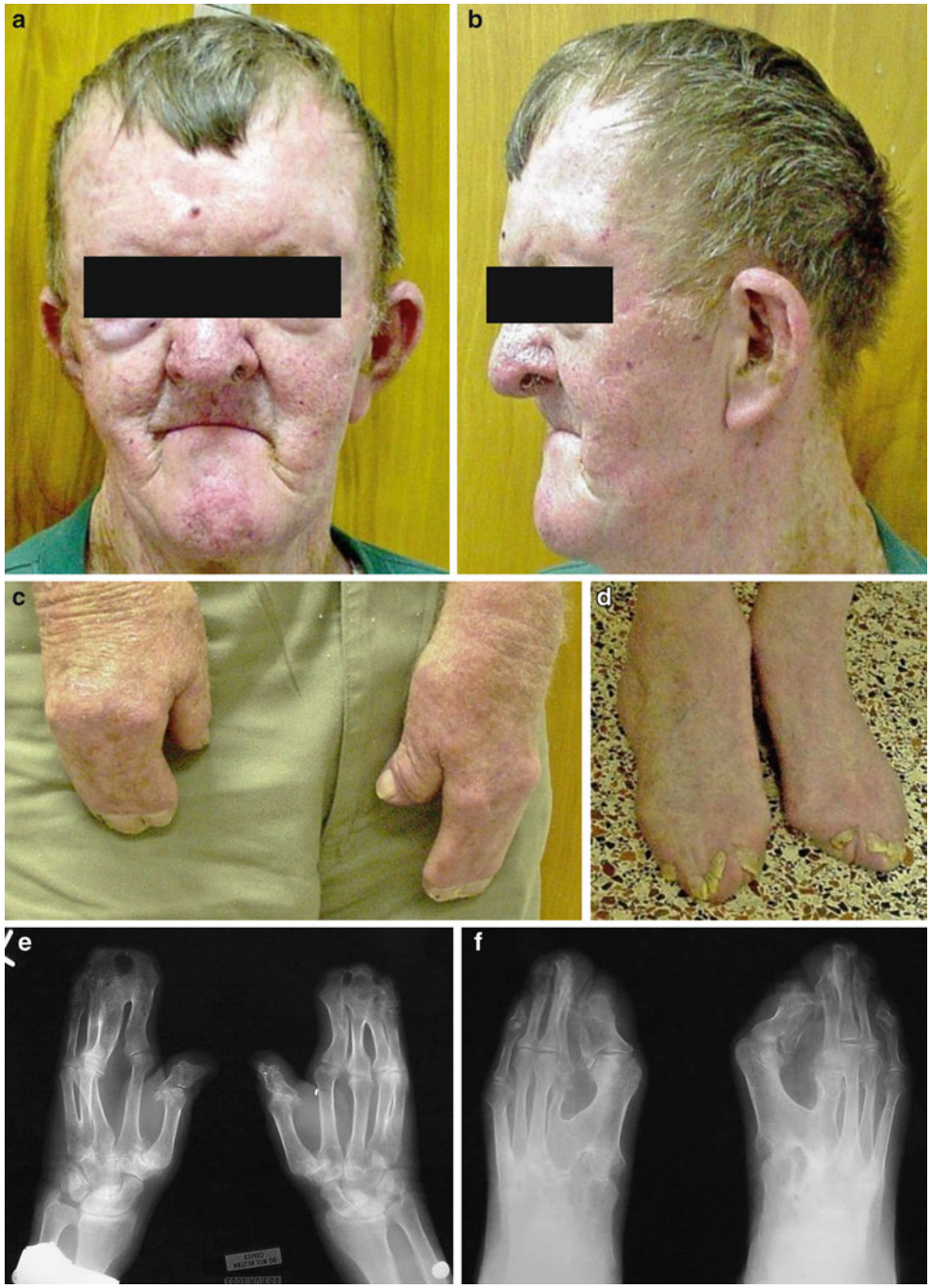

Fig. 4 (continued)

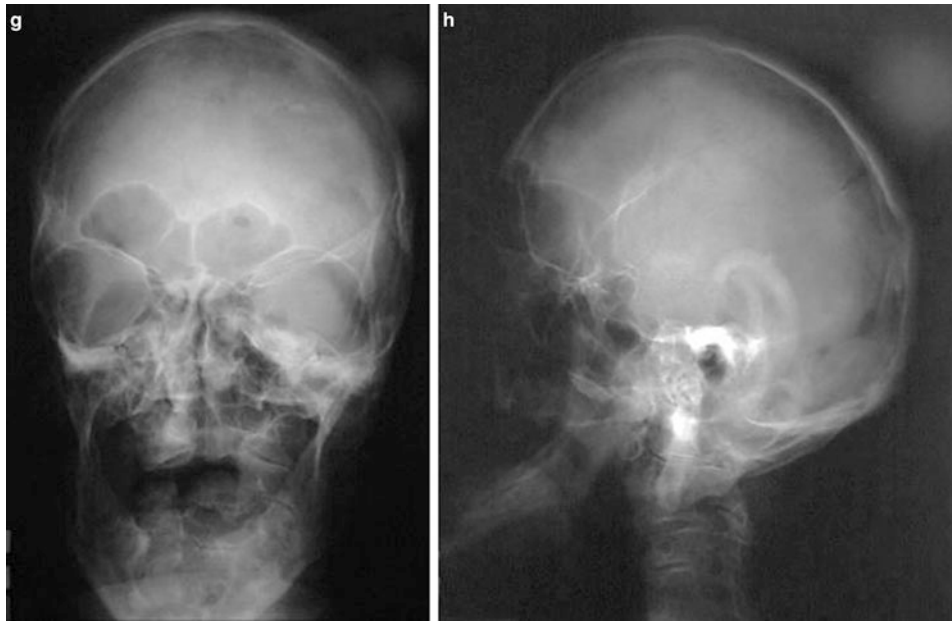

Fig. 4 (**a**–**h**) An adult with Apert syndrome showing typical craniofacial appearance with mitten hands and socked feet. Radiographs of hands and feet and skull showed cutaneous and osseous syndactyly, turribrachycephaly, shallow orbits, and hypoplastic maxilla

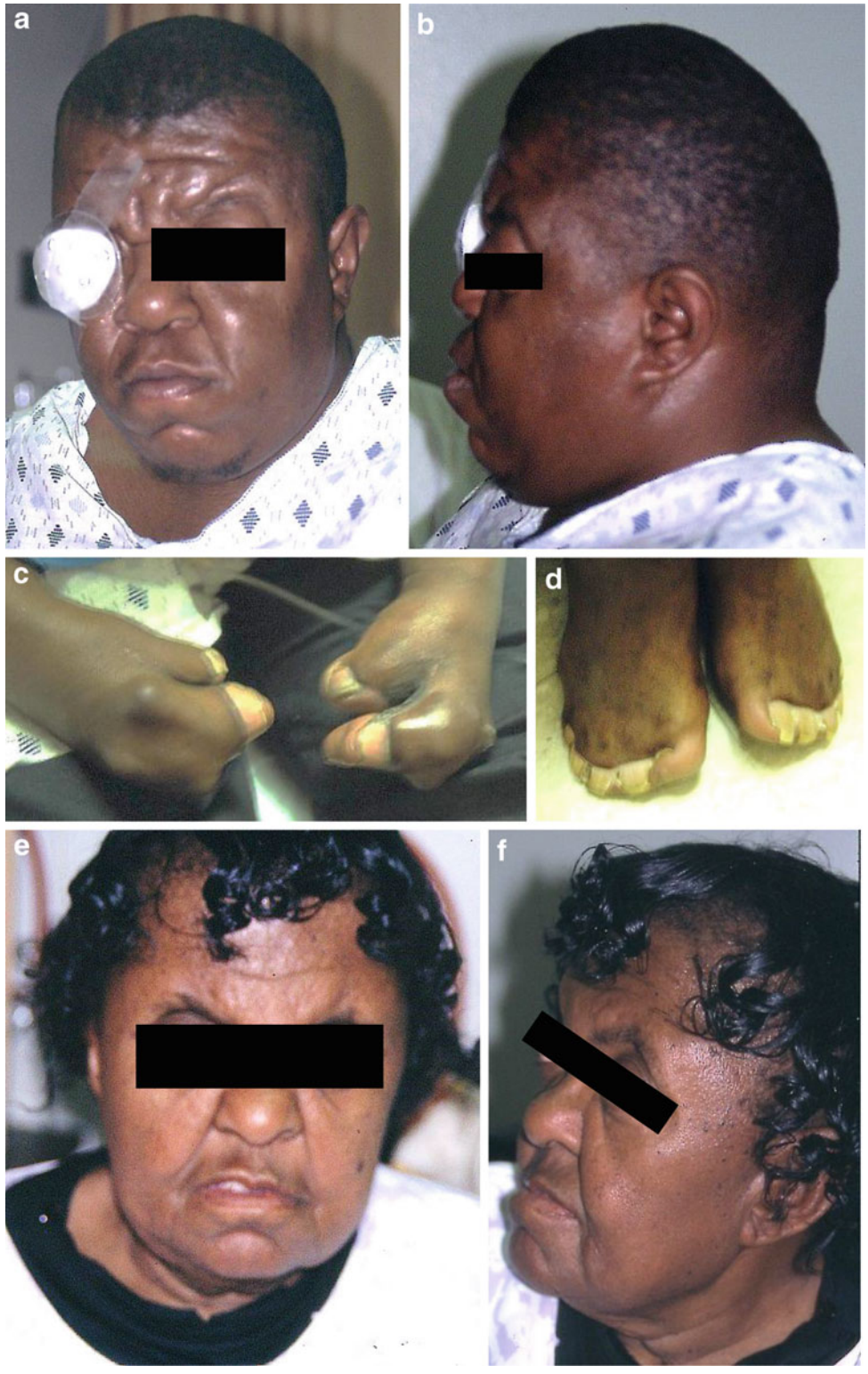

Fig. 5 (continued)

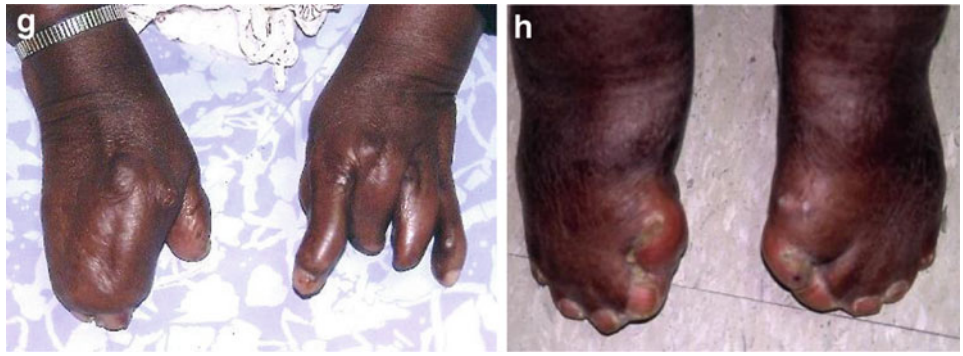

Fig. 5 (**a**–**h**) A daughter and a mother with Apert syndrome showing characteristic craniofacial features, mitten hands, and socked feet

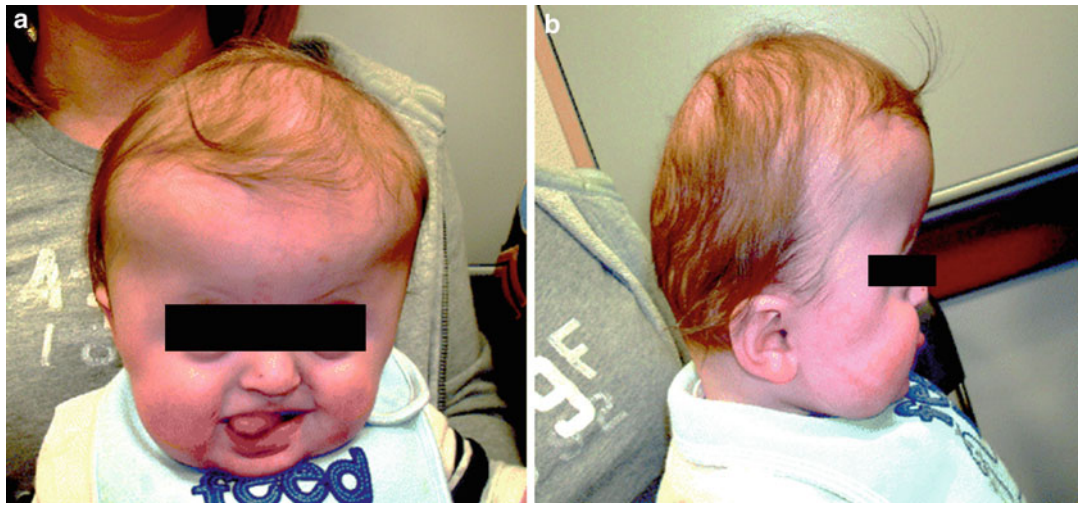

Fig. 6 (**a**, **b**) A 6-month-old male infant was evaluated for Apert syndrome which was diagnosed prenatally. The fetus was noted to have abnormal craniofacial features with mitten hands by ultrasonography. Molecular testing from cultured amniocytes indicated the presence of a C > G transversion at nucleotide 755 (c.755 C > G) of the fibroblast growth factor receptor 2 (*FGFR2*) gene. This change substitutes a tryptophan for a serine at amino acid 252 (p. S252W). The presence of this mutation is consistent with a clinical diagnosis of Apert syndrome. The infant showed severe acrocephaly, palpable coronal suture ridge, ocular hypertelorism with proptotic eyes, low-set ears, depressed nasal bridge, small soft palate cleft, hitchhiker-like thumbs, mitten hands, and sock feet

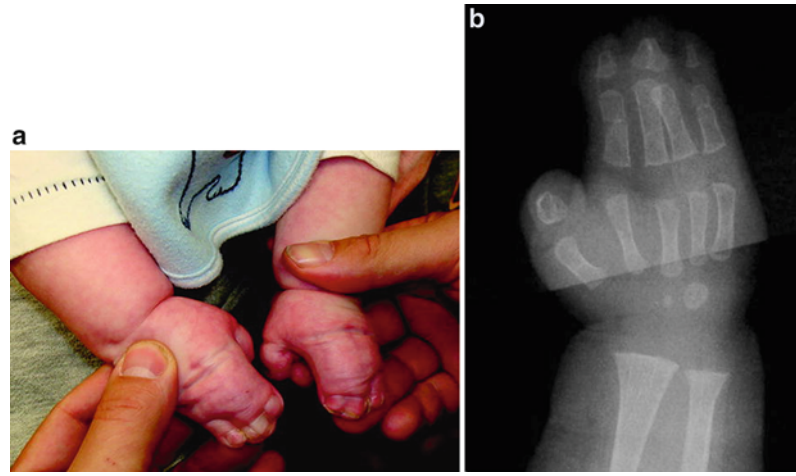

Fig. 7 (**a**, **b**) Mitten-shaped hands with cutaneous syndactyly and synonhychia (**a**) Radiograph of the right hand (**b**) showing coalition of distal phalanges, symphalangism, cutaneous and osseous syndactyly, and delta-shaped deformity of the proximal phalanx of the thumb

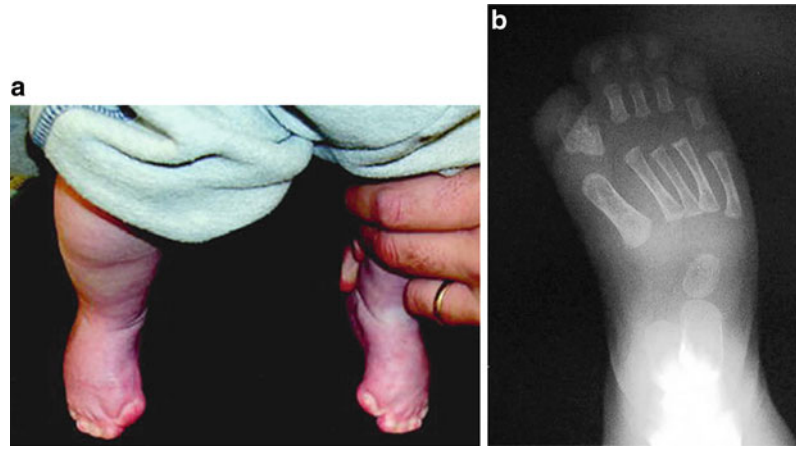

Fig. 8 (**a**, **b**) Both feet (**a**) showing socket-shaped feet, syndactyly of the feet with partial-to-complete fusion of the digits, involving second, third, and forth digits. Radiograph of the right foot (**b**) showing complete cutaneous syndactyly involving the second, third, and fourth digits and delta-shaped deformity of the proximal phalanx of the first toe

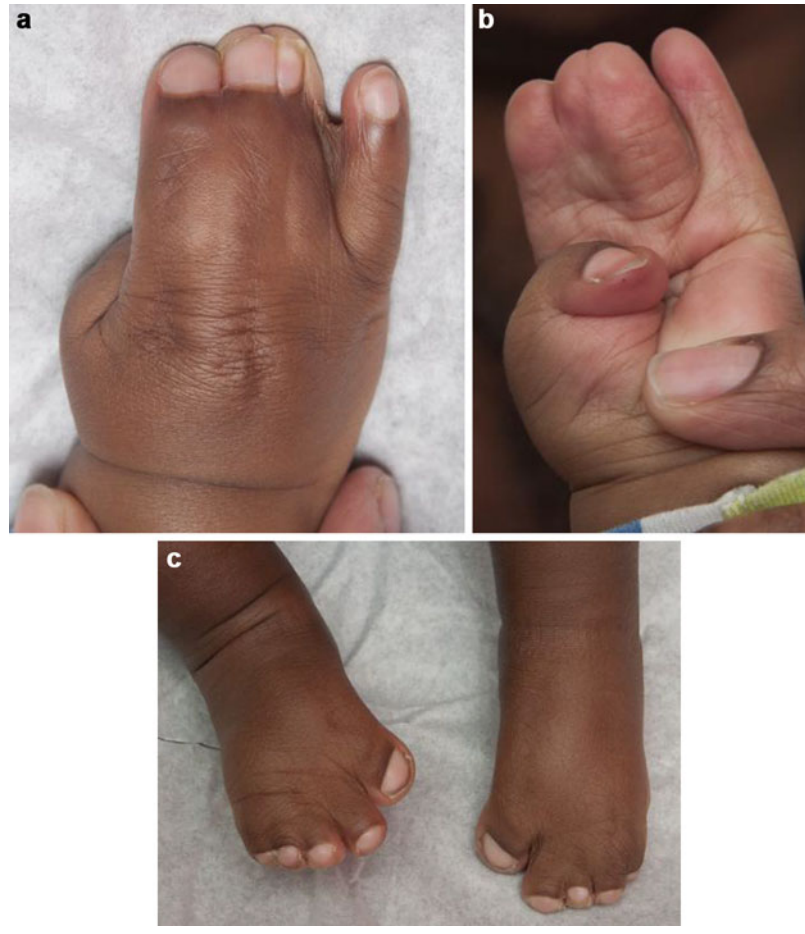

Fig. 9 (a-c) The 9-month-old girl was seen because of syndactyly of the hands and feet associated with craniofacial anomalies. The family and pregnancy histories were non-contributory. There were broad thumbs with 2-5 digit cutaneous syndactyly (**a, b**) (only right hand is shown here). The feet were characterized by brachydactyly and syndactyly of 2-5 toes (**c**). Genomic DNA analysis showed heterozygous for a C to G mutation at nucleotide 755 of fibroblast growth factor receptor 2 (FGFR2) gene (c.755C>G) that changes a codon for serine (TCG) to one for tryptophan (TGG) at amino acid position 252 (p. Ser252Trp). This mutation is diagnostic for Apert syndrome (Park et al, Am J hum Genet 57:321-328, 1995). (Courtesy of Dr. Grace Guo)

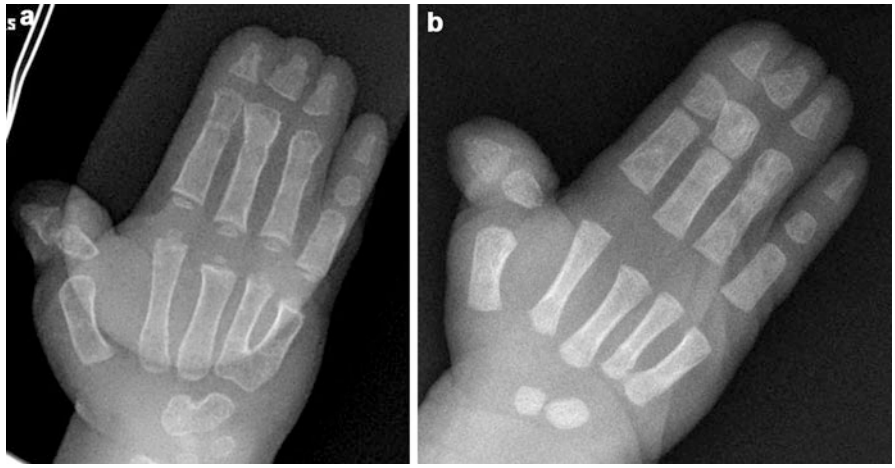

Fig. 10 (a, b) Right hand radiograph at 15 month of age (a) showed soft tissue fusion between the second through fourth digits and fusion of the proximal soft tissues between the fourth and fifth digit. Hypoplastic, deformed phalanges were present with fusion of the proximal and middle phalanges of the second through fourth digits. Bony fusion was also seen at the bases of the fourth and fifth metacarpals and fusion of the capitate and hamate. The thumb was pointing laterally with a sharp angulation at the 1st MCP joint. Right hand radiograph at 1 month of age (b) is provided here for comparison. Similar abnormalities are also seen in the left hand (not shown). (Courtesy of Dr. Grace Guo)

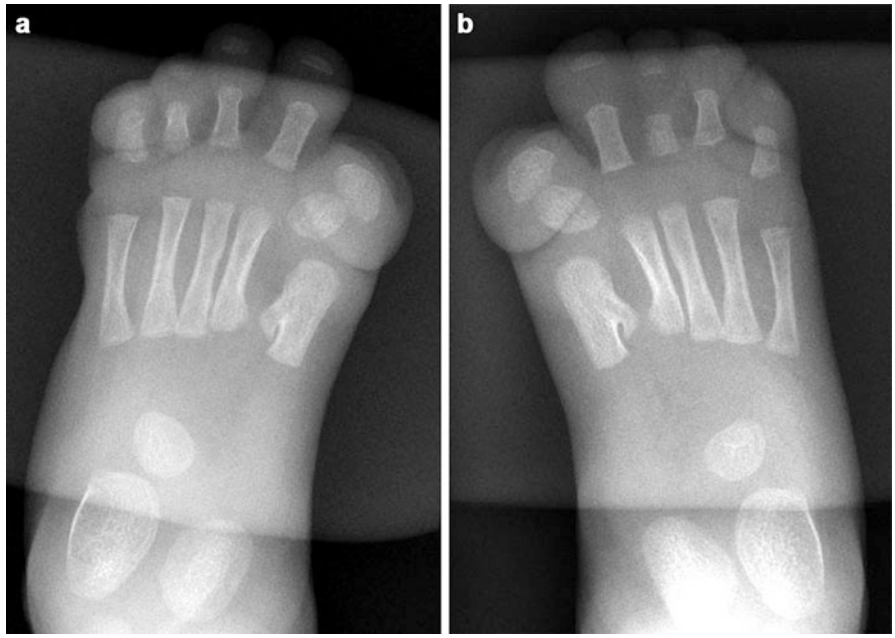

Fig. 11 (**a**, **b**) Radiographs of bilateral feet at 1 month of age (**a**, **b**) showed foreshortening of bilateral second metatarsals, right third proximal phalanx and left fourth phalanx, and distal phalanges of bilateral left second, third, fourth, and fifth digits. Bilateral great toes are bulbous and foreshortened with deformed phalanges and partially duplicated metatarsals. Soft tissue fusion was present in the bilateral second through fifth digits

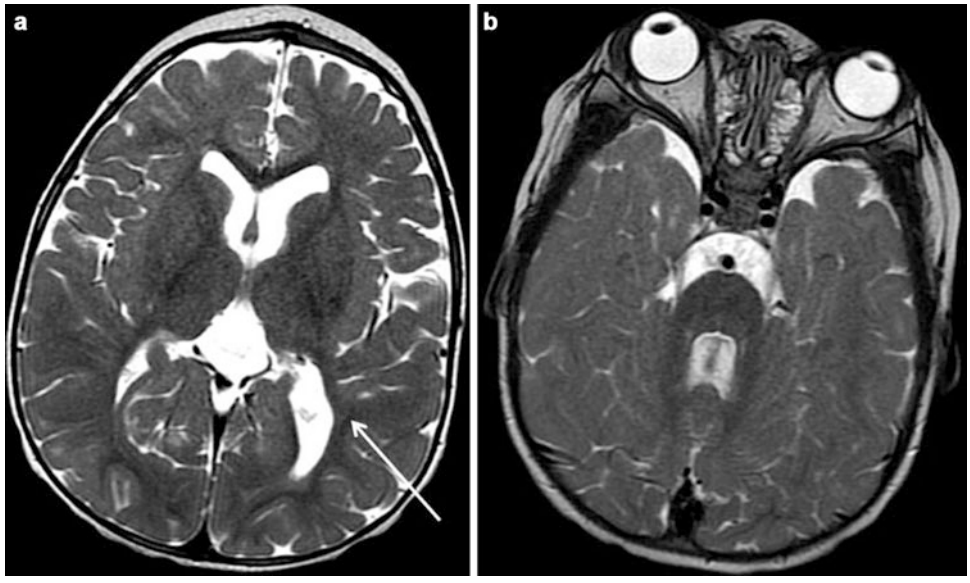

Fig. 12 (**a**, **b**) MRI images of the brain obtained at 16 month of age showed hypoplasia of the parietooccipital white matter with undulating bilateral lateral ventricle occipital horns (arrow) (**a**). Shallow orbits are appreciated bilaterally with ocular hypertelorism (**b**)

Aplasia Cutis Congenita

Contents

Aplasia cutis congenita (ACC) is a clinical description of the absence of the skin at birth, first described by Cordon in 1767. It is a heterogeneous group of disorders characterized by absence of epidermis, dermis, and, sometimes, subcutaneous tissue, muscle, or bone on one or more parts of the body. The incidence is estimated to be 1 in 10,000 births.

Synonyms and Related Disorders

Adams-Oliver syndrome; Aplasia cutis congenita associated with epidermolysis bullosa (simplex, junctional, dystrophic) (Bart syndrome); Congenital scalp defect; Congenital skull and scalp defect

Genetics/Basic Defects

1. Etiological theories
    1. Amniogenic theory (Frieden 1986)
        1. Adhesion of the amniotic membrane to the fetal skin might tear off, leaving absent areas of skin.
        2. Not supported by the study of placentas because most placentas are normal
    2. Vascular theory (Classen 1999): assumes thromboplastic material from a fetus papyraceus (mummified dead fetus) as the causes of skin damage
    3. Placental abnormalities
    4. Biomechanical forces on the vertex during the embryogenesis
    5. Intrauterine trauma: a history of trauma in only a minority of cases
    6. Intrauterine infections
        1. Varicella
        2. Herpes simplex
    7. Intrauterine involution of a hemangioma
    8. Teratogens
        1. Methimazole (Farine et al. 1988; Vogt et al. 1995; Rodriguez-Garcia et al. 2011)
        2. Misoprostol (Fonseca et al. 1993)
    9. Familial cases reported (Fisher and Schneider 1973; De Groot et al. 1978; Sybert 1985; Chitnis et al. 1996)
2. Frieden's classification of aplasia cutis congenita (Frieden 1986; Browning 2013; Brzezinski et al. 2015)
    1. Group I: ACC of the scalp without multiple anomalies: sporadic occurrence or autosomal dominant inheritance

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Group II: ACC of the scalp with associated limb abnormalities (Adams-Oliver syndrome): autosomal dominant inheritance
3. Group III: ACC of the scalp with associated epidermal, organoid nevus, or epidermal nevus syndrome, ophthalmic, and neurologic problems (seizures, mental retardation, corneal opacities, and eyelid colobomas): sporadic occurrence
4. Group IV: ACC overlying embryologic malformations (meningomyelocele, porencephaly, leptomeningeal angiomatosis, cranial stenosis, spinal dysraphism, gastroschisis, or omphalocele): inheritance depending on underlying conditions
5. Group V: ACC with associated fetus papyraceous (results from the death of a twin fetus in the second trimester) (Mannino et al. 1977; Joshi et al. 1991; Boente et al. 1995; Classen 1999; Cambiaghi et al. 2001; Kelly et al. 2002; Pieretti et al. 2015) or placental infarcts; ACC is extensive on the trunk or limbs, linear or stellate configuration: sporadic occurrence
6. Group VI: ACC associated with epidermolysis bullosa (Bart syndrome): autosomal dominant or recessive inheritance depending on the type of the epidermolysis bullosa
7. Group VII: ACC localized to extremities without blistering: autosomal dominant or recessive inheritance
8. Group VIII: ACC caused by specific teratogens: scalp (methimazole treatment during pregnancy), any area (intrauterine infections with varicella-zoster virus, herpes simplex virus)
9. Group IX: ACC associated with malformation syndromes
    1. Trisomy 13
    2. Trisomy 18
    3. 4p- (Wolf-Hirschhorn syndrome)
    4. 46,XY gonadal dysgenesis
    5. Amniotic band disruption complex
    6. Ectodermal dysplasias
    7. Johanson-Blizzard syndrome
    8. Focal dermal hypoplasia (Goltz syndrome)
    9. Setleis syndrome
    10. Oculocerebrocutaneous (Delleman) syndrome
    11. Scalp-ear-nipple syndrome (Finlay-Mark syndrome)
    12. Kabuki syndrome
3. Aplasia cutis congenita associated with epidermolysis bullosa (Bart syndrome) (Achiron et al. 1992; Aygun et al. 2010)
    1. Simplex
        1. An autosomal dominant disorder
        2. Lysis of the epidermis occurring within the cytoplasm of the basal cell layer
    2. Junctional
        1. An autosomal recessive disorder
        2. Damage at the level of the lamina lucida
    3. Dystrophic (scarring) (Chiaverini et al. 2014)
        1. An autosomal dominant or recessive disorder.
        2. Defect situated in the anchoring fibrils attaching the basal lamina to the dermis.
        3. ACC is a frequent manifestation in patients with dystrophic epidermolysis bullosa (DEB) irrespective of the severity of the disease and is due to leg rubbing in utero.
        4. In children with a moderate form of DEB with no or moderate skin fragility, a glycine substitution near the triple helix domain interruption of the collagen VII leading to thermolabile protein could explain this phenomenon.
4. Summary of identified genes in ACC and syndromes with ACC (Marneros 2015)
    1. Familial ACC: *BMS1* mutation (Marneros 2013)
    2. Scalp-ear-nipple syndrome: *KCTD1* mutation (Marneros et al. 2013) (Please see the chapter)
    3. Adams-Oliver syndrome (AOS) (Please see the chapter)
        1. AOS-1: *ARHGAP31* mutation (Southgate et al. 2011)
        2. AOS-2: *DOCK6* mutation (Shaheen et al. 2011)

3. AOS-3: *RBPJ* mutation (Hassed et al. 2012)
4. AOS-4: *EOGT* mutation (Shaheen et al. 2013)
5. AOS-5: *NOTCH1* mutation (Stittrich et al. 2014)

Clinical Features

1. Aplasia cutis of the scalp (aplasia cutis vertices) (Cambiaghi et al. 1998)
   1. The most common form
   2. Single or multiple noninflammatory ulcers
   3. Occurrence at or near the scalp vertex
   4. Variable in shape and size
   5. Heals leaving a hairless scar
   6. Membranous aplasia cutis congenita of the scalp with the "hair collar sign" (growth of long dark coarse hair encircling the lesion) reported (Bassi et al. 2014)
   7. Occurrence
      1. An isolated condition
      2. Associated with other congenital abnormalities
2. Aplasia cutis with extracranial symmetrical involvement (a distinctive type of "non-scalp" aplasia cutis congenita)
   1. Linear lesions with a symmetrical pattern of distribution on the trunk and limbs
   2. Aplasia cutis with fetus papyraceous: usually associated with in utero death of a monozygotic twin during pregnancy, with or without the presence of a fetus papyraceous (persistence of a mummified dead fetus; vanishing twin) (Bourque and Preloger 2015)
   3. Other terms
      1. Truncal aplasia cutis
      2. Bilateral abdominal aplasia cutis
3. Associated congenital anomalies (Evers et al. 1995; Mesrati et al. 2015)
   1. Craniofacial anomalies
      1. Underlying skull bony defect (Kosnik and Sayers 1975): 15–20% of cases of scalp ACC and as high as 75% in cases of extensive scalp ACC (Burkhead et al. 2009)
      2. Microphthalmia
      3. Colobomas
      4. Myopia
      5. Epibulbar dermoid
      6. Cleft lip
      7. Cleft palate
      8. Ear malformations
   2. CNS malformation
      1. Hydrocephalus
      2. Mental retardation
      3. Spastic paralysis
   3. Ectodermal dysplasia
      1. Hypoplasia of the teeth
      2. Delayed dentition
      3. Nail hypoplasia
      4. Skin blisters
      5. Skin hyperpigmentation
      6. Cutis marmorata
   4. Gastrointestinal abnormalities (Al-Sawan et al. 1999; Lane and Zanol 2000)
      1. Tracheoesophageal fistula/esophageal atresia
      2. Omphalocele
      3. Gastroschisis
      4. Pyloric atresia (Carmi et al. 1982; Cowton et al. 1982): especially in association with junctional (atrophicans) type of epidermolysis bullosa
      5. Ileal atresia
      6. Mesenteric herniation
      7. Biliary atresia
      8. Midgut atresia
      9. Intestinal lymphangiectasia
   5. Musculoskeletal abnormalities
      1. Terminal transverse limb defects (Adams-Oliver syndrome) (Snape et al. 2009)
      2. Arthrogryposis
      3. Polydactyly
      4. Syndactyly
   6. Other malformations (Mesrati et al. 2015)
      1. Hemangiomas
      2. Terminal phalangeal hypoplasia
      3. Deviation of gluteal furrow
4. Prognosis (Burkhead et al. 2009)

1. Scalp lesion (1–3 cm): resolves spontaneously in majority of cases (85%)
2. Prognosis usually determined by underlying anomalies and extent of the lesions
3. Complications (Ribuffo et al. 2003)
    1. Hemorrhage
    2. Brain trauma
    3. Venous thrombosis
    4. Infection
    5. Meningitis
    6. Electrolyte abnormalities
    7. Seizures
4. Mortality rate (20–50%) (Basterzi et al. 2007)

Diagnostic Investigations

1. Imaging
    1. Radiography
        1. Scalp/skull
        2. Hands
        3. Feet
    2. CT scan or MRI of the brain
2. Karyotyping to detect chromosome abnormality
3. Histology: heterogeneous appearance of lesions
    1. Ulcerated lesions at birth
        1. Complete absence of all layers of skin
        2. Occasionally extending to the bone or dura
    2. In utero healing of some lesions
    3. Healed lesions
        1. Flattened epidermis
        2. Proliferation of fibroblasts in a loose connective tissue stroma
        3. Newly formed capillaries
        4. Complete absence of adnexal structures
4. Culture/serology
    1. Varicella zoster
    2. Herpes simplex virus
5. Amniotic fluid findings in some cases (Dror et al. 1994; Gerber et al. 1995)
    1. Elevated amniotic fluid AFP levels
    2. Positive acetylcholinesterase

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal dominant: not increased unless a parent is affected
        2. Autosomal recessive: 25%
    2. Patient's offspring
        1. Autosomal dominant: 50%
        2. Autosomal recessive: not increased unless the spouse is a carrier
2. Prenatal diagnosis
    1. Ultrasound diagnosis of aplasia cutis congenita of the trunk (Liu et al. 2014)
        1. Absence of strong echoes (In normal fetus, the abdominal skin surrounding the trunk generates strong echoes)
        2. Absence of the skin over intra-abdominal organs: a typical finding
    2. Ultrasonography for at-risk family with aplasia cutis congenita associated with epidermolysis bullosa and pyloric atresia (Achiron et al. 1992)
        1. Hydramnios
        2. A dilated stomach
        3. A deformed external ear
        4. A contracted fisted hand
    3. Amniocentesis for associated chromosomal abnormality
3. Management
    1. Conservative treatment (Morrow et al. 2013; Puvabanditsin et al. 2015)
        1. Careful and standard wound treatment for small defects involving only epidermis: usually uneventful healing of the lesion (Kulali et al. 2015)
        2. Control of infection
        3. Control of electrolyte abnormalities, especially with larger wounds
    2. Requires a scalp flap for most lesions
    3. A split-thickness skin grafting or full-thickness pedicle grafts (for defects of the scalp extending to the dura mater)
    4. Reconstruction of skull and scalp for a large lesion involving scalp, skull, and dura (Argenta and Dingman 1986)
    5. Large-sized skin grafting (Liu et al. 2015)
        1. Ideal for treating large skin defects

2. A good option for treating small skin defects that do not heal or may heal with scarring after conservative treatment
6. Calvarial regeneration with use of acellular dermal matrix in aplasia cutis congenita (Mericli et al. 2015)
7. Emergency intervention to control life-threatening hemorrhage
8. Surgical intervention also useful later in life for revision of scars and correction of alopecia with rotation flaps, simple excision and closure, scalp reduction techniques, or local hair transplantation
9. Management of associated anomalies

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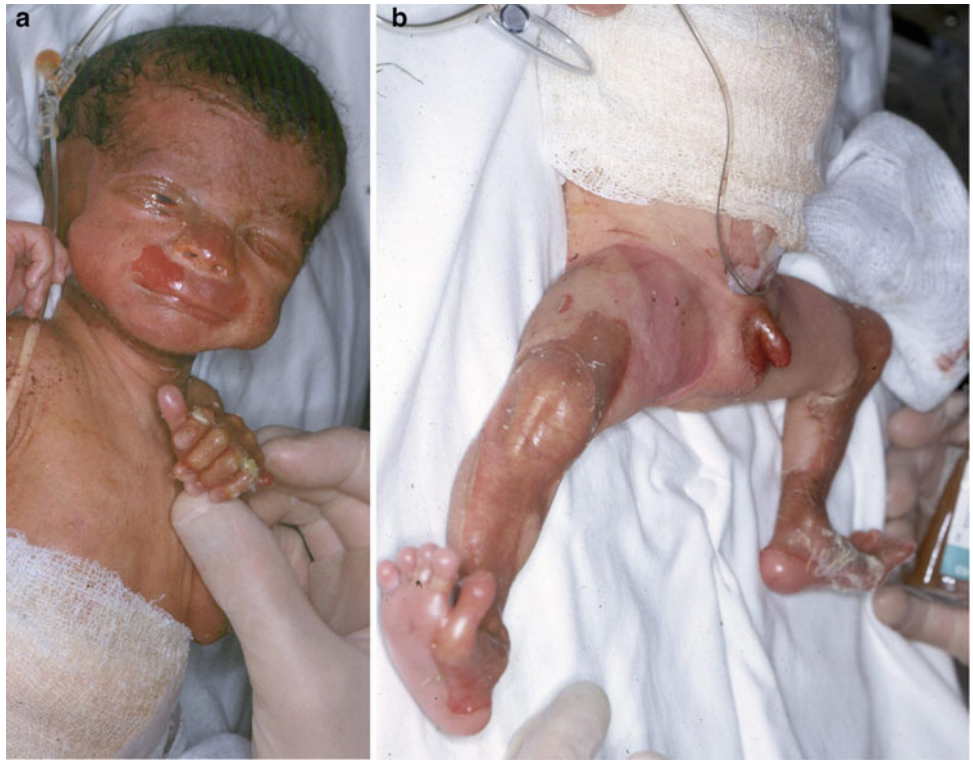

Fig. 1 (**a**, **b**) An infant with aplasia cutis congenita with epidermolysis bullosa showing lesions on the face, trunk, and extremities

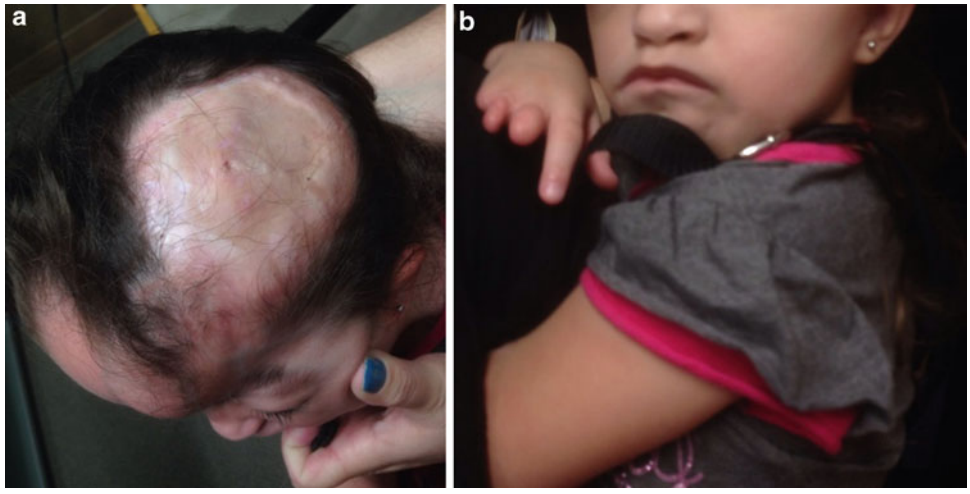

Fig. 2 (**a**, **b**) This 3-year-7-month-old girl was evaluated for scalp defect (**a**) and terminal transverse limb defect (**b**). For details of this case, please see the chapter of Adams-Oliver syndrome

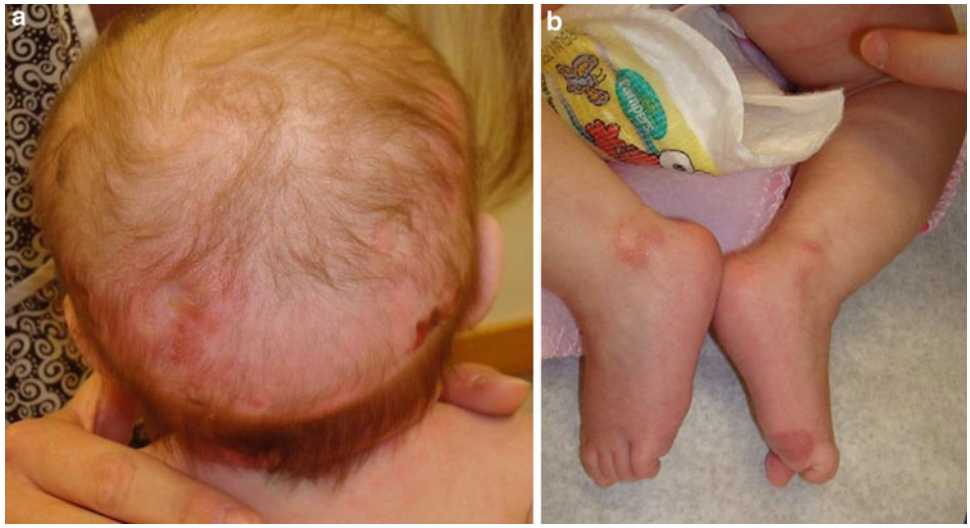

Fig. 3 (**a**, **b**) This 3-month-old infant was evaluated for blisters over the neck, trunk, and extremities (**b**) (only lower extremities are shown here). In addition, the baby has aplasia cutis congenita on the scalp (**a**)

Arthrogryposis Multiplex Congenita

Contents

Arthrogryposis multiplex congenita comprises nonprogressive conditions characterized by multiple joint contractures throughout the body at birth. The term encompasses a very heterogeneous group of disorders having the common feature of multiple congenital joint contractures. The overall prevalence of arthrogryposis is approximately 1 in 3,000 live births (Hall 1985a, b; Fahy and Hall 1990).

Synonyms and Related Disorders

Amyoplasia; Distal arthrogryposis (distotarlar dysmorphism, Freeman-Sheldon syndrome, Sheldon-Hall syndrome, Gordon syndrome, Hecht syndrome, Beals syndrome)

Genetics/Basic Defects

1. Major causes
    1. Arthrogryposis as a physical sign observed in many specific clinical conditions:
        1. Single-gene defects
        2. Chromosomal abnormalities
        3. Known or unknown syndromes or conditions
        4. Environmental effects: mutagenic agents, mitotic abnormalities, toxic chemicals or drugs, hyperthermia, neuromuscular blocking agents, and mechanical immobilization (Swinyard and Bleck 1985)
    2. Fetal akinesia due to fetal abnormalities:
        1. Neurogenic abnormalities: the most common cause of arthrogryposis
            1. Meningomyelocele
            2. Anencephaly
            3. Hydranencephaly
            4. Holoprosencephaly
            5. Spinal muscular atrophy
            6. Cerebro-oculo-facio-skeletal syndrome
            7. Marden-Walker syndrome
        2. Muscular abnormalities: relatively rare causes of arthrogryposis
            1. Congenital muscular dystrophies
            2. Congenital myopathies
            3. Intrauterine myositis
            4. Mitochondrial disorders
        3. Connective tissue abnormalities in tendon, bone, joint, or joint lining restricting fetal movements, resulting in congenital contractures. Examples include:
            1. Synostosis
            2. Lack of joint development

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3. Aberrant fixation of joints (as in diastrophic dysplasia and metatropic dwarfism)
4. Aberrant laxity of joints with dislocations (as in Larsen syndrome)
5. Aberrant soft tissue fixations (as in popliteal pterygium syndrome)
6. Failure of normally developed tendon to attach to the appropriate place around the joint or bone in some forms of distal arthrogryposis, resulting in abnormal lack of movement of the joints with secondary contractures at birth

4. Mechanical limitations to movement. Limited space for fetal movement inside the uterus may contribute to development of contractures. Examples include:
   1. Multiple births
   2. Uterine structural abnormalities such as bicornuate uterus
   3. Umbilical cord wrapping
   4. Oligohydramnios in renal agenesis
   5. Early persistent leakage of amniotic fluid
5. Intrauterine vascular compromise resulting in loss of nerve and muscle function with development of fetal akinesia and secondary joint contractures. Examples include:
   1. Severe maternal bleeding during pregnancy
   2. Failed attempts at termination of pregnancy (Hall 1996)

3. Fetal akinesia due to maternal disorders, examples include:
   1. Infections
      1. Rubella
      2. Poliomyelitis
   2. Drugs/chemicals
      1. Methocarbamol
      2. Alcohol
      3. Carbon monoxide poisoning
   3. Trauma
   4. Vitamin deficiency
   5. Hyperthermia (e.g., prolonged sauna)
   6. Radiation
   7. Other maternal illnesses
      1. Maternal autoantibodies
      2. Diabetes mellitus
      3. Myotonic dystrophy
      4. Maternal multiple sclerosis

2. Pathophysiology
   1. Joint development
      1. Almost always normal during early embryogenesis
      2. Fetal motion essential for normal development of joints and their contiguous structures
   2. Lack of fetal movement (Hall 1989)
      1. Causing extra connective tissue to develop around the joint
      2. Resulting in fixation of the joint
      3. Limiting movement that further aggravates the joint contracture
      4. Contractures secondary to fetal akinesia: more severe in patients who are diagnosed early in pregnancy and who experience akinesia for longer periods of time during gestation

Clinical Features

1. Family history (Hall 1997, 2014):
   1. Presence of congenital contractures in the family
      1. Affected siblings
      2. Other affected family members
   2. Marked intrafamilial variability
      1. Mildly affected parent
      2. A parent with contractures early in infancy
   3. Consanguinity
      1. Increasing the chance that the parents will both carry the same disease gene
      2. Observed more frequently in families with rare recessive diseases than in those with common recessive diseases
   4. Increased parental age
      1. Some chromosomal abnormalities: increasing dramatically with advanced maternal age
      2. Single-gene dominant mutations: increasing with advanced paternal age

5. History of previous miscarriages or stillbirths
6. Multiple consecutively affected child: consider maternal antibodies to fetal neurotransmitter

2. Pregnancy history (Hall 2014)
    1. Diminished fetal movement
    2. Infants born to mothers affected with the following disorders:
        1. Myotonic dystrophy: A child who inherits the gene and is severely affected with resistant contractures.
        2. Myasthenia gravis and multiple sclerosis: Children may be born with congenital contractures.
        3. Diabetes.
    3. Maternal infections leading to CNS or peripheral nerve destruction with secondary congenital contractures:
        1. Rubella
        2. Rubeola
        3. Coxsackievirus
        4. Enterovirus
        5. Akabane
    4. Maternal fever or hyperthermia causing contractures due to abnormal nerve growth or migration
    5. Exposure to teratogens leading to decreased fetal movement
        1. Additive drugs
        2. Alcohol
        3. Curare
        4. Methocarbamol
        5. Misoprostol
        6. Phenytoin
        7. Radiation
        8. Robaxin
    6. Amniotic fluid volume
        1. Oligohydramnios, chronic leakage of amniotic fluid: causes fetal constraint and secondary deformational contractures
        2. Polyhydramnios, hydrops: indicating fetal compromise
    7. Uterine abnormalities
        1. Bicornuate uterus with a septum
        2. Uterine fibroid
    8. Other maternal complications
        1. Toxemia
        2. Severe hypotension at critical time
        3. Severe hypoxia (e.g., carbon monoxide poisoning) during pregnancy
        4. Abnormal fetal lies
        5. Threatened abortion
        6. Attempted termination
        7. Trauma such as trauma to the abdomen
        8. Early amniocentesis
3. Delivery history (Hall 2014)
    1. Breech or transverse fetal position.
        1. Relatively common
        2. Usually normal length of gestation
        3. Induction of labor often prolonged
        4. Fracture of a limb during traumatic delivery in 5–10% of cases
    2. Abnormal placenta, membranes, or cord insertion in case of amniotic bands or vascular compromise. The umbilical cord may be shortened or wrapped around a limb, leading to compression.
    3. Prematurity.
    4. Multiple births or twins.
        1. Lack of movement due to uterine crowding.
        2. The death of one twin may lead to vascular compromise in the remaining twin.
4. Common physical characteristics
    1. Involved extremities
        1. Fusiform or cylindrical in shape
        2. Thin subcutaneous tissue
        3. Absence of skin creases
    2. Deformities
        1. Usually symmetric
        2. Severity increasing distally
        3. Hands and feet typically being the most deformed
    3. Joint rigidity
    4. Associated joint dislocations, especially the hips and, occasionally, the knees
    5. Muscles
        1. Atrophy
        2. Absence
    6. Sensation
        1. Usually intact
        2. Diminished or absent deep tendon reflexes
5. Contractures
    1. Distal joints affected more frequently than proximal joints

2. Types of contractures
    1. Flexion versus extension
    2. Limitation of movement (fixed vs. passive vs. active)
    3. Complete fusion vs. ankylosis and soft tissue contracture
3. Intrinsically derived contractures
    1. Frequently associated with polyhydramnios
    2. Symmetric contractures
    3. Accompanied by taut skin
    4. Pterygia across joints
    5. Lack of flexion creases
    6. Recurrence risk and prognosis dependent on etiology
4. Extrinsically derived contractures
    1. Associated with positional limb anomalies, large ears, loose skin, and normal or exaggerated flexion creases
    2. Excellent prognosis
    3. A low recurrence risk

6. Deformities (Hall 2014)
    1. Limb deformities
        1. Pterygium (webbing)
        2. Shortening
        3. Cord wrapping
        4. Amniotic bands
        5. Compression (e.g., due to cord wrapping)
        6. Absent patella
        7. Dislocated radial heads
        8. Dimples
    2. Face deformities
        1. Asymmetry
        2. Flat nasal bridge
        3. Hemangioma
        4. Jaw deformities including micrognathia and trismus
    3. Other deformities
        1. Scoliosis/kyphosis (fixed or flexible)
        2. Genital deformities
            1. Cryptorchidism
            2. Microphallus
            3. Lack of labia
        3. Hernias
            1. Inguinal
            2. Umbilical
    4. Other features of the fetal akinesia sequence
        1. Intrauterine growth retardation
        2. Pulmonary hypoplasia
        3. Craniofacial anomalies
            1. Hypertelorism
            2. Cleft palate
            3. Depressed nasal tip
            4. High nasal bridge
        4. Functional short gut with feeding problems
        5. Short umbilical cord
    5. Absent or distorted crease abnormalities resulting from aberrant form or function in early hand or foot development
7. Malformations (Hall 2014)
    1. Craniofacial malformations
        1. CNS
            1. Structural malformations
            2. Seizures
            3. Mental retardation/intellectual disability
        2. Skull
            1. Craniosynostosis
            2. Asymmetry
            3. Microencephaly
        3. Eyes
            1. Small and malformed eyes
            2. Corneal opacities
            3. Ptosis
            4. Strabismus
        4. Palate
            1. High-arched
            2. Cleft
            3. Submucous cleft
    2. Respiratory problems affecting lung function
        1. Tracheal and laryngeal clefts and stenosis
        2. Hypoplasia or weak muscles of diaphragm
    3. Limb malformations
        1. Reduction anomalies
        2. Radioulnar synostosis
        3. Syndactyly
        4. Shortened digits
    4. Skin/vasculature abnormalities
        1. Hemangiomas and cutis marmorata
        2. Cold and blue distal limbs
    5. Cardiac problems
        1. Congenital heart defects
        2. Cardiomyopathy

6. Urogenital structural anomalies
    1. Kidneys
    2. Ureters
    3. Bladder
7. Nervous system problems
    1. Loss of vigor
    2. Lethargy
    3. Slow, fast, or absent deep tendon reflexes
    4. Sensory deficits
8. Muscle malformations
    1. Decreased muscle mass
    2. Soft muscle texture
    3. Fibrous bands
    4. Abnormal tendon attachments
    5. Muscle changing with time

8. Connective tissue abnormalities (Hall 2014)
    1. Skin webs (pterygia) across joints with limitation of movement
    2. Skin dimples observed frequently over joints where movement is limited
    3. Soft, doughy, thick, or extensible skin
    4. Decreased or increased subcutaneous fat
    5. Inguinal, umbilical, or diaphragmatic hernias
    6. Thickness in joints
    7. Symphalangism
    8. Abnormalities in tendon attachment and length
    9. Associated skin defects including scalp defects, amniotic bands on limbs, and nail defects
9. Disorders with mainly limb involvement (Hall 1997; Bamshad et al. 2009)
    1. Amyoplasia (Hall et al. 1983a, b, 2014; Sarwark et al. 1990; Sells et al. 1996; Bevan et al. 2007)
        1. The most common type of arthrogryposis seen in clinical practice and constitutes about one third of cases
        2. Incidence: about 1 in 10,000 live births
        3. A sporadic condition, not observed in siblings or offspring (recurrence risk not increased)
        4. Characterized by typical and symmetric congenital, rigid contractures of the limbs
        5. Internally rotated and adducted shoulders
        6. Fixed extended elbows
        7. Pronated forearms
        8. Flexed wrists and fingers
        9. A severe talipes equinovarus deformity
        10. Gracile, osteoporotic long bones
        11. Muscles: hypoplastic (marked decrease in limb muscle mass) and usually replaced by fibrous and fatty tissue
        12. Normal intelligence
    2. Distal arthrogryposes: Bamshad classification (Hall et al. 1982a; Bamshed et al. 1996; Hall 2014)
        1. Type 1A (distotarlar dysmorphism)
            1. An autosomal dominant disorder
            2. Medially overlapping fingers
            3. Tightly clenched fists at birth
            4. Ulnar deviation of fingers and camptodactyly in adults
            5. Positional foot contractures
            6. Usually normal intelligence
            7. Caused by mutations in TPM2, MYBPC1, TNN12, and MYH3
        2. Type 2A (Freeman-Sheldon syndrome, also known as whistling face syndrome)
            1. An autosomal dominant disorder
            2. A mask-like face with a small mouth, giving a whistling face appearance
            3. Deep-set eyes
            4. Small nose with a broad nasal bridge
            5. Epicanthal folds
            6. Strabismus
            7. High-arched palate
            8. Small tongue
            9. An H-shaped cutaneous dimpling on the chin
            10. Flexion of fingers
            11. Equinovarus feet with contracted toes
            12. Kyphoscoliosis
            13. Caused by MYH3 mutation
        3. Type 2B (Sheldon-Hall syndrome) (Toydemir et al. 2006; Toydemir and Bamshad 2009)
            1. An autosomal dominant disorder
            2. Contractures of the distal joints of the limbs
            3. Triangular face

4. Down-slanting palpebral fissures
5. Small mouth
6. High-arched palate
7. Caused by mutations in either *MYH3*, *TNNI2*, or *TNNT3* (~50% of cases)

4. Type 3 (Gordon syndrome)
   1. Short stature (90%)
   2. Cleft palate
   3. Bifid uvula
   4. Epicanthal folds
   5. Congenital ptosis
   6. Short neck
   7. Camptodactyly
   8. Caused by PIEZO2 mutation
5. Type 4 (may include Goodman syndrome)
   1. Scoliosis
   2. Finger contractures
6. Type 5
   1. Ophthalmoplegia (limited ocular motility)
   2. Ptosis
   3. Finger contractures
   4. Caused by PIEZO2 (AD) or ECEL1 (AR) mutations
7. Type 6
   1. Sensorineural hearing loss
   2. Finger contractures
   3. Caused by FGFR3 mutation
8. Type 7 (Hecht syndrome, Kentucky Dutch syndrome)
   1. Trismus pseudocamptodactyly
   2. Inability to fully open mouth
   3. Facultative camptodactyly
   4. Caused by MYH8 mutation
9. Type 8 (autosomal dominant multiple pterygium syndrome)
   1. Multiple pterygium
   2. Finger contractures
10. Type 9 (Beals syndrome, congenital contractural arachnodactyly)
    1. An autosomal dominant disorder
    2. Joint contractures
    3. A long, thin body builds
    4. Crumpling ears
    5. Lacking cardiovascular and ocular abnormalities of Marfan syndrome
    6. Caused by fibrillin 2 mutation
11. Type 10 (congenital plantar contractures)

3. Bony fusion likely to be confused with arthrogryposis
   1. Symphalangism (e.g., fusion of phalanges)
   2. Coalition (e.g., fusion of the carpals and tarsal bones)
   3. Synostosis (e.g., fusion of long bones)
4. Other associated syndromes and conditions
   1. Absence of dermal ridges
   2. Absence of distal interphalangeal (DIP) joint creases
   3. Amniotic bands
   4. Antecubital webbing
   5. Camptodactyly
   6. Congenital clasped thumbs
   7. Familial impaired pronation and supination of forearm
   8. Humeroradial synostosis
   9. Liebenberg syndrome
   10. Nail-patella syndrome
   11. Nievergelt-Pearlman syndrome
   12. Poland anomaly
   13. Radioulnar synostosis
   14. Tel-Hashomer camptodactyly

10. Disorders with involvement of limbs and other body parts (Hall 1997)
    1. Multiple pterygium syndrome (Chen et al. 1980)
       1. Autosomal recessive type: characterized by multiple joint contractures with marked pterygia, dysmorphic facies (flat, sad, motionless facial appearance), and cervical vertebral anomalies
       2. Autosomal dominant type: characterized by multiple pterygia with or without mental retardation
    2. Multiple pterygium syndrome (pterygia with flexion contractures) associated with scoliosis, cleft palate, and malignant hyperthermia
    3. Multiple pterygium syndrome, Escobar type (Escobar et al. 1978)
       1. Webbing of the neck that increases with age
       2. Webbing of the knees and elbows that develops before adolescence
       3. Multiple joint contractures

4. Lumbar lordosis
4. Lethal multiple pterygium syndrome (Chen et al. 1983, 1984; Hall 1984c; Porter 1995; Chen 2015)
    1. An autosomal recessive disorder
    2. Characteristic features
        1. Early lethality
        2. Hydrops fetalis
        3. Cystic hygroma
        4. Dysmorphic facies (hypertelorism, markedly flattened nasal bridge with hypoplastic nasal alae, cleft palate, micrognathia, and low-set ears)
        5. Marked webbing and flexion contractures of multiple joints
        6. Short neck
        7. Small chest
        8. Hypoplastic lungs
    3. Classification by Hall (1984a, b, c) and Entezami et al. (1998)
        1. Type I (Gillin-Pryse-Davis syndrome): multiple pterygia, pulmonary hypoplasia, genital anomalies, and marked flexed extremities with a reduced muscle mass
        2. Type II (Chen syndrome) (Chen et al. 1984): multiple pterygia, hygroma colli, facial anomalies, undermodeled long bones, cartilaginous fusion of joints and bony fusion of the spinous processes of the vertebrae, polyhydramnios, hypoplastic lungs and heart, and diaphragmatic hernia
        3. Type III (van Regemorter syndrome): multiple pterygia, pulmonary hypoplasia, facial anomalies, thin extremities with reduced muscle mass, and fusions of the long tubular bones
        4. Type IV (Herva syndrome): multiple pterygia, degeneration of the anterior horn cells of the spinal cord, and observed particularly in Finland
5. Popliteal pterygium syndrome
    1. An autosomal dominant disorder
    2. Popliteal webs
    3. Cleft lip or palate
    4. Webs in the mouth
    5. Unusual nails
6. Lethal popliteal pterygium syndrome (Bartsocas-Papas syndrome)
    1. An autosomal recessive disorder
    2. Severe webs across the knee
    3. Associated with facial clefting and fused digits (synostosis of the hand and foot bones) in the newborn period
    4. Usually lethal
7. Osteochondrodysplasias known to be associated congenital contractures
    1. Camptomelic dysplasia
    2. Conradi-Hünermann (chondrodysplasia punctata)
    3. Diastrophic dysplasia
    4. Focal femoral dysplasia
    5. Geleophysic syndrome
    6. Kniest dysplasia
    7. Metaphyseal dysplasia, Jansen type
    8. Metatropic dysplasia
    9. Larsen dysplasia
    10. Nail-patella syndrome
    11. Oculodentodigital syndrome
    12. Orocraniodigital syndrome
    13. Osteogenesis imperfecta type II
    14. Otopalatodigital syndrome
    15. Parastremmatic dysplasia
    16. Perinatal lethal osteogenesis imperfecta
    17. Pfeiffer syndrome
    18. Saul-Wilson syndrome
    19. Synspondylism
    20. Spondyloepiphyseal dysplasia congenita
    21. Otospondylomegaepiphyseal dysplasia
8. Other associated syndromes and conditions
    1. Hand muscle wasting and sensorineural deafness
    2. Holt-Oram syndrome
    3. Kuskokwim syndrome
    4. Leprechaunism
    5. Megalocornea with multiple skeletal anomalies
    6. Möbius syndrome
    7. Nemaline myopathy
    8. Ophthalmomandibulomelic dysplasia

9. Prader-Willi habitus/osteoporosis/hand contractures
10. Pseudothalidomide syndrome
11. Puretic-Murray syndrome
12. Sacral agenesis
13. Schwartz-Jampel syndrome
14. Sturge-Weber syndrome
15. Tuberous sclerosis
16. VATER (*v*ertebral defects, imperforate *a*nus, *t*racheo*e*sophageal fistula, *r*adial and *r*enal dysplasia) complex
17. Weaver syndrome
18. Winchester syndrome
19. X-trapezoidocephaly with midfacial hypoplasia and cartilage abnormalities

11. Disorders with limb involvement and CNS dysfunction (Hall 1997)
    1. Associated chromosome abnormalities.
        1. Sex chromosome anomalies (45,X, 47, XXY/48,XXXY, 49,XXXXX, 49, XXXXY)
        2. Autosomal trisomies (4p, 8, 8 mosaicism, 9, 9q, 10p, 10q, 11q, 13, 14, 15, 18, 21)
        3. Other chromosome anomalies
    2. Cerebro-oculo-facio-skeletal syndrome.
        1. A common lethal condition
        2. Contractures
        3. Brain anomalies
        4. Dysmyelination
        5. Microphthalmia
        6. Cataracts
        7. Renal anomalies
        8. Other visceral anomalies
    3. Neu-Laxova syndrome.
        1. A lethal autosomal recessive disorder
        2. Dramatic contractures
        3. Intrauterine growth retardation
        4. Microcephaly
        5. Open eyes
        6. Tight ichthyotic skin
        7. Severe CNS anomalies
    4. Restrictive dermopathy (Verloes et al. 1992).
        1. A lethal autosomal recessive disorder
        2. Contractures and failure of fetal skin to grow normally restricting fetal movement and leading to secondary contractures
    5. Pena-Shokeir phenotype (Chen et al. 1980; Moerman and Fryns 1990): Phenotype is caused by fetal akinesia rather than a specific syndrome.
        1. Short, fixed limbs
        2. Pulmonary hypoplasia
        3. Intrauterine growth retardation
        4. Polyhydramnios
        5. Short umbilical cord
        6. Unusual craniofacies

12. Other associated syndromes and conditions
    1. Adducted thumbs
    2. Bowen-Conradi syndrome
    3. C syndrome
    4. Congenital myotonic dystrophy
    5. Congenital myasthenia gravis
    6. Faciocardiomelic syndrome
    7. Fetal alcohol syndrome
    8. FG syndrome
    9. Marden-Walker syndrome
    10. Meckel syndrome
    11. Meningomyelocele
    12. Mietens-Weber syndrome
    13. Miller-Dieker syndrome
    14. Neu-Laxova syndrome
    15. Neurofibromatosis
    16. Popliteal pterygium with facial clefts
    17. Potter syndrome
    18. Pseudotrisomy 18
    19. Spinal muscular atrophy
    20. Syndrome of cloudy cornea, diaphragmatic defects, and distal limb deformities
    21. Syndrome of craniofacial and brain anomalies and intrauterine growth retardation
    22. Syndrome of cryptorchidism, chest deformity, and contractures
    23. Toriello-Bauserman syndrome
    24. Walker-Warburg syndrome
    25. X-linked lethal arthrogryposis (Hall et al. 1982b)
    26. Zellweger syndrome
13. Prognosis (Hall 1986)
    1. Poor prognosis for ventilator-dependent neonates (Bianchi and Van Marter 1994)

2. Prenatal factors that potentially predict respiratory insufficiency
    1. Decreased fetal movements
    2. Polyhydramnios
    3. Micrognathia
    4. Thin ribs
    5. Decreased fetal movement often resulting in delayed developmental milestones
3. Skeletal changes secondary to the original deformities
    1. Scoliosis
    2. Deformed carpal and tarsal bones
    3. Under growing of limbs after longstanding contractures
    4. External genitalia often abnormal (e.g., cryptorchidism, absent labia majora) because of abnormal hip position
4. Intrinsically or extrinsically derived defects
    1. Extrinsically derived contractures: an excellent prognosis
    2. Intrinsically derived contractures: a prognosis dependent on etiology
5. Prognosis depending on the condition's natural history
    1. Developmental landmarks (attainment of motor, social, and language milestones)
    2. Growth of affected limbs
    3. Progression of contractures
    4. CNS damage (lethal, stable, improving)
    5. Asymmetry of contractures (improving, worsening)
    6. Changes in trunk or limbs
    7. Intellectual ability
    8. Socialization
6. Prognosis depending on the patient's response to therapy
    1. Spontaneous improvement
    2. Response to physical therapy
    3. Response to casting
    4. Types of surgery at appropriate time
    5. Development of motor strength proportionate to limb size

Diagnostic Investigations

1. Laboratory evaluation (Hall 1981, 2014)
    1. Laboratory tests, in general, are not useful.
    2. Creatine phosphokinase (CPK) levels when the following conditions are present:
        1. Generalized weakness
        2. Doughy or decreased muscle mass
        3. Progressive worsening
    3. Viral cultures for an infectious process (intrauterine growth retardation, eye involvement, and hepatosplenomegaly)
    4. Immunoglobulin M levels and specific viral titers (e.g., coxsackievirus, enterovirus, Akabane virus) in the newborn for intrauterine infection
    5. Maternal antibodies to neurotransmitters in the infant indicating myasthenia gravis or recurrent affected pregnancies without diagnosis
    6. Video of movement including facial, range of movement, and strength repeat at regular intervals
    7. Cytogenetic study/comparative genomic hybridization (CGH) array indicated in the following situations:
        1. Multiple organ or system involvement
        2. Presence of CNS abnormalities, such as microcephaly, mental retardation, lethargy, degenerative changes, or eye anomalies
        3. Streaky or segmental involvement
        4. Fibroblast chromosome study if lymphocyte chromosomes are normal and the patient has mental retardation/intellectual disability without diagnosis
        5. Consider exome studies if family available
    8. Nuclear DNA mutation analysis to identify certain disorders
        1. Exome sequencing identifies aa dominant TNNT3 mutations in a large family with distal arthrogryposis (Daly et al. 2014)

2. Spinal muscular dystrophy
9. Mitochondrial mutation analysis to identify certain disorders, such as mitochondrial myopathy
10. Spinal muscular atrophy (SMN) DNA testing if accompanying hypotonia and intellectual disability
11. Metabolic screening if presence of organomegaly

2. Imaging studies
   1. Patient's photographs
      1. To document the extent of deformities (range of motion and position of arthrogryposis)
      2. To assess progress during treatment
   2. Radiographs to evaluate the following skeletal and joint abnormalities:
      1. Bony abnormalities (e.g., gracile bones, fusions, extra or missing carpals, and tarsals)
      2. Disproportionately short stature (i.e., skeletal dysplasias)
      3. Scoliosis
      4. Ankylosis
      5. Absence of patella
      6. Humeroradial synostosis
      7. Dislocations (hips, radial head, patella)
   3. Ultrasonography
      1. To evaluate the CNS and other viscera for anomalies
      2. To establish potential muscle tissue
   4. CT scan to evaluate the CNS and the muscle mass
   5. MRI to evaluate CNS (brain and spinal cord) and muscle mass obscured by contractures
   6. Ophthalmological evaluation for opacity and retinal degeneration
3. Histologic studies (Banker 1985, 1986)
   1. Neurogenic types
      1. Muscle fiber type predominance or disproportion is the most common neurogenic abnormality in arthrogryposis (26%). These are nonspecific alterations.
      2. Dysgenesis of the motor nuclei of the spinal cord and brainstem causes the replacement of fasciculi of muscle fibers by small muscle fibers and adipose tissue. Examples include Pierre Robin syndrome and Möbius syndrome.
      3. Dysgenesis of the CNS: the second most common neurogenic abnormality in arthrogryposis (23%), with disorganization and decrease in neurons of the cortex and motor nuclei of the brainstem and spinal cord. Clinical syndromes with this abnormality include trisomy 18, partial deletion of the long arm of chromosome 18 syndrome, and Zellweger syndrome.
      4. Dysgenesis of the anterior horn, another common neurogenic abnormality in arthrogryposis.
      5. Spinal muscular atrophy (e.g., Werdnig-Hoffmann disease): another neurogenic abnormality in arthrogryposis.
   2. Myopathic types
      1. Central core disease: a form of arthrogryposis in which the central portion of each muscle fiber contains a zone in which oxidative enzyme activity is absent.
      2. Nemaline myopathy indicated by abnormal thread-like structures in muscle cells. In type I nemaline myopathy, nemaline rods are present. In type II, the number of fibers with central nuclei is increased.
      3. Congenital muscular dystrophy indicated by muscle fibers that demonstrate a rounded configuration and conspicuous variation in diameter. Perimysial and endomysial connective tissues are increased markedly.
      4. Mitochondrial cytopathy indicated by numerous ragged red fibers on muscle biopsy. It is associated with CNS abnormalities consistent with mitochondrial disease (Gordon 1998).
      5. Myoneural junction abnormality (e.g., congenital myasthenia gravis): another myopathic type of arthrogryposis.

4. Procedures
    1. Eye examination for opacities and retinal degeneration.
    2. Skin biopsy for culture of fibroblasts to be used for chromosome analysis and metabolic studies.
    3. Muscle biopsy:
        1. Probably the most important diagnostic procedure (Thompson and Bilenker 1985). It should be included in all autopsies and at time of surgery.
        2. Do biopsy earlier and examine mitochondria, if elevated CPK or unusual muscle response present.
        3. Distinguish myopathic from neuropathic conditions by obtaining muscle specimens from normal and affected areas.
        4. Special histopathologic and electron micrographic studies to evaluate fatty and connective tissue replacement of muscle fibers and variations in fiber size, such as decreased fiber diameter. All are nonspecific signs of muscle atrophy.
    4. Electromyography (EMG) (Södergård et al. 1997) in normal and affected areas useful in differentiating neurogenic and myopathic causes (Gordon 1998).
    5. Nerve conduction tests to measure conduction velocities in motor and sensory nerves. These should be performed when a peripheral neuropathy is suspected.
    6. An autopsy to investigate the following:
        1. CNS (i.e., brain neuropathology)
        2. Spinal cord (number and size of anterior horn cells, presence or absence of tracts at various levels)
        3. Ganglia and peripheral nerves
        4. Eye (i.e., neuropathology)
        5. Muscle tissue from different muscle groups (i.e., electron microscopy and special stains)
        6. Fibrous bands replacing muscle
        7. Tendon attachments
        8. Other visceral anomalies, malformations, deformations, and disruptions

Genetic Counseling

1. Recurrence risk: Recurrence risk depends on whether the contractures are extrinsically or intrinsically derived. Extrinsically derived contractures have a low recurrence risk, while the recurrence risk for intrinsically derived contractures depends on etiology. Arthrogryposis may be inherited in the following ways with different recurrence risks:
    1. Patient's sib
        1. Autosomal recessive: 25%
        2. Autosomal dominant: not increased unless a parent is affected or having gonadal mosaicism
        3. X-linked recessive: 50% of male sibs affected if the mother is a carrier
    2. Patient's offspring
        1. Autosomal recessive: not increased unless the spouse is also a carrier.
        2. Autosomal dominant: 50%.
        3. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
    3. Multifactorial: Combined effects of multiple genes and environmental factors cause multifactorial traits. For most multifactorial diseases, empirical risks (risks based on direct observation of data) have been derived. For example, empirical recurrence risks of neural tube defects for siblings of an affected individual range from 2% to 5% in most populations.
    4. Mitochondrial: A small but significant number of diseases are caused by mitochondrial mutations. Because of the unique properties of mitochondria, these diseases display characteristic modes of inheritance (i.e., inherited exclusively through the maternal line) with wide phenotypic variability. Only females can transmit the disease mutation to their offspring (e.g., distal type IIB arthrogryposis).
    5. Sporadic: For those families in which a specific diagnosis cannot be made, the empiric recurrence risk to unaffected parents of an affected child, or to the affected

individual with arthrogryposis, is about 3–5%.

2. Prenatal diagnosis (Bendon et al. 1987; Baty et al. 1988; Hageman et al. 1988; Dimitraki et al. 2011):
    1. Prenatal ultrasonography to detect the following:
        1. Diminished fetal movement (main manifestation shared by various conditions with congenital contractures)
        2. Joint contractures (bilateral fixed flexion deformities of the hands, elbows, shoulders, hips and knees, or talipes)
        3. Detection of subcutaneous edema (fetal hydrops)
        4. Cystic hygroma
        5. Increased nuchal translucency (Madazli et al. 2002)
        6. Abnormal fetal lie
        7. Polyhydramnios or oligohydramnios
        8. Other associated anomalies (e.g., distended bladder in early urethral obstruction sequence; microcephaly, hydrocephaly, or hydranencephaly in "cerebral dysgenesis"-induced congenital contractures)
    2. Chromosome analysis by amniocentesis or CVS for chromosome disorders
    3. Molecular genetic analysis for certain genetic disorders with demonstrable mutations
3. Management (Shriner's Manual) (McCall and Gates, 1999, Personal communication):
    1. No completely successful approach to treatment
    2. Overall goals
        1. Proper alignment of the lower limbs
        2. Upper limb function for self-care
    3. Early vigorous physical therapy to stretch contractures
        1. To improve joint motion
        2. To avoid muscle atrophy
        3. Excellent functional outcome in patients with amyoplasia or distal arthrogryposis
        4. May be harmful in diastrophic dysplasia because it may lead to joint ankylosis
        5. Frequent recurrence of deformities following stretching, often requires surgery
    4. Splinting combined with physical therapy
        1. Preferable to continuous casting
        2. Night splinting after surgical procedures indicated to maintain increased range of motion
    5. Feeding assistance and intubation needed in patients with severe trismus
    6. Specific joint problems
        1. Should be addressed with regard to treatment of other joints and the goals for the patient
        2. Early soft tissue surgery with osteotomies when the growth is completed
        3. Tenotomies accompanied by capsulotomies in soft tissue release procedures
        4. Long-term bracing and assistive devices usually needed
    7. Feet
        1. A rigid talipes equinovarus deformity: the most common deformity (Guidera and Drennan 1985)
        2. Bilateral talectomy in the management of bilateral rigid clubfeet (Letts 1999)
        3. Goal of treatment: a plantigrade, braceable foot
    8. Knees (Thomas et al. 1985; Murray and Fixsen 1997)
        1. Goal of treatment: an extended knee for ambulation
        2. Fixed flexion knee deformities more common than fixed extension knee deformities and more resistant to treatment
    9. Hips (Huurman and Jacobsen 1985; Staheli et al. 1987)
        1. Hip surgery follows foot and knee surgery, especially in the presence of knee extension deformities.
        2. Hip surgery in patients younger than 1 year to facilitate ambulation. In some patients with bilateral hip dislocations and extremely mobile hips, open reduction may be attempted.

3. A one-stage open reduction and varus shortening femoral derotational osteotomy for all unilateral hip dislocations and those bilateral hip dislocations that have a less severe generalized involvement and an aggressive traction program with appropriate soft tissue releases during the neonatal period for patients with subluxation and/or marked limitation of motion of the hip (St. Clair and Zimbler 1985)

10. Upper extremities (Bennett et al. 1985; Williams 1985)
    1. Treatment involves development of self-help skills (e.g., feeding and toileting) (Bayne 1985) and mobility skills (e.g., pushing out of chair and using crutches).
    2. Consider overall function of the entire extremity rather than function of the individual joints in evaluating the upper extremities.
    3. Consider upper extremity surgery until the patient is older than 5–6 years.
    4. Emphasis is placed on evaluation of the disability by repeated testing and observation. In many cases, the deformities will be accepted and improvements in function will be gained by orthoses or attention to details of seating, dressing, and toileting.
    5. Surgery is indicated in some cases, especially at the elbow, to obtain mobility, flexor power, or both. Arthrodesing the wrist is also useful in some cases.
    6. When surgery is indicated, it is often desirable to rearrange all three levels – shoulder, elbow, and wrist.
11. Elbows
    1. Goals: passive or active flexion capability (feeding arm) and extension capability (toilet arm) (Axt et al. 1997).
    2. Achieve elbow mobility before correcting a wrist deformity because the elbow is crucial to hand function.
12. Wrists
    1. Stretching and splinting for the major wrist deformity (flexion with ulnar deviation)
    2. Proximal row carpectomy with or without fusion for a severe deformity
13. Fingers
    1. Passive stretching and splinting for minimal to moderate flexion deformities
    2. Soft tissue releases with proximal interphalangeal joint fusions for more severe deformities
    3. Thumb-in-palm deformity to be corrected to provide opposition-improved grasp
14. Spine
    1. The spine affected in about one third of patients.
    2. Scoliosis beginning early and progressing to become a long, severe, rigid, C-shaped curve. This curve responds poorly to orthoses, as it is progressive.
    3. Curves greater than 35°: treated with spinal fusion and instrumentation.
15. Complications
    1. Anesthesia: difficult to administer because vascular access often is restricted.
    2. Intubation: posing problems for patients with a small underdeveloped jaw, limited movement of the temporomandibular joint, or a narrow airway.
    3. Osseous hypoplasia associated with decreased mechanical use in developing bone: prone to fracture at multiple sites. Multiple perinatal fractures have been observed in osteopenic bones.
16. Feeding and toileting devices for a child with arthrogryposis (Hall and Hammock 1979)
17. Summary of the 2nd International Symposium on Arthrogryposis, St. Petersburg, Russia, September 17–19, 2014 (Hall et al. 2015)
    1. Ponseti type casting should begin by 1–2 months of age for clubfeet, and knee dislocations should be casted.
    2. Early imaging of muscle by ultrasound or MRI: important as a baseline for

determination of best therapy and long-term outcomes, for instance, as to whether or not walking can be anticipated.
3. Reports of dramatic improvement in the upper limbs of individuals with amyoplasia, utilizing vigorous physical therapy and muscle transfers.
4. Orthotics for adults with arthrogryposis for stabilization during walk and a carbon spring built into an ankle-foot orthosis may function as muscle when muscles are absent or very weak.
5. Use of the "8-plate": provides temporary hemiepiphysiodesis with a small plate and screws. It has revolutionized the treatment of malaligned knees in the older child, since it is less traumatic than osteotomies and spares muscle tissue.
6. Growing rods: very useful in individuals with arthrogryposis and scoliosis.
7. Adults with arthrogryposis should keep as active as possible, since immobilization in adults with arthrogryposis leads to disproportionate weakness and muscle atrophy.

18. Physical activity
    1. Limited because of existing orthopedic problems
    2. Passive motion therapy for infants with arthrogryposis (Palmer et al. 1985).
    3. As a group, patients cope well socially and participate in social activities corresponding to their needs.
    4. More restricted walking in patients with flexion contractures of the lower extremities than in those with extension contractures. Flexion contractures of the hips severely impair walking ability.
    5. Contracture of the elbow causing a significant degree of disability in hand function.
    6. Impossible to use crutches in patients with upper extremity involvement associated with severe spinal deformity.
    7. Dependent on help from other people to a higher degree in patients with more severe joint involvement than those with less severe joint involvement.
    8. Independent living with productive lives for most children with normal intelligence despite severe handicaps. However, many remain partially dependent on others, such as parents, relatives, and government subsidy. Dependency is related more closely to personality, education, and overall coping skills than to the degree of physical deformity.
    9. Good family support, a proper educational environment, and promotion of independence at an early age: required to achieve maximal function in addition to appropriate surgical correction (Carlson et al. 1985; Hahn 1985).

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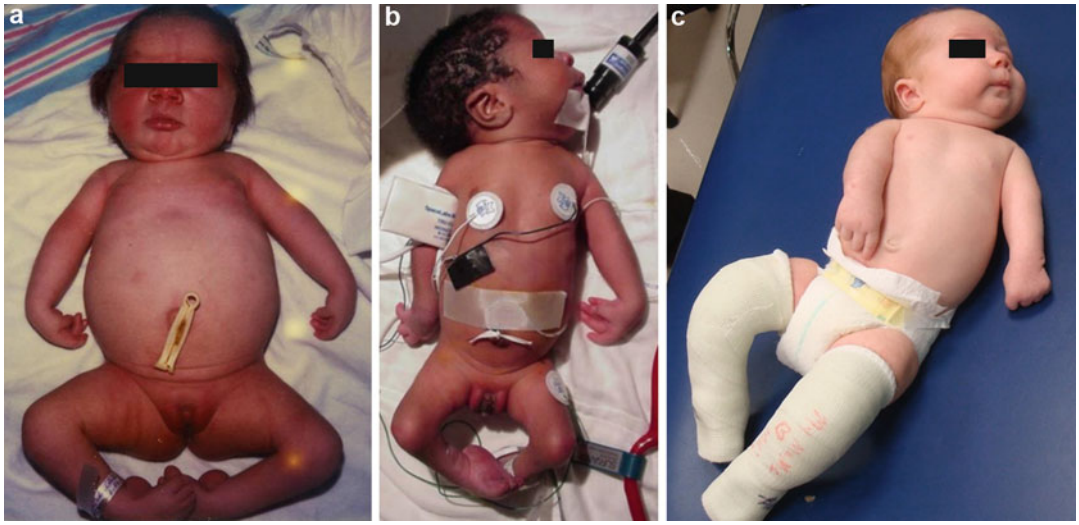

Fig. 1 (**a**–**c**) Three infants with amyoplasia congenita showing typical, symmetrical positioning of the limbs, internally rotated and adducted shoulders, fixed extended elbows, pronated forearms, flexed wrists and fingers, and severe talipes equinovarus deformity

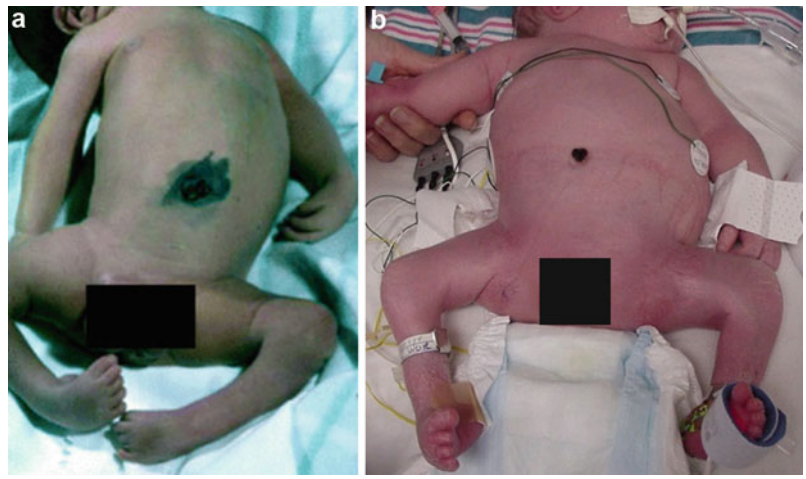

Fig. 2 (**a**–**b**) Two infants with arthrogryposis multiplex congenita characterized by flexion contractures of the knees and fingers and equinovarus deformities of the feet

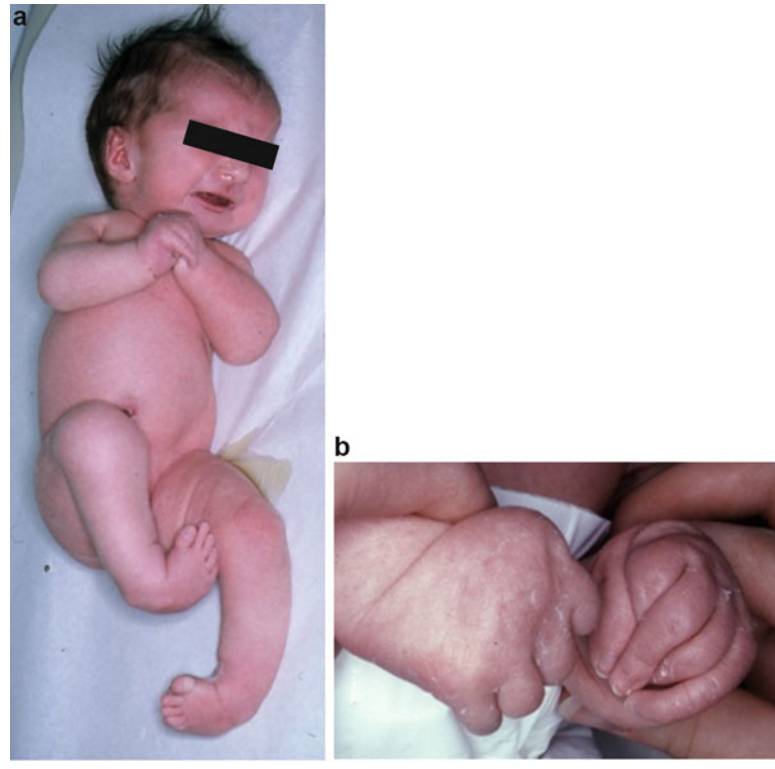

Fig. 3 (**a**–**b**) An infant with distal arthrogryposis showing predominantly distal contractures with overlapping finger contractures, ulnar deviation of fingers, and clubfeet

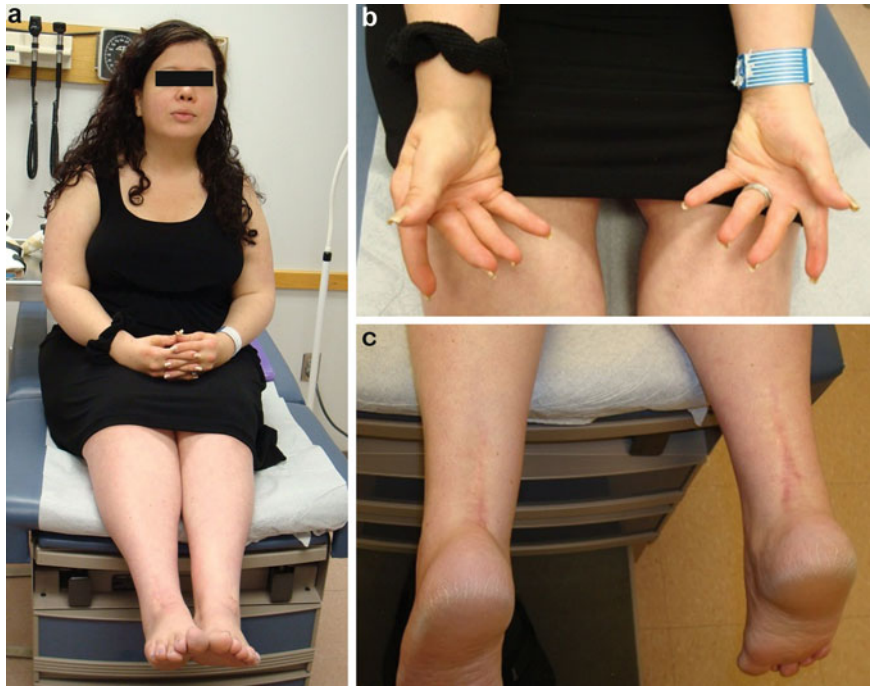

Fig. 4 (**a**–**c**) A 33-year-old female was followed for arthrogryposis multiplex congenita. At birth, flexion contractures of the fingers and hands, dysplastic hips, bilateral rocker bottom feet, and "generalized stiffness" were noted. At recent visit, flexion contractures of the elbows, limitation of supination of the wrists, contractures of the thumbs and PIP joints, and operation scars of webbing release between 1st and 2nd fingers and Achilles tendon release were noted

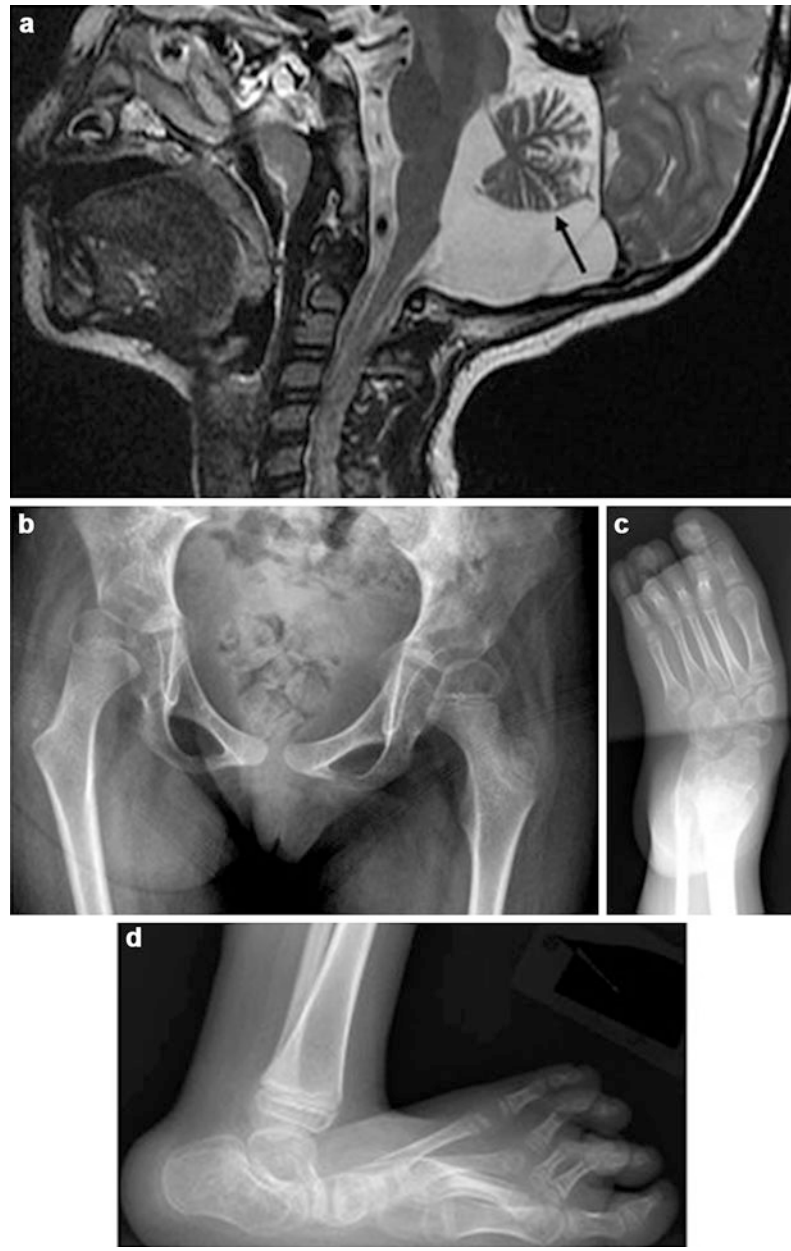

Fig. 5 (**a**–**d**) A 4-year-old girl was seen for arthrogryposis multiplex congenita. MRI image of the brain (**a**) demonstrates hypoplastic cerebellum, particularly the vermis (*black arrow*). This finding can be seen in the neurogenic arthrogryposis multiplex. Pelvic radiography (**b**) demonstrates generalize osteopenia, bilateral coxa valga, and mild lateral uncovering of the femoral heads. Radiographs of the left foot demonstrate osteopenia, exaggerated planovalgus deformity (**c**), and a rocker-bottom configuration (**d**). The right foot has similar deformities (not shown). The family and birth histories were not available since the patient was adopted. High-resolution chromosome study was normal. Molecular studies, including *TPM2*, *MYH3*, and *SMN1* (homozygous deletion of *SMN1*) genes, were negative (Courtesy of Dr. Grace Guo)

Asphyxiating Thoracic Dystrophy

Contents

In 1955, Jeune et al. described familial asphyxiating thoracic dystrophy (ATD) in a pair of siblings with severely narrow thoraxes. This condition is also known as Jeune syndrome. Incidence is estimated at 1 per 100,000–130,000 live births (den Hollander et al. 2001).

Jeune syndrome, a potentially lethal congenital dwarfism, is a rare autosomal recessive disorder characterized by typical skeletal dysplasias, such as a narrow thorax and micromelia, with respiratory and renal manifestations. Respiratory manifestations vary widely from respiratory failure and infantile death to a latent phenotype without respiratory symptoms.

Synonyms and Related Disorders

Jeune Syndrome; Thoracic-pelvis-phalangeal dystrophy/dysplasia

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Genetically heterogeneous
    1. One locus mapped to chromosome 15q13 (Morgan et al. 2003).
    2. Families with both mild and severe forms of ATD mapped to 15q13.
    3. Five consanguineous families sharing a 1.2 cM region of homozygosity between D15S165 and D15S1010.
    4. Mutations in the intraflagellar transport 80 (*IFT80*) gene (Beales et al. 2007) have been recently identified in 3/39 families originating from Pakistan and Turkey, ascribing ATD to the ciliopathy group (Morgan et al. 2003). However, *IFT80* was excluded in a series of 26 fetuses and children belonging to 14 families diagnosed with either ATD or short rib-polydactyly syndrome, type III (SRP III) (Dagoneau et al. 2009).
    5. *DYNC2H1* Mutations: cause asphyxiating thoracic dystrophy (also cause SRP III) (Dagoneau et al. 2009).
        1. Studying a consanguineous family from Morocco, another locus was mapped to chromosome 11q14.3-q23.1 in a 20.4 Mb region and identified homozygous mutations in the cytoplasmic dynein 2 heavy chain

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1 (*DYNC2H1*) gene in the affected children.
2. Compound heterozygosity for *DYNC2H1* mutations was also identified in four additional families.
3. Among the five families, three were diagnosed with ATD and two included pregnancies terminated for SRP type III.
4. *DYNC2H1* is a component of a cytoplasmic dynein complex and is directly involved in the generation and maintenance of cilia.
5. ATD and SRP type III are variants of a single disorder belonging to the ciliopathy group.

6. To date, mutations in IFT80, DYNC2H1, TTC21B, and WDR19 have been reported in ATD (Baujat et al. 2013). The identification of IFT80 mutations in ATD has first confirmed that ATD belongs to the spectrum of cilia disorders (Beales et al. 2007). More recently, mutations in DYNC2H1 (dynein cytoplasmic 2 heavy chain 1), TTC21B (Tetratricopeptide repeat-containing Hedgehog Modulator 1), and WDR19 (WD Repeat-Containing Protein 19) have been reported in ATD cases (Dagoneau et al. 2009; Merrill et al. 2009; Davis et al. 2011; Bredrup et al. 2011).

Clinical Features

1. Wide phenotypic variability (Oberklaid et al. 1977; Özçay et al. 2001; Tüysüz et al. 2009; de Vries et al. 2010)
2. Classification of ATD
    1. Lethal form
    2. Severe form
    3. Mild form (Giorge et al. 1990)
    4. Latent form (Kozlowski and Masel 1976)
3. Short-limbed dwarfism
4. Growth retardation
5. Respiratory distress
    1. Respiratory distress secondary to a small thorax.
        1. Motionless thorax
        2. Abdominal respiration
        3. Considerable supraclavicular, suprasternal, and intercostal space retraction on inspiration
    2. Severe dyspnea and extreme cyanosis in severe cases.
    3. Some infants with only respiratory symptoms in conjunction with infection.
    4. Some individuals lack respiratory symptoms in infancy or childhood.
6. Chest deformity of varying degree.
    1. A long, narrow, and abnormally small thorax with reduced thoracic cage capacity.
    2. Lung hypoplasia and respiratory distress usually leading to early death.
    3. The symptom of small thorax usually improves with age for those who survive early childhood.
7. Limbs.
    1. Variable micromelia and short digits with bulbous terminal phalanges
    2. Occasional postaxial polydactyly of the hands and feet
8. Eyes: occasional retinal degeneration (Allen et al. 1979; and retinal aplasia (Phillips et al. 1979).
9. Occasional intestinal malabsorption.
10. Renal lesions (Herdman and Lalnger 1968; Bernstein et al. 1974; Shah et al. 1980):
    1. Focal cystic change and severe cystic dysplasia
    2. Renal failure developing during infancty, early adolescence, or second decade of life
11. Polyuria, polydipsia, and hypertension occur during the second or third year of life.
12. Occasional involvement of the liver.
    1. Prolonged neonatal jaundice
    2. Polycystic liver disease
    3. Hyperplasia of the bile ducts
    4. Congenital hepatic cirrhosis
13. Occasional involvement of the heart.
    1. Cardiac failure secondary to increased pulmonary vascular resistance, thoracic constriction, and alveolar hypoplasia

2. Possible intrinsic myocardial disease
14. Cystic changes of pancreatic ducts and pancreatic exocrine insufficiency occur in long-term survivors.
15. Occasional involvement of the teeth, nails, and other organs.
16. Occasional association with Hirschsprung disease (Aurora and Wallis 1999)
17. Prognosis.
    1. Difficult to predict in each individual case because frequent pulmonary complications and cystic renal lesions are not always directly related to severity of skeletal changes.
    2. The skeletal dysplasia of this entity is compatible with life, though respiratory failure and infections are often fatal during infancy.
    3. Considerable variation in the severity of thoracic constriction: For those patients who survive infancy, the thorax tends to revert to normal with improving respiratory function. This suggests that the lungs have a normal growth potential and the respiratory problems are secondary to restricted rib cage deformity.
    4. Renal failure: Renal involvement is the major prognostic factor in those patients who survive the respiratory insufficiency during infancy.
    5. Short stature in survivors.
18. Morbidity and mortality.
    1. Alveolar hypoventilation
        1. The most common and prominent clinical presentation
        2. Caused by impaired chest expansion as a result of short horizontally placed ribs
    2. Bilateral microcystic renal disease gradually progressing to tubular atrophy and renal failure
    3. Most patients (approximately 60–70%) dying from respiratory failure in early infancy and early childhood
    4. Chronic renal failure ensuing in survivors
    5. Few patients reaching adolescence or adulthood
19. ATD overlapping with SRP III (Verma-Naumoff syndrome).
    1. Both conditions share the same radiological features (including the polydactyly).
    2. SRP type III (Ho et al. 2000; Superti-Furga and Unger 2007).
        1. More severe condition
        2. Early prenatal expression and lethality
        3. Variable malformations
            1. Cleft lip and/or palate
            2. Polycystic kidneys
            3. Gastrointestinal, urogenital, brain, and/or cardiac malformations
        4. Severely shortened tubular bones having round metaphyseal ends with lateral spikes

Diagnostic Investigations

1. Laboratory studies
    1. Urinalysis.
        1. Hematuria
        2. Proteinuria
        3. Defective urine-concentrating capacity
    2. Arterial blood gas (ABG): hypoxia and hypercarbia in room air reflecting severe restrictive lung disease.
    3. Whole-genome sequencing screen reveals *DYNC2H1* mutations as a frequent cause of Jeune asphyxiating thoracic dystrophy, affecting about a third of all families (Schmidts et al. 2013).
2. Imaging studies (Pirnar and Neuhauser 1966; Langer 1968; Cortina et al. 1979; Chen 2015)
    1. Newborn and infant radiography
        1. Small and bell-shaped thorax with reduced transverse and anterior-posterior diameter
        2. Abnormal clavicles (“bicycle handlebar shaped”)
        3. Short and horizontally oriented ribs with irregular costochondral junctions and bulbous and irregular anterior ends
        4. Abnormal pelvis
            1. Short squared iliac wings

2. Trident appearance of acetabular margin
5. Short limbs relative to trunk
6. Variable limb shortening
7. Short phalanges, metacarpals, or metatarsals with or without polydactyly
8. Premature ossification of the capital femoral epiphyses

2. Childhood radiology
1. Relatively larger thorax with growth of ribs compared to infancy
2. Short ilium with normal flaring of iliac wings
3. Striking cone-shaped epiphyses and early fusion between the epiphyses and metaphyses of the distal and middle phalanges
4. Short distal and middle phalanges
5. Varying shortening of extremities relative to trunk
6. Subtypes of ATD
1. Type I: irregular metaphyseal ends
2. Type II: smooth metaphyseal ends

3. Pulmonary function test to detect severe restrictive lung disease
4. Histology (Turkel et al. 1985; Chen 2015)
1. Lungs: Hypoplastic due to a marked reduction in the number of alveolar ducts and alveoli (hypoplasia of alveoli) (Finegold et al. 1971)
2. Cartilages (Yang et al. 1976, 1987): retarded endochondral ossification in both types
1. ATD type I: irregular cartilage-bone junction with patchy distribution of physeal growth zone of chondrocytes
2. ATD type II: smooth cartilage-bone junctions
3. Kidneys
1. Cystic renal dysplasia and hypoplasia
2. Nephronophthisis or interstitial nephritis
1. Diffuse interstitial and periglomerular fibrosis
2. Round cell lymphocytic infiltration
3. Hyalinized glomeruli
4. Pericapsular thickening
5. Thickened basement membrane
6. Dilated or atrophic tubules
3. Pyelonephritis with scarring
4. Distortion of renal parenchyma
4. Liver (Yerian et al. 2003)
1. Periportal hepatic fibrosis
2. Bile duct proliferation
3. Early cirrhosis

Genetic Counseling

1. Recurrence risk
1. Patient's sib: 25%
2. Patient's offspring: usually lethal, not surviving to reproductive age
2. Prenatal diagnosis by ultrasonography
1. Detection of affected second- and third-trimester fetuses of at-risk families
2. Characteristic ultrasonographic findings (Elejalde et al. 1985; Schinzel et al. 1985; Skiptunas and Weiner 1987; Chen et al. 1996; Hsieh et al. 1999; Tongsong et al. 1999; Das et al. 2002; Chen 2015)
1. Narrow thorax
2. Short hypoplastic ribs
3. Short tubular bones
4. Renal cystic changes
3. Other ultrasonographic findings
1. Polyhydramnios
2. Absent or feeble fetal respiratory movements
3. Increased nuchal translucency
4. With or without polydactyly
5. Ventriculomegaly
6. A single umbilical artery
3. Management (Chen 2015)
1. Medical care
1. Supportive care
2. Mechanical ventilation
1. Urgently required in the most severe cases, those when

respiratory distress develops immediately after birth
2. Less severe cases gradually progressing to respiratory failure as a result of multiple recurrent pulmonary infections
3. Treat respiratory infections vigorously with antibiotics, endotracheal suctioning, and postural drainage
4. Nasogastric or gastrostomy feedings if needed
5. Ursodeoxycholic acid used to control the progression of the hepatic dysfunction (Labrune et al. 1999)

2. Surgical care
1. Surgery indicated only in the most severe cases in which failure to intervene will result in progressive pulmonary damage and eventual death (Sharoni et al. 1998). No data is currently available on long-term follow-up care of patients who have been surgically treated.
2. Expansion thoracoplasty utilizing various surgical techniques (Barnes et al. 1971; Kaddoura et al. 2001).
1. Splitting the sternum or the rib cage and maintaining the separation with methacrylate (Todd et al. 1986; Sarimurat et al. 1998).
2. Rib grafts.
3. Homologous bone grafts.
4. Lateral rib cage expansion (Davis et al. 1995) using staggered superiosteal rib osteotomies and rigid titanium miniplate and screw augmentation and stabilization.
5. Modified Bailey rib approximator to provide a calibrated dynamic separation for the sternum after the primary procedure of midsternotomy and methylmethacrylate sternoplasty.
6. Treating Jeune syndrome patients with Dynamic Postero-Lateral Expansion Thoracoplasty, using 70 mm radius VEPTR, likely translates into improved respiratory function, decreasing mortality, and clinical respiratory morbidity (O'Brien et al. 2015).
3. Dialysis and renal transplantation (Amirou et al. 1998) indicated for renal failure. Recently, cadaver renal transplantation was successful in a 10-year-old boy with Jeune syndrome type 2 (Amirou et al. 1998).
4. Surgical complications.
1. Pneumothorax
2. Mucous plugging of a bronchus
3. Repeated infections
4. Progressive herniation of lung through sternal defect
5. Cardiac insufficiency

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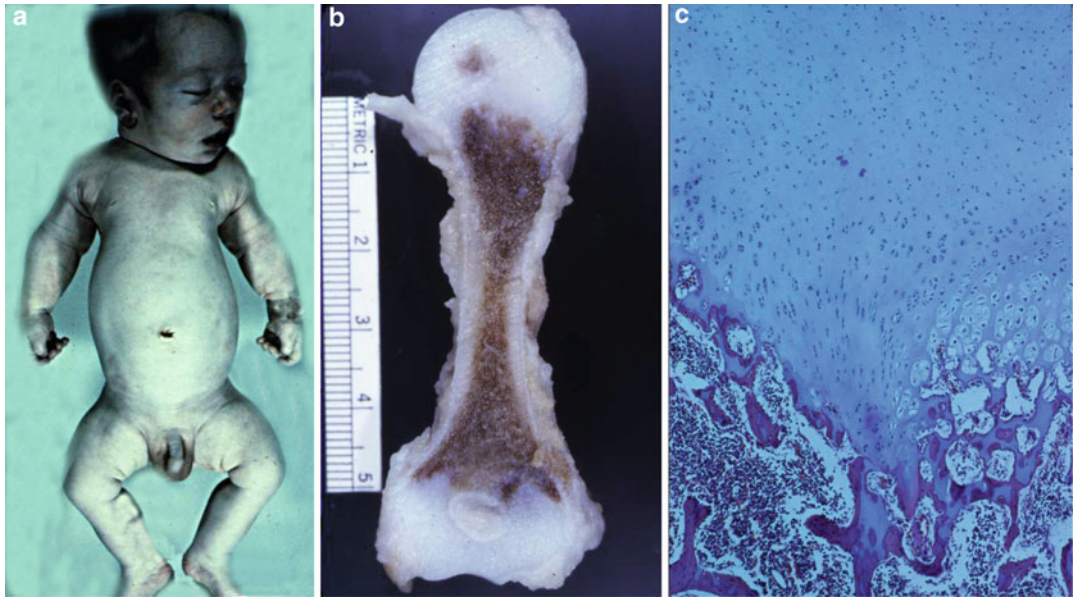

Fig. 1 (**a**–**c**) A neonate died of respiratory insufficiency. The chest is severely narrow and limbs mildly shortened (Yang et al. 1976). The longitudinal section of the humerus shows irregular cartilage-bone junctions. There is a premature ossification center in the proximal epiphysis. The photomicrograph of the physeal growth zone shows scattered areas (*left* two third of the picture) of severe retardation and disorganization. Consequently, the cartilage-bone junction is irregular

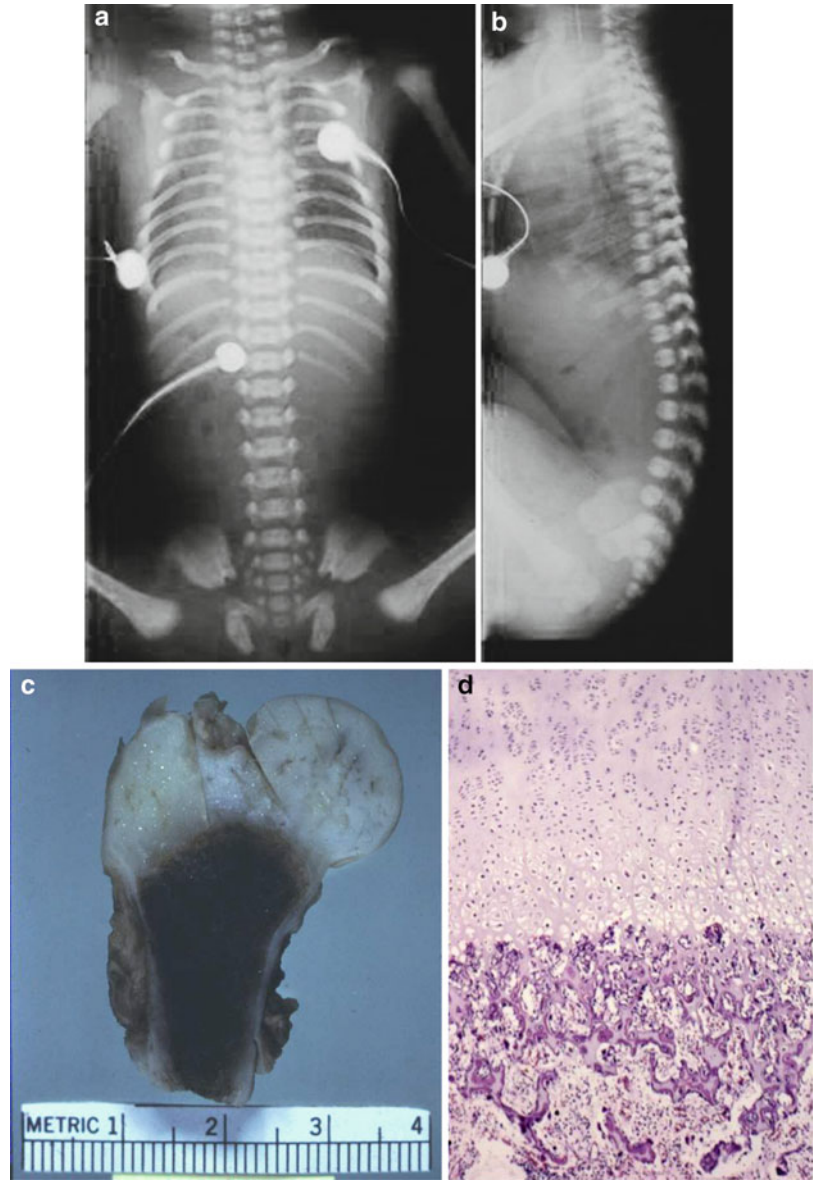

Fig. 2 (**a**–**d**) Radiographs of the skeletal system of a neonate with type II asphyxiating thoracic dystrophy. The ribs are short. The ilia are vertically shortened. The findings are similar in both types I and II. However, the metaphyseal ends of tubular bones do not show irregularity or spurs as in type I. Photomicrograph of the proximal femur shows generalized retardation and disorganization of the physeal growth zone. The cartilage columns in the metaphysis form a lattice-like meshwork

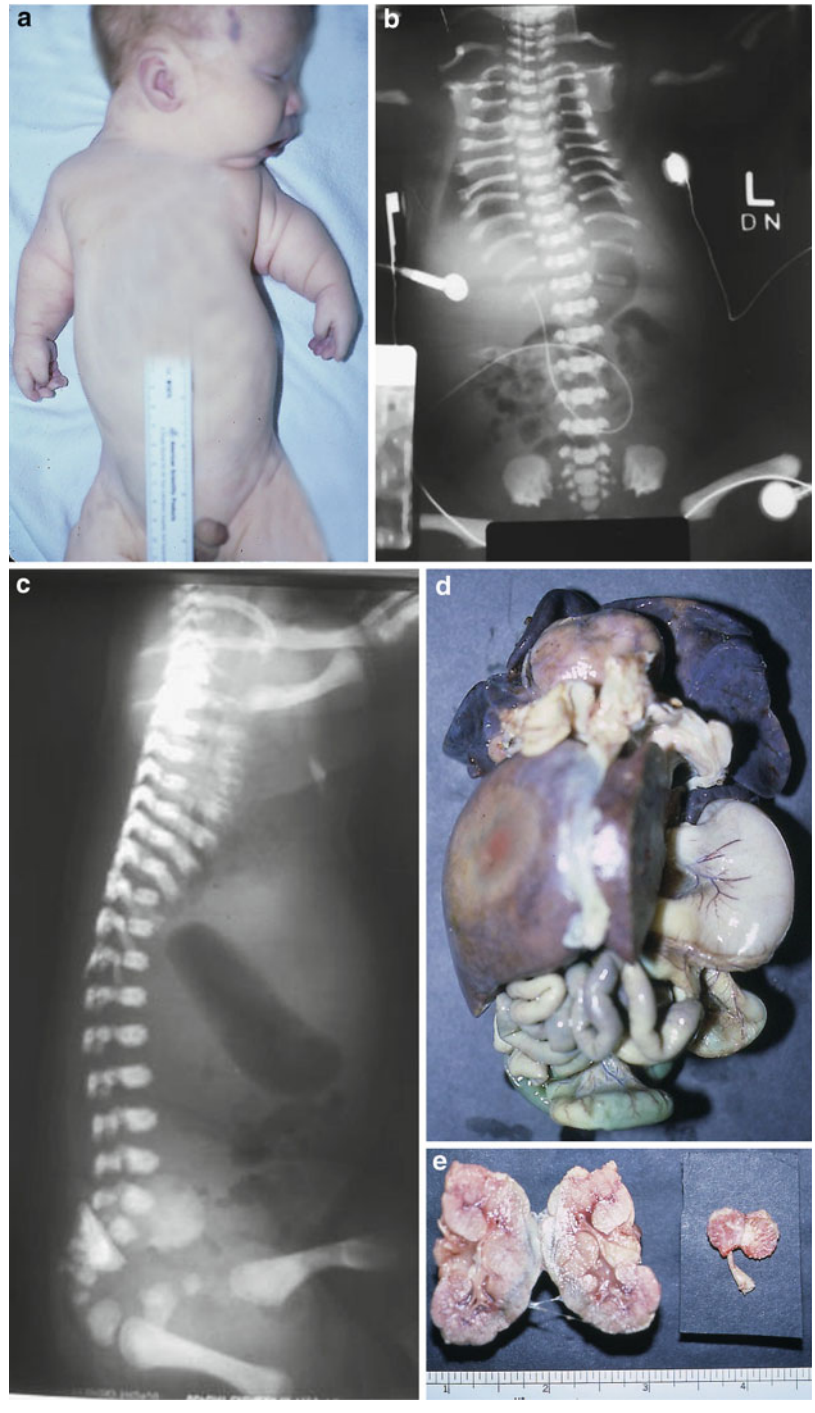

Fig. 3 (**a**–**e**) An infant with type II asphyxiating thoracic dystrophy showing a narrow thorax and short *upper* extremities. The radiographs showed the handlebar clavicles, short horizontal ribs with widened/cupped anterior rib ends, and *square-shaped* iliac bones with the medial spurs of both acetabular roofs. The necropsy showed lung hypoplasia and renal cystic dysplasia and hypoplasia

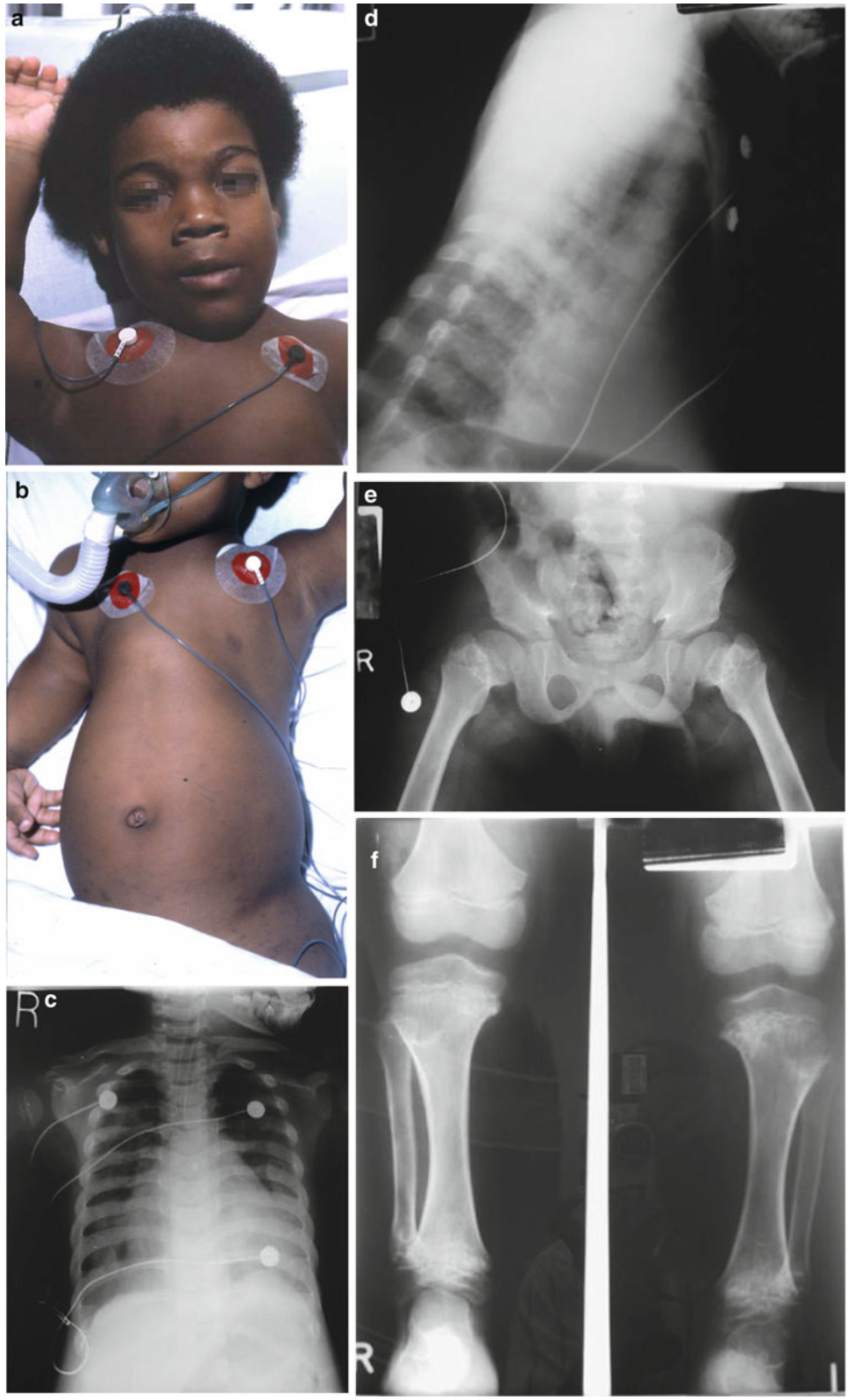

Fig. 4 (continued)

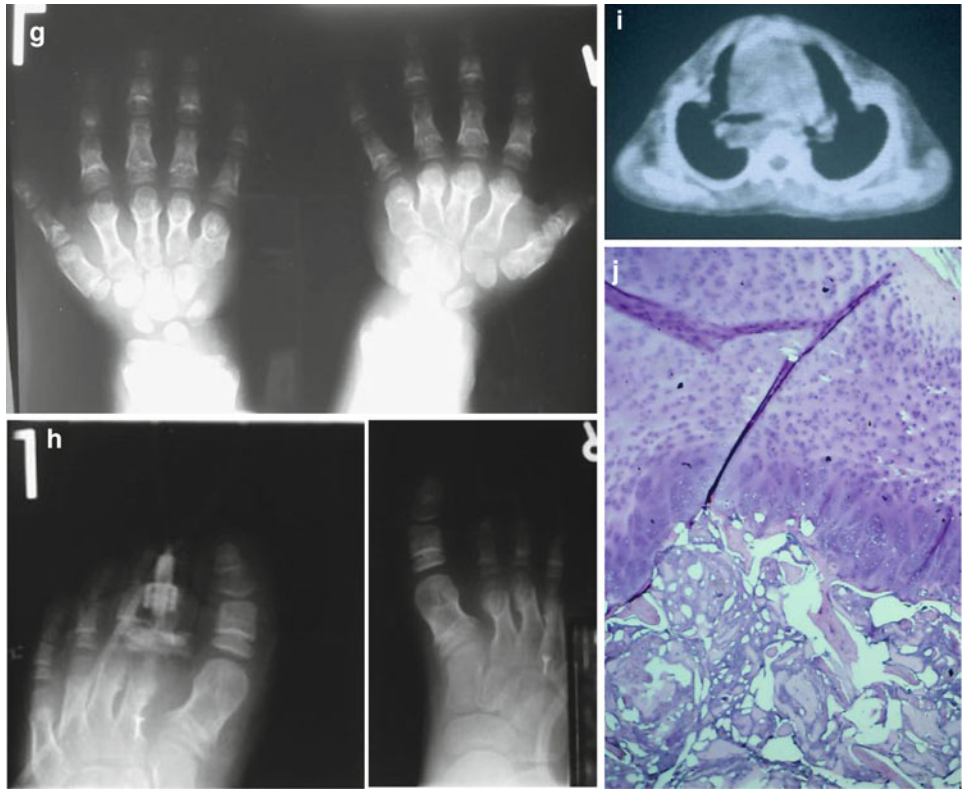

Fig. 4 (**a**–**j**) A 7-year-old boy with asphyxiating thoracic dystrophy showing a narrow thorax and short limbs. He had dwarfism, postaxial polydactyly, and respiratory distress since birth. Radiographs showed handlebar clavicles, short horizontal ribs, oblique superior acetabular margins, shortened tubular bones, shortened phalanges especially the middle and distal phalanges, and *cone-shaped* epiphyses. CT of the chest showed a narrow thorax, shortened ribs, and lung hypoplasia. Histology of the ribs showed that resting chondrocytes were widely separated by abundant cartilaginous matrix. Histology of a rib physeal growth zone shows greatly reduced number of chondrocytes. In some areas, they are completely nonexistent

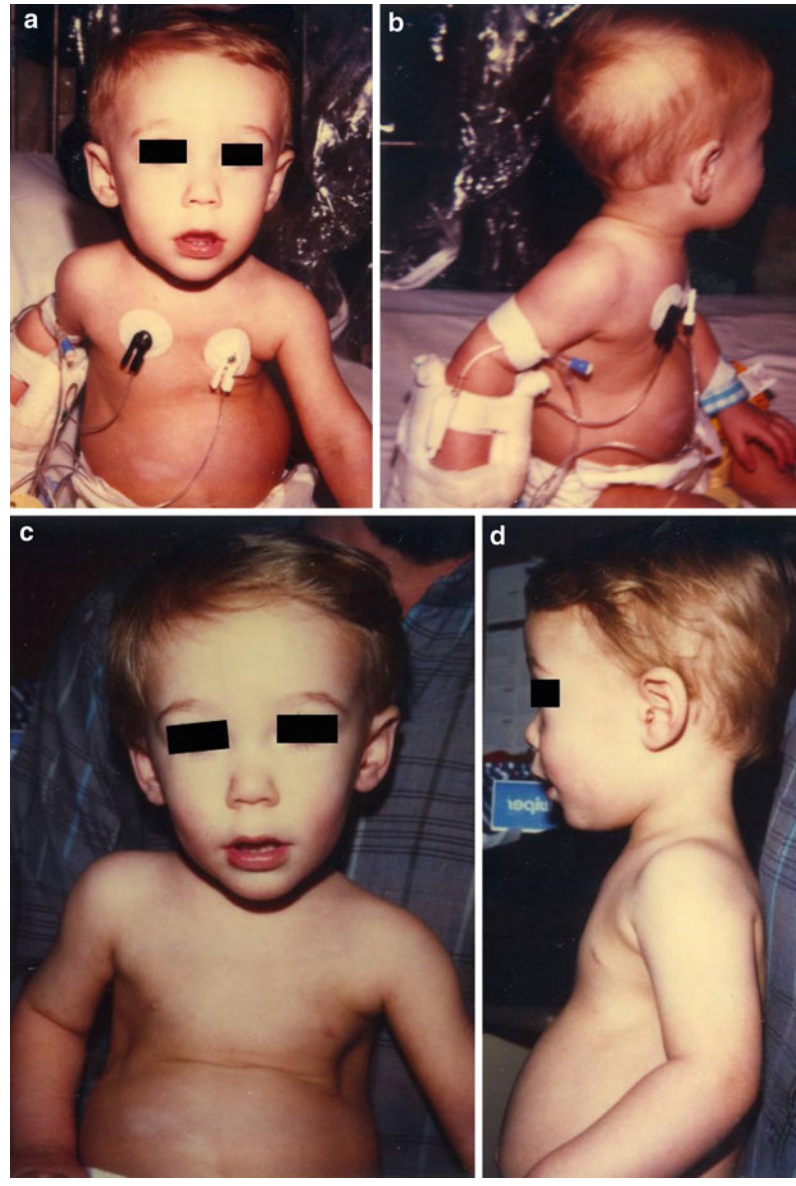

Fig. 5 (**a**–**d**) A boy with type II asphyxiating thoracic dystrophy at 7 months and 15 months

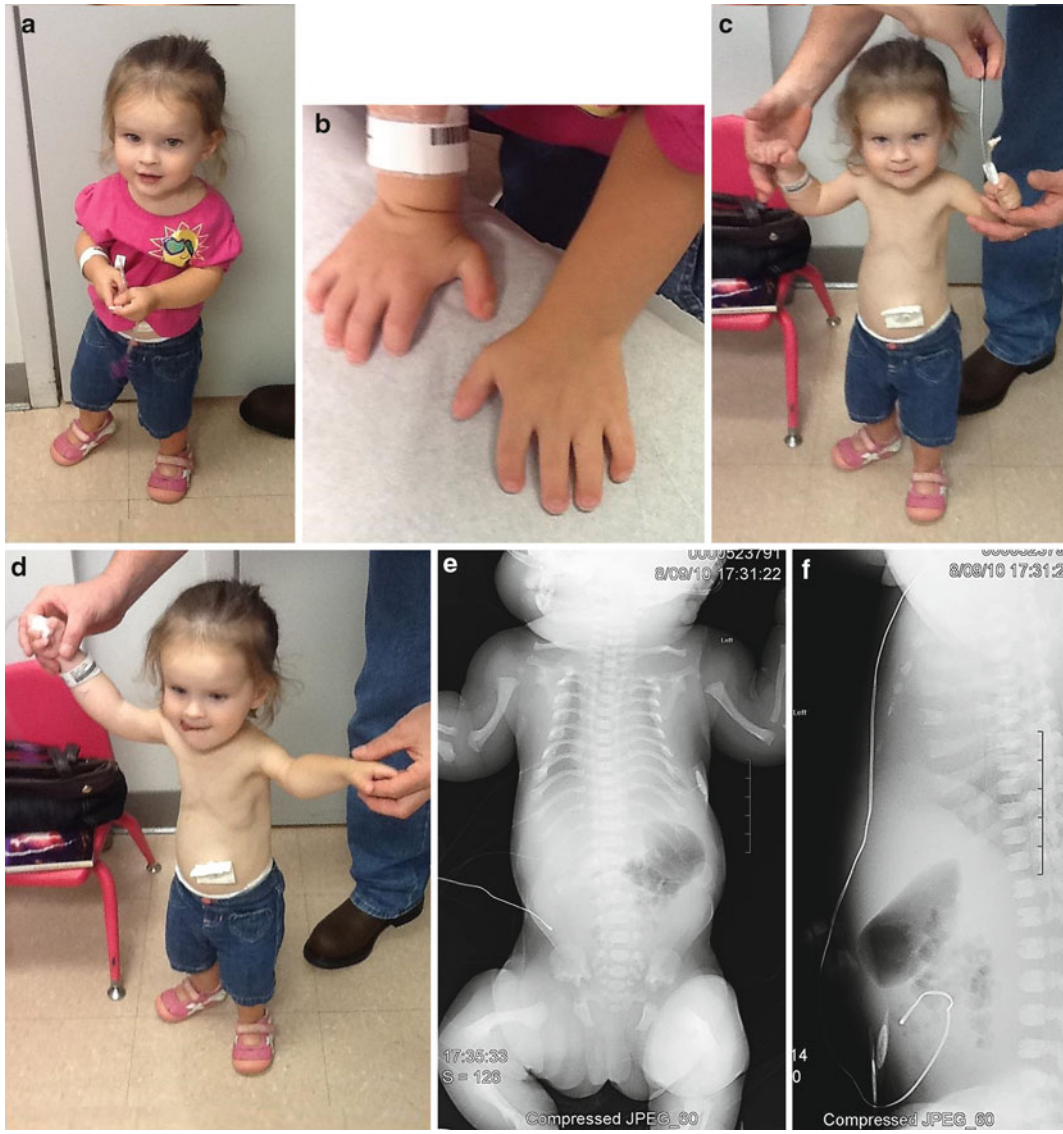

Fig. 6 (**a**–**f**) This 3-year-old Caucasian girl (**a**–**d**) was evaluated for short stature, short limbs, and a narrow chest. The prenatal ultrasonography at 16 weeks gestation showed short limbs and small rib cage. The fetus was suspected to have the same condition as the first female sibling, who died shortly after birth of asphyxiating thoracic dystrophy. On examination, the patient showed short-limb dwarfism and a long, narrow, and small thorax with history of respiratory distress. She required a PEG tube for feeding. Radiographs shortly after birth (**e**, **f**) showed the handlebar clavicles, short horizontal ribs with widened/cupped anterior rib ends, and square-shaped iliac bones with the medial spurs of both acetabular roofs (Courtesy of Dr. Eric Chen)

Ataxia-Telangiectasia

Contents

Ataxia-telangiectasia (A-T) is a rare hereditary disorder characterized by progressive cerebellar ataxia, conjunctival telangiectasias, recurrent sinopulmonary infections, radiosensitivity, and a predisposition to malignancy. It is the most common cause of progressive cerebellar ataxia in childhood. The prevalence is estimated to be 1 in 40,000–1 in 100,000 live births.

Synonyms and Related Disorders

Louis-Bar syndrome

Genetics/Basic Defects

1. Inheritance
   1. Autosomal recessive
   2. Genetic heterogeneity in at least five complementation groups (A–E)
2. Cause
   1. Mutations in the ataxia-telangiectasia mutated gene (*ATM*) which is mapped to 11q22.3
   2. Results from inactivation of the ATM kinase (Frappart and McKinnon 2006)
   3. Affected individuals completely lack functional ATM protein
   4. Diversity of ATM gene mutations (Concannon and Gatti 1997; Gatti 1997)
   5. A high prevalence of specific *ATM* mutations in certain ethnic groups (Amish, Mennonite, Costa Rican, Polish, British, Italian, Turkish, Iranian, Israeli) with a founder effect (Telatar et al. 1998), resulting in a small number of mutations that accounts for the majority of disease-causing mutant alleles
3. Pathophysiology
   1. Basic defect: abnormal sensitivity of A-T cells to X-rays and certain radiomimetic chemicals, leading to chromosome and chromatid breaks. However, sensitivity of A-T cells to ultraviolet irradiation is normal (Janniger 2015).
   2. Random distribution of breakpoints
   3. Nonrandom chromosome rearrangements selectively affect chromosomes 7 and 14 at sites that are concerned with T-cell receptors and heavy-chain immunoglobulin coding and with the development of hematologic malignancies
   4. Mechanisms responsible for neurologic disease, thymus aplasia, telangiectasias,

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growth retardation, and impaired organ mutation
1. Have not been elucidated
2. Most likely linked to accelerated telomere loss

5. NADPH oxidase 4 (NOX4): involved in manifesting A-T disease (Weyemi et al. 2015)

4. Analyses of ATM mutations in A-T patients and in sporadic tumors suggest the existence of two classes of ATM mutation (Meyn 1999):
   1. Null mutations that lead to A-T
   2. Dominant negative missense mutations that may predispose to cancer in the heterozygous state
5. To date, more than 780 mutations in the *ATM* gene have been reported (Taylor and Byrd 2005; Chen et al. 2015)
   1. Truncating mutations
   2. Missense mutations
   3. Splice site mutations
   4. Founder mutations
   5. Small indels
   6. Large deletions
   7. Duplications
6. Genotype-phenotype correlations (Gatti 2010)
   1. 576ins137nt mutation
      1. Somewhat slower rate of neurological deterioration
      2. Later onset of symptoms
      3. Intermediate radiosensitivity
      4. Little or no cancer risk
   2. 8494C>T mutation
      1. Milder phenotype
      2. Longer life span
7. Genetic and clinical heterogeneity (Taylor et al. 2015)
   1. Allelic heterogeneity in *ATM* results in a striking clinical heterogeneity
   2. Locus heterogeneity: mutation of *MRE11* gene can cause an obvious A-T-like disorder both clinically and also at the cellular level and mutation of the *RNF168* gene results in a much milder clinical phenotype, neurologically, with the major clinical feature being an immunological defect

Clinical Features

1. CNS manifestations (Woods and Taylor 1992; Regueiro et al. 2000)
   1. Functional neurologic abnormalities rare in infancy
   2. Cerebellar ataxia
      1. A presenting symptom
      2. Slowly progressive
      3. Truncal ataxia preceding appendicular ataxia and peripheral incoordination
      4. Swaying of the head and trunk while standing and sitting: early sign of ataxia
   3. Diminished or absent deep reflexes by school age
   4. Hypotonia
   5. Dystonia and progressive spinal muscular atrophy affecting hands and feet in affected young adults, resulting in extension contractures
   6. Dysarthric speech
   7. Flexor plantar response
   8. Choreoathetosis in almost all patients
   9. Myoclonic jerking and intention tremors in about 25% of patients
   10. Drooling
   11. Oculomotor apraxia (total or partial loss of the ability to perform coordinated movement or manipulate objects in the absence of motor or sensory impairment) affecting reading (eye tracking) and writing (affected by 7–8 years of age)
   12. Intellectual function generally preserved
2. Telangiectasias (dilated small blood vessels)
   1. Ocular conjunctiva: most frequently observed
   2. Other sites: nose, ears, behind the knees, antecubital fossae, suprasternal notch, dorsum of the hands and feet, and hard and soft palate

3. Usually noticed during 3–6 years of age, i.e., a few years after ataxia
3. Immunodeficiency
   1. Frequent sinopulmonary infections
      1. Mucopurulent rhinitis, retropharyngeal discharge, otitis media, and sinusitis
      2. Bronchitis and pneumonia
      3. Progress to chronic lung disease: bronchiectasis, pulmonary fibrosis, respiratory insufficiency
   2. A small embryonic-like thymus
   3. Problems associated with defects in humoral and cellular immunity
      1. T-cell deficiency in about 30% of patients
      2. Severe immunodeficiency in about 10% of patients
      3. IgA and IgG_2 deficiency: most common
   4. Most frequent cause of death in adolescence: bronchiectasis complicated by pneumonitis
4. Malignancy
   1. The second most frequent cause of death
   2. Eventual malignancy during lifetime in 38% of patients
   3. Malignancy of hematologic origin most common (Taylor et al. 1996) (85% of patients)
      1. Predominance of malignant lymphomas, usually of B-cell type
      2. Acute lymphocytic leukemia of T-cell origin in younger patients
      3. T-cell prolymphocytic leukemia in older patients
   4. Other neoplasms (Swift et al. 1987, 1991)
      1. Breast cancer, even in female relatives who do not have ataxia telangiectasia
      2. Gastric cancer
      3. Melanoma
      4. Leiomyoma
      5. Sarcoma
5. Ectodermal changes
   1. Appearance of premature aging
      1. Diffuse graying of the hair
      2. Atrophic and hidebound facial skin
      3. Inelastic ears
      4. Facial wasting
   2. Frequent pigmentary changes (Greenberger et al. 2013)
      1. Hyper-/hypopigmentation with cutaneous atrophy and telangiectasia
      2. Partial albinism
      3. Vitiligo
      4. Hypopigmentary macules
      5. Café-au-lait spots
      6. Melanocytic nevi
   3. Hypertrichosis
   4. Seborrheic dermatitis
6. Respiratory manifestations (Bhatt et al. 2015)
   1. Recurrent respiratory tract infections including otitis media, sinusitis, bronchitis and pneumonia
   2. Bronchiectasis secondary to recurrent/chronic infection and aspiration
   3. Interstitial lung disease
   4. Obliterative bronchiolitis
   5. Aspiration syndromes due to incoordinate swallowing
   6. Opportunistic infections
   7. Restrictive lung disease due to scoliosis, neuromuscular disease or fibrosis
7. Endocrine manifestations
   1. Infertility has been described as a major feature of A-T; several reports of fertile A-T female patients have been reported (Stankovic et al. 1998; Worth et al. 2013; Dawson et al. 2015)
   2. Occasional female hypogonadism associated with ovarian hypoplasia or dysplasia
   3. Male hypogonadism with delayed puberty and characteristic high-pitched voice
8. Clubbing: Observed in 40% of Costa Rican patients not correlated with chronic lung disease, humoral immunodeficiency, or with a particular mutation
9. Other features
   1. Mild postnatal growth retardation
   2. Hypersensitivity to ionizing radiation
   3. Wheelchair-bound by 10 years of age
10. Clinical diagnosis (Gatti et al. 1991)

1. Presents with two diagnostic hallmarks of disease – the early-onset cerebellar ataxia and the oculocutaneous telangiectasia
2. Association of these hallmarks with the characteristic hypotonic cerebellar facies and posture: striking

11. A-T shares similar clinical symptoms and cellular characteristics with two other syndromes: A-T-like disorder (ATLD) and Nijmegen-breakage syndrome (NBS) (Lavin 2008)
    1. Defective protein
        1. A-T: ATM
        2. ATLD: MRE 11
        3. NBS: NBS1
    2. Appearance of symptoms
        1. A-T: infancy
        2. ATLD: first decade
        3. NBS: infancy
    3. Progression
        1. A-T: rapid
        2. ATLD: slow
        3. NBS: rapid
    4. Neurological defect
        1. A-T: cerebellar atrophy
        2. ATLD: cerebellar atrophy
        3. NBS: microencephaly
    5. Oculomotor apraxia
        1. A-T: present
        2. ATLD: present
        3. NBS: absent
    6. Immunodeficiency
        1. A-T: present
        2. ATLD: absent
        3. NBS: present
    7. Telangiectasia
        1. A-T: present
        2. ATLD: absent
        3. NBS: absent
    8. Alpha-fetoprotein
        1. A-T: high
        2. ATLD: normal
        3. NBS: normal
    9. Growth defect
        1. A-T: absent
        2. ATLD: absent
        3. NBS: present
    10. Radiosensitivity
        1. A-T: marked
        2. ATLD: present
        3. NBS: present
    11. Cell-cycle checkpoint defect
        1. A-T: present
        2. ATLD: present
        3. NBS: present
    12. DNA-repair defect
        1. A-T: present
        2. ATLD: questionable
        3. NBS: present
    13. Chromosomal instability
        1. A-T: present
        2. ATLD: present
        3. NBS: present
    14. Cancer predisposition
        1. A-T: present
        2. ATLD: absent
        3. NBS: present

Diagnostic Investigations

1. Immune workup: presence of significant humoral and cellular immune defects in most patients (Gatti 2010; Regueiro et al. 2000)
    1. Thymic hypoplasia
    2. Low numbers of circulating T-cells
    3. Functional impairment of T-cell-mediated immunity
    4. Selective deficiencies of IgA, IgE (Ammann et al. 1969), IgG_2, and IgG_4
    5. Low or absent serum levels of IgA in 60% of patients
    6. Low or absent serum levels of IgG2 in 80% of patients
    7. Hyper IgM in approximately 1% of patients, sometimes associated with myeloma-like gammopathy, lymphadenopathy, hepatosplenomegaly, and lymphocytic interstitial pneumonitis
    8. Poor in vivo response to pneumococcal polysaccharides (Sanal et al. 1999)
    9. Immunoblotting for ATM protein (Gatti 2010)
        1. Severely depleted intracellular ATM protein in most patients with A-T
            1. About 90% have no detectable ATM protein

   2. About 10% have trace amounts of ATM protein
   3. About 1% have a normal amount of ATM protein that lacks ATM serine/threonine kinase activity (so-called kinase-dead)
2. The most sensitive and specific clinical test, to date, for establishing a diagnosis of A-T
3. Small amounts of ATM protein: occasionally associated with a milder prognosis, although there are many exceptions to this and the association needs further validation

2. Increased serum levels of alpha-fetoprotein (AFP) levels in over 95% of A-T cases (Chun and Gatti 2004): a simple, rapid, and reliable screening test for A-T
3. Liver disease (Weiss et al. 2015)
   1. Elevated liver enzymes: frequent finding in A-T (43% of patients)
   2. Presence of positive correlation between dyslipidemia and elevated liver enzymes
   3. Patients with elevated liver enzymes should be evaluated for liver disease emphasizing hepatic steatosis.
   4. Progression to advanced liver disease may occur at a young age.
4. Increased plasma levels of carcinoembryonic antigen
5. Colony survival assay (Sun et al. 2002; Chun and Gatti 2004) by in vitro testing for radiosensitivity on lymphoblastoid cell line to measure the colony survival fraction after 1 Gy of in vitro radiation: sensitivity and specificity exceeding 95% but takes 2–3 months to complete
6. Western blot analysis to detect ATM protein in lysates of a lymphoblastoid cell line
7. DNA-based mutation analysis of the *ATM* gene available clinically
   1. Sequence analysis of the *ATM* coding region
   2. Deletion/duplication analysis
   3. Targeted mutation analysis
   4. Linkage analysis/ethnic haplotype analysis to identify carriers among family members at risk if direct DNA testing fails to identify two disease-causing mutations in the index case
8. Targeted next-generation sequencing (Chen et al. 2015): identification of causative variants of *ATM* gene
9. Chromosome analysis to identify genetic instability (Mavrou et al. 2008), a hallmark of the A-T phenotype
   1. Types of spontaneous in vitro chromosome aberrations, frequent in both lymphoid and non-lymphoid cells
      1. Chromosome breaks
      2. Acentric fragments
      3. Dicentric chromosomes
      4. Structural arrangements
      5. Telomeric fusions
      6. An increased rate of telomeric shortening (Metcalfe et al. 1996)
      7. Aneuploidy
   2. A-T lymphocytes
      1. Increased chromosome breaks. Common breakage points include 7p14, 7q35, 14q12, 14qter, 2p11, 2p12, and 22q11-q12
      2. Clonal rearrangements involving abnormalities of chromosome 14, especially tandem duplication of 14q at 14q11-q12 and characteristic t(7;14) (Chun and Gatti 2004)
   3. Non-lymphoid cells: break points randomly distributed
10. Radiography
    1. Decreased or absent adenoidal tissue in the nasopharynx
    2. Small or absent thymic shadow
    3. Decreased mediastinal lymphoid tissue
    4. Pulmonary changes similar to those seen in cystic fibrosis
11. EEG and nerve conduction velocities
    1. Frequently normal in children
    2. Showing denervation on EEG and reduced nerve conduction in the late stage of the disease, especially in sensory fibers
12. Electrooculography
    1. Shows characteristic oculomotor abnormality of A-T
    2. Differentiates A-T from Friedreich ataxia

13. MRI of the brain (Chun and Gatti 2004; Sauma et al. 2015)
    1. A small cerebellum (cerebellar atrophy)
    2. Multiple T1 and T2 hypointense foci suggestive of hemosiderin, probably related to thrombosis and vascular leaks from multiple capillary telangiectasias (Lin et al. 2014; Sahama et al. 2014)
    3. Widened sulci
    4. Enlargement of the fourth ventricle
14. Histology (Janniger 2015)
    1. Degeneration of Purkinje and granule cells in the cerebellum: the major pathological marker of A-T in the CNS
    2. Late degenerative gliovascular nodules in the white matter
    3. Lesions of the basal ganglia observed only occasionally
    4. Degeneration of spinal tracts and anterior horn cells often present in late stages
    5. Nucleocytomegaly, a feature of several cell types throughout the body

Genetic Counseling

1. Recurrence risk: counseling according to autosomal recessive inheritance
    1. Patient's sib
        1. A 25% recurrence risk
        2. Two thirds of unaffected sibs are carriers.
    2. Patient's offspring: most patients with A-T do not reproduce.
2. Prenatal diagnosis
    1. Elevated maternal serum alpha-fetoprotein levels
    2. Demonstration of chromosome breaks in amniocytes
    3. Molecular genetic analysis
        1. Direct DNA mutation analysis on fetal DNA obtained from amniocentesis (Mancebo et al. 2007) or CVS (Chessa et al. 1999) for pregnancies at risk with previously identified specific disease-causing mutation
        2. DNA-based testing with linkage analysis for at-risk family members if no specific disease-causing mutation identified
        3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified
3. Management
    1. No specific treatment available
    2. Antibiotics for infections
    3. Prevention of infection by regular injection of immunoglobulins in patients with antibody deficiency
    4. IV IG replacement therapy for individuals with frequent and severe infections and very low IgG levels (Nowak-Wegrzyn et al. 2004)
    5. Aggressive pulmonary hygiene for individuals with chronic bronchiectasis before the final stages of the disease (Tangsinmankong et al. 2001)
    6. Supportive therapy to minimize drooling, choreoathetosis, and ataxia; individual responses to specific medications vary (Perlman et al. 2003)
    7. Beta-adrenergic blockers may improve fine motor coordination in some cases
    8. Controversial use and doses of radiation therapy and chemotherapy
    9. Avoid bleomycin, actinomycin D, and cyclophosphamide
    10. Regular cancer surveillance of heterozygotes essential. ATM heterozygosity is a risk factor for breast and lung cancers.
    11. Desferroxamine: recently shown to increase genomic stability of A-T cells and may present a promising tool in A-T treatment
    12. Early physical therapy, occupational therapy, and speech therapy
    13. A wheelchair: usually necessary by age 10
    14. Although steroids can temporarily improve the neurologic symptoms of A-T in children, the symptoms reappear within days of their discontinuation (Gatti and Perlman 2009)

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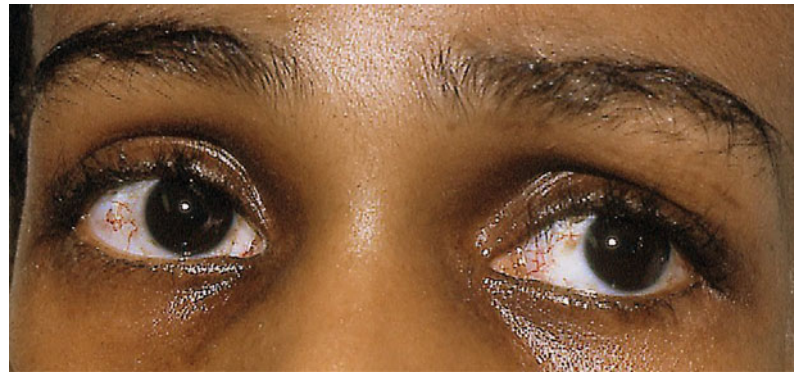

Fig. 1 A boy with ataxia-telangiectasia showing conjunctival telangiectasis and chronic lung disease requiring oxygen support

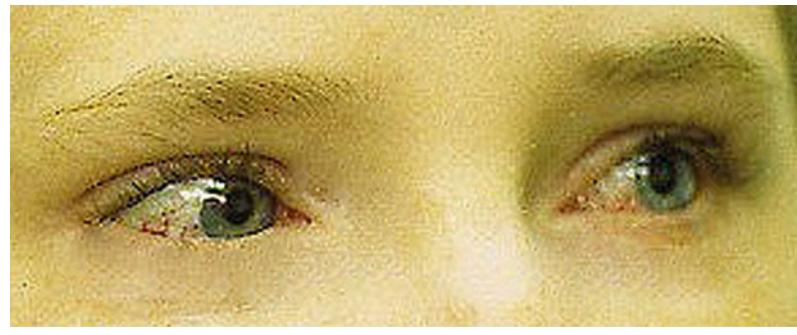

Fig. 2 A girl with ataxia-telangiectasia showing conjunctival telangiectasis and anemia

Atelosteogenesis

Contents

In 1982, Maroteaux et al. proposed the term "atelosteogenesis" for a newborn skeletal dysplasia characterized by specific patterns of aplasia/hypoplasia of humeri, femora, spine, and other skeletal elements (Maroteaux et al. 1982). Atelosteogenesis encompasses a heterogeneous group of disorders with overlapping phenotypic features.

Synonyms and Related Disorders

Atelosteogenesis type I (giant cell chondrodysplasia, spondylohumerofemoral hypoplasia, boomerang dysplasia); Atelosteogenesis type II (neonatal osseous dysplasia I, de la Chapelle dysplasia); Atelosteogenesis III

Genetics/Basic Defects

1. Atelosteogenesis I (AOI)/boomerang dysplasia (BD)
    1. Inheritance: de novo autosomal dominant mutation, suggested by:
        1. Sporadic in all observed cases
        2. No familial cases reported
    2. Previously known as spondylohumerofemoral dysplasia and giant cell chondrodysplasia
    3. Caused by mutations in filamin B (*FLNB*) gene (Li et al. 2013), which also causes the following disorders (Krakow et al. 2004; Robertson 2013):
        1. Atelosteogenesis type III
        2. Autosomal recessive spondylocarpotarsal syndrome
        3. Autosomal dominant Larsen syndrome
    4. A common pathogenesis suggested for atelosteogenesis type I and boomerang dysplasia
        1. Forming a spectrum of findings within the same nosologic entity with boomerang dysplasia
        2. Similar histopathology in boomerang dysplasia
        3. Overlapping radiologic features with boomerang dysplasia
2. Atelosteogenesis II (AOII) (Karniski 2001)
    1. Inheritance: autosomal recessive suggested by:
        1. Recurrence in the subsequent pregnancy
        2. Parental consanguinity
    2. Synonymous with de la Chapelle dysplasia (Schrander-Stumpel et al. 1994).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Phenotypic and radiographic overlap with atelosteogenesis I but with distinctive matrix histopathology with a major disturbance in cartilage matrix macromolecules.
4. Common pathogenetic features with disorders of sulfation of connective tissue matrix macromolecules. An overlap of phenotypic, radiographic, morphological, and cartilage histochemical features with the following conditions:
    1. Diastophic dysplasia
    2. Achondrogenesis type IB
5. Caused by mutated diastrophic dysplasia sulfate transporter (*DTDST*; *SLC26A2*) gene which also causes the following recessively inherited chondrodysplasias (Hastbacka et al. 1996; Rossi and Superti-Furga 2001; Dwyer et al. 2010):
    1. Diastrophic dysplasia (Rossi et al. 1996; Macias-Gomez et al. 2004)
    2. Multiple epiphyseal dysplasia
    3. Achondrogenesis IB (Cai et al. 1998)
6. The *DTDST* gene.
    1. Encodes a sulfate transporter that also accepts chloride and possibly bicarbonate as substrates
    2. Reduced sulfate transport in chondrocytes of individuals with *DTDST* mutations resulting in the under-sulfation of proteoglycans, which in turn leads to abnormal cartilage formation
7. Factors in addition to the intrinsic sulfate transport properties of the DTDST protein may influence the phenotype in individuals with *DTDST* mutations.

3. Atelosteogenesis III (AOIII)
    1. Inheritance: autosomal dominant (Schultz et al. 1999)
    2. Features overlapping with atelosteogenesis I and II but most similar to those of atelosteogenesis I
    3. Caused by mutations in *FLNB* gene
4. Genotype-phenotype correlation in a compound heterozygote (atelosteogenesis type II diastrophic dysplasia)
    1. Atelosteogenesis type II.
        1. R178X mutations of the *SLC26A2* gene
        2. Features typical of AO II
            1. Severe and progressive cervical kyphosis
            2. V-shaped distal humerus
            3. Bowed radii
            4. Horizontal sacrum
            5. Gap between the first and second toes
    2. Diastrophic dysplasia.
        1. R279W mutations of the *SLC26A2* gene
        2. Features suggestive of diastrophic dysplasia
            1. Cystic swelling of the external ears
            2. Cervical kyphosis
            3. Rhizomelia
            4. “Hitchhiker” thumbs
            5. Bilateral talipes equinovarus
            6. Short toes
    3. Combination of a severe and a mild mutation leads to an intermediate clinical picture, representing an apparent genotype-phenotype correlation.

Clinical Features

1. Atelosteogenesis I
    1. Stillborn or neonatal death due to respiratory distress
    2. Polyhydramnios
    3. Facial dysmorphism
        1. Depressed nasal bridge
        2. Eyelid edema
        3. Micrognathia
        4. Cleft soft palate
    4. Small chest
    5. Protuberant abdomen
    6. Deficient ossification of various bones
        1. Humerus
        2. Femur
        3. Thoracic spine
        4. Hand bones
    7. Rhizomelic micromelic dwarfism
        1. Short and broad hands
        2. Incurved legs
        3. Clubfeet
        4. Often dislocation of the elbows

8. Laryngeal hypoplasia (stenosis): an important role in the respiratory failure and death (Yang et al. 1983; Bejjani et al. 1998; Ueno et al. 2002)

2. Boomerang dysplasia (Kozlowski et al. 1985; Winship et al. 1990)
   1. Distinct facial features
      1. Horizontal palpebral fissures
      2. Broad nasal root
      3. Hypoplastic nasal septum
      4. Prominent philtrum
      5. Cleft palate
   2. Small chest
   3. Protuberant abdomen
   4. Marked rhizo-/mesomelic shortening of limbs
   5. Well-developed hands (broad, paddle shaped) and feet
   6. Bowed lower limbs
   7. Calcaneo-valgus deformities
3. Atelosteogenesis II (Whitley et al. 1986; Newbury-Ecob 1998)
   1. Lethal in neonatal period
      1. Pulmonary hypoplasia
      2. Tracheobronchomalacia
      3. Laryngeal stenosis
   2. Deficient ossification of parts of the skeleton
   3. Facial dysmorphism
      1. Midface hypoplasia
      2. Depressed nasal bridge
      3. Epicanthal folds
      4. Micrognathia
      5. Cleft palate
   4. Small chest
   5. Protuberant abdomen
   6. Extremities
      1. Severe rhizomelic limb shortening
      2. Talipes
      3. Abducted (hitch-hiked) thumbs and toes
      4. Ulnar deviation of the fingers
      5. Gap between the first and second toes
4. Atelosteogenesis III (Kuwashima et al. 1992; Schultz et al. 1999)
   1. Milder, usually nonlethal
   2. Limb anomalies
      1. Rhizomelic shortening
      2. Clubfeet
      3. Short broad thumbs and great toes
   3. Craniofacial abnormalities
      1. Ocular hypertelorism
      2. A flat nasal bridge
      3. Micrognathia
      4. Cleft palate
   4. Small chest
   5. Protuberant abdomen
   6. Multiple dislocations of elbows, hips, and knees
   7. Respiratory and feeding difficulties secondary to laryngomalacia
   8. Features overlapping 2 with oto-palato-digital syndrome type II (Stern et al. 1990)
   9. Apparent cause of death
      1. Respiratory complications
      2. Cervical spine instability
   10. Long survival possible

Diagnostic Investigations

1. Atelosteogenesis I (Sillence et al. 1997)
   1. Radiography: overlapping radiological features with boomerang dysplasia (Hunter and Carpenter 1991; Greally et al. 1993)
      1. Humeri: absent/geometric (AOI), absent (AOI/BD), absent (BD)
      2. Hand phalanges: presence of distal and absent middle (AOI), hypoplastic middle (AOI/BD), presence of distal and absent proximal/middle (BD)
      3. Femora: pointed distally (AOI), geometric (AOI/BD), absent (BD)
      4. Tibia: bowed (AOI), hypoplastic (AOI/BD), bowed/boomerang (BD)
      5. Fibula: absent (AOI), absent (AOI/BD), absent (BD)
      6. Spine: coronal clefts in the lumbar vertebrae (AOI), coronal clefts in the vertebrae, and uniform lack of ossification of the center of the vertebral bodies (BD)
      7. Pelvis: hypoplasia of the ischiopubis (AOI), lack of ossification of ischiopubis (BD), flared ilia with hypoplasia of the inferior one third (AOI, BD), producing a keyhole shape
      8. Foot: lack of ossification of the calcaneal centers (AOI, BD)
      9. Ribs: 10–13 pairs (BD)

2. Histopathology
    1. Uniformly abnormal
    2. Lack of ossification
    3. Nonhomogeneous cell distribution with hypocellular and acellular areas
    4. Occasional multinucleated giant chondrocytes in the relatively acellular areas of resting cartilage (alternatively named "giant cell chondrodysplasia") (Rimoin et al. 1980; Sillence et al. 1978, 1982)
    5. Disorganized growth plate in some cases
    6. Similar histopathology in boomerang dysplasia
3. Exome sequencing: a useful tool in identifying *FLNB* gene mutations (Jeon et al. 2014)

2. Boomerang dysplasia (Kozlowski et al. 1985)
    1. Radiography (Odent et al. 1999)
        1. Triangular, boomerang-shaped long bones, diagnostic of the syndrome
        2. Missing some tubular bone ossification centers
        3. Ossified fingers and toes from the periphery
        4. Characteristic shaped pelvis
        5. Retarded ossification of the spine, especially cervical and thoracic spine
        6. Coronal clefts in the lower thoracic and lumbar spine
    2. Histopathology
        1. Chondrocytes in the resting cartilage are irregularly reduced in number with focal acellularity. Multinucleated giant chondrocytes have been noted.
        2. The physeal growth zones are markedly retarded and disorganized.

3. Atelosteogenesis II (Bonafe et al. 2014)
    1. Radiography.
        1. Normal size skull with disproportionately short skeleton
        2. Spine
            1. Platyspondyly.
            2. Hypodysplastic vertebrae.
            3. Cervical kyphosis.
            4. Ossification of the upper thoracic vertebrae and coronal clefts of the lumbar and lower thoracic vertebrae may be incomplete.
        3. Pelvis
            1. Hypoplastic/flared ilia
            2. Flat/horizontal acetabula with a spicule at the medial border of the acetabula
            3. Often unossified pubic bones
        4. Long bones
            1. Shortened with metaphyseal flaring
            2. Distal humerus: sometimes bifid or V shaped, sometimes pointed and hypoplastic
            3. Femur: distally rounded, clubbed distally
            4. Tibia: bowed/hypoplastic
            5. Fibula: hypoplastic
            6. Radius: typically bowed
        5. Hands
            1. Hitchhiker thumbs
            2. Ulnar deviation of the fingers
            3. Hand phalanges: irregular size and shape
            4. Gap between the first and second toe
            5. Hypoplasia of the first metacarpal bone
    2. Histopathology (Sillence et al. 1987).
        1. Irregularly distributed resting cartilage chondrocytes
        2. Attenuation of cartilage matrix with concentric matrix condensation rings around degenerating chondrocytes
        3. Shortened proliferative and hypertrophic zones
        4. Histopathology of cartilage essentially similar to that of diastrophic dysplasia and achondrogenesis IB reflecting the paucity of sulfated proteoglycans in cartilage matrix
    3. Targeted mutation analysis (mutation detection rate about 60%), deletion/duplication analysis using (multi)exonic and whole-gene deletion/duplication (detection rate unknown), and sequence analysis (mutation detection rate >90%) of *DTDST* (*SLC26A2*) gene (Bonafe et al. 2014): Mutations in the *DTDST* gene can be found in more than 90% of patients with radiologic and histologic

features compatible with the diagnosis of atelosteogenesis II.
4. Carrier testing for AOII.
    1. Carrier testing available to at-risk family members once the mutation of the *DTDST* gene has been identified in the proband.
    2. For the partner of a heterozygous individual. The partners can be screened for the four most common pathogenic alleles, R279W, IVS1 + 2T > C, delV340, and R178X. When these four alleles are excluded, the risk of carrying *DTDST* mutation is reduced from the general risk of 1:100 to about 1:300.

4. Atelosteogenesis III
    1. Radiography
        1. Humeri: pointed distally
        2. Hand phalanges: tombstone-shaped proximal phalanges (Fallon et al. 1994), widened distal phalanges
        3. Femora: pointed distally
        4. Tibia: short
        5. Fibula: absent
        6. Spine: coronal clefts in the lumbar vertebrae, severe thoracolumbar kyphosis with an S-shaped cervical spine in lateral profile
        7. Pelvis: hypoplastic ischiopubis, banana-shaped pubic rami
    2. Histopathology: hypocellularity without clustering, acellular areas, or "giant cells"

Genetic Counseling

1. Recurrence risk
    1. AOI
        1. Patient's sib: low
        2. Patient's offspring: a lethal entity not surviving to reproduce
    2. AOII
        1. Patient's sib: 25%
        2. Patient's offspring: a lethal entity not surviving to reproduce
    3. AOIII
        1. Patient's sib: low
        2. Patient's offspring: 50%

2. Prenatal diagnosis
    1. Fetal ultrasonography (Herzberg et al. 1988; Bejjani et al. 1998; Luewan et al. 2009).
        1. Short limbs (micromelia)
        2. Abnormal facial profile (depressed nasal base, micrognathia, apparent hypertelorism)
        3. Absence of ossification in the humerus, radius, ulna, and cervical and upper thoracic vertebral bodies (Fryer and Carty 1996)
        4. Coronal clefts in the ossified vertebral bodies (Nores et al. 1992)
        5. Talipes equinovarus
    2. 3D helical computed tomography (Cordier et al. 2008).
        1. Not dependent on amniotic fluid volume and fetal position and not limited at specific fetal parts
        2. Theoretical fetal exposure to radioactivity similar to that of conventional fetal radiological examination
        3. Identifies more characteristic findings than 3D ultrasonography due to its advantage of being able to image the entire skeleton and its possibilities of rereading
    3. Fetal MRI using an ultrafast sequence.
        1. Dysmorphic features
        2. Pulmonary hypoplasia
        3. A large cisterna magna
    4. Fetal MRI of atelosteogenesis type II (Miller et al. 2008).
        1. Bilateral short upper extremities
        2. Short fingers and hitchhiker thumb
        3. Bilateral short and bowed lower extremities
        4. Bilateral severe equinovarus deformity
    5. Prenatal diagnosis by analysis of DNA extracted from fetal cells obtained by CVS or amniocentesis or preimplantation genetic diagnosis: Mutation analysis of *SLC26A2* gene for pregnancy at risk is possible for AOII for families in which the disease-causing mutations have been identified (Bonafe et al. 2014).

3. Management
    1. AOI and AOII: supportive measures for these two lethal conditions
    2. AOIII
        1. Ventilatory support and tracheostomy often necessary for respiratory distress due to laryngotracheomalacia
        2. Treat recurrent respiratory tract infections
        3. Cleft palate repair
        4. Conductive hearing loss evaluation and management
        5. Orthopedic care for clubfeet and joint dislocations

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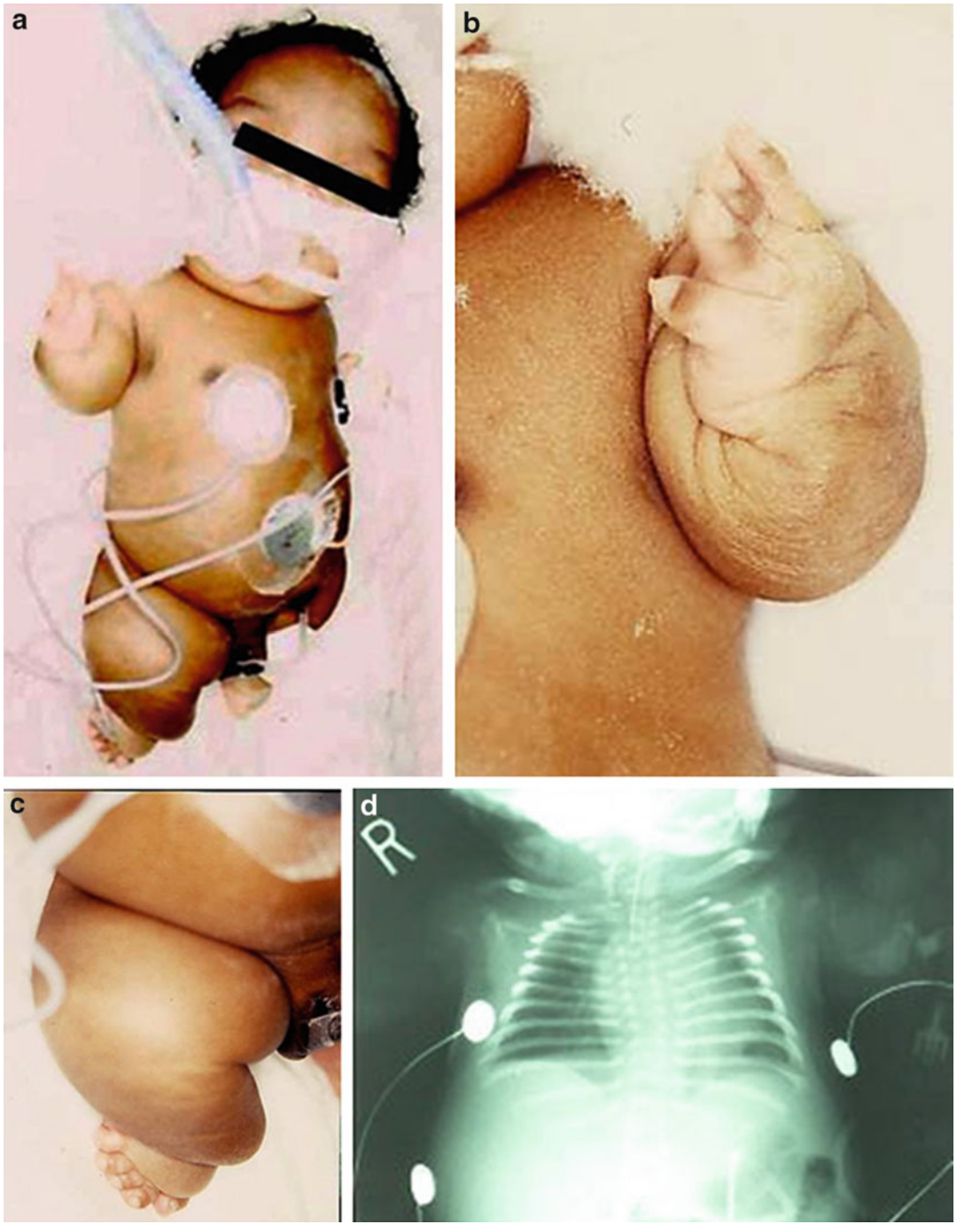
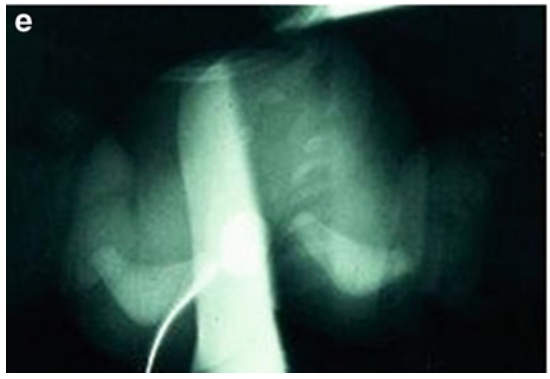


Fig. 1 (continued)



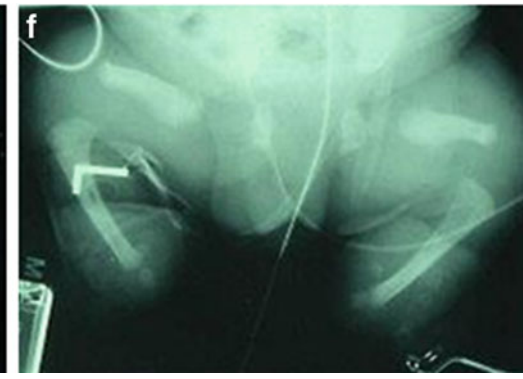


Fig. 1 (**a**–**f**) A male infant with atelosteogenesis I/boomerang dysplasia. Prenatal ultrasound showed polyhydramnios and a short limb dwarf. The infant died at 57 days. He showed relatively large head, hypertelorism, depressed nasal bridge, midfacial hypoplasia, micrognathia, cleft palate, short neck, relatively narrow chest, protuberant abdomen, severe "rhizomelic" micromelia, absent elbow joints, genu varus, and talipes equinovarus. Radiographic features included unossified vertebrae (T6–T9), single boomerang-like long bone (between acromion and wrist), short tapered femora, short bowed tibiae, absent fibulae, calcified distal phalanges, non-ossified carpals and metacarpals, proximal phalanges, and irregularly ossified tarsals and metatarsals. Histopathology of the cartilage showed disorganized physeal growth zones and irregular areas of hypocellularity in the resting cartilage. Multinucleated giant chondrocytes were not observed

Autism

Contents

Autism is a pervasive developmental disorder, defined by impairments in social and communication function and repetitive and stereotyped behavioral patterns. It occurs in approximately 7–40 out of 10,000 persons. Autism spectrum disorders (ASDs) represent a heterogeneous group of neurodevelopmental disorders, including autism, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified, and are characterized by social and communication deficits accompanied by repetitive and stereotype behaviors, with onset before 3 years of age (American Psychiatric Association 2013; DiCicco-Bloom et al. 2006; Caglayan 2010). The prevalence of autism spectrum disorders is at least 5–6/1,000 and may be higher (Bryson and Smith 1998).

Synonyms and Related Disorders

Autism spectrum disorders (autism, Asperger syndrome, childhood disintegrative disorder, pervasive developmental disorder); Autistic disorder

Genetics/Basic Defects

1. Secondary autism (nongenetic and genetic conditions associated with autism): accounts for a small minority of individuals with autism (<10%) in population-based studies (Miles et al. 2005; Muhle et al. 2004)
   1. Obstetric complications including uterine bleeding, despite the absence of demonstrable causal relationship in many studies
   2. Intrauterine exposure to teratogenic drugs in a few affected children
      1. Thalidomide
      2. Valproate
   3. Elevated cord blood levels of the following substances:
      1. Neuropeptide substance P
      2. Vasoactive intestinal peptide
      3. Pituitary adenylate cyclase-activating polypeptide
      4. Calcitonin gene-related peptide
      5. Neurotrophin nerve growth factor

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Various epidemiologic data
    1. Cerebral palsy (a static motor deficit of brain origin present from early life): present in 2.1–2.9% of individuals with autism and mental retardation
    2. Congenital rubella infection: present in 0.75% of cases
    3. Other pre- and postnatal infections (e.g., Haemophilus influenzae and cytomegalovirus): may cause autism when they significantly damage the immature brain
    4. No association between autism and inflammatory bowel disease or with a live MMR vaccination
    5. Epilepsy with the highest association with autism: reported in up to a third of individuals with an autistic spectrum disorder by adulthood
    6. Behavioral symptoms of autism: frequent in tuberous sclerosis complex and fragile X syndrome but account for only a minority of the total cases of autism
5. Genetic causes associated with autism: more than 25% of individuals with autism spectrum disorder have an identifiable genetic cause (Baker and Jeste 2015)
    1. Cytogenetically visible chromosomal abnormalities (~5%) (Gillberg 1998; Wassink et al. 2001)
        1. Angelman syndrome (more commonly associated with autism than Prader-Willi syndrome) can result from the loss or mutations of the maternally derived *UBE3A* or the *ATP10C* gene in 15q11-q13 region.
        2. Chromosomal duplication in the Prader-Willi/Angelman region of proximal 15q in about 3% of individuals with autism: more commonly a supernumerary isodicentric 15q chromosome detectable by routine cytogenetic studies or less commonly an interstitial duplication of the region detected by fluorescence in situ hybridization (FISH) analysis of the *SNRPN* gene.
        3. Other chromosome abnormalities in 3–5% of individuals with autism.
        4. A subtelomeric deletion detected by FISH telomere studies in 10% of unselected patients with autism.
        5. Down syndrome (Kent et al. 1999): autism was found in at least 7% in one study in children with Down syndrome.
        6. Turner syndrome: known to have specific cognitive and behavioral deficits that overlap with but are also distinct from those found in children with idiopathic autism (Caglayan 2010).
        7. Inv dup(15) or idic(15) syndrome: characterized by early central hypotonia, developmental delay and intellectual disability, epilepsy, and autistic behavior with no facial dysmorphic features (Battaglia 2008).
    2. Copy number variants (CNVs) (Miles et al. 2010): Array comparative genomic hybridization (aCGH)
        1. Steadily replacing high-resolution chromosome analysis and FISH in the evaluation of children with autism.
        2. Designed to test for known deletion/duplication syndromes on the entire genome plus assessment of subtelomeric regions.
        3. Currently, aCGH identifies clinically relevant de novo genomic imbalances in 7–10% of individuals with autism of unknown cause (Sebat et al. 2007; Christian et al. 2008; Kumar et al. 2008; Marshall et al. 2008; Weiss et al. 2008).
        4. Most common autism-related CNVs: 15q11.2-11.3 duplications and reciprocal 16p11.2 microdeletions and duplications (Miles 2011).
        5. Examples of CNVs associated with autism: 16p11.2 deletion syndrome in approximately 1% of individuals with autism (Marshall et al. 2008) and 15q13.3 deletion syndrome associated with mental retardation,

epilepsy, and ASDs (Ben Shachar et al. 2009; Miller et al. 2009; Pagnamenta et al. 2009).

3. Single gene causes of autism in which neurologic findings are associated with ASDs (~5%)
    1. Fragile X syndrome (Wassink et al. 2001) found in a few percent of children with autism: At least 50% of children with fragile X syndrome have autistic behaviors, including avoidance of eye contact, language delays, repetitive behaviors, sleep disturbances, tantrums, self-injurious behaviors, hyperactivity, impulsiveness, inattention, and sound sensitivities
    2. Rett syndrome: Children affected with both autism and Rett syndrome (almost universally female sex) have a period of normal development, followed by loss of language with stereotypic hand movements (hand-wringing behavior)
    3. Tuberous sclerosis complex: Mentally retarded individuals with tuberous sclerosis complex frequently have autism (almost 50% in some studies)
    4. Neurofibromatosis type 1: Much less frequently associated with autism than is tuberous sclerosis and fragile X syndrome
    5. Duchenne muscular dystrophy: An unexpectedly large proportion of boys with Duchenne muscular dystrophy have autistic spectrum
    6. Sotos syndrome: A number of affected individuals diagnosed to have ASDs or autistic features
    7. Joubert syndrome: A few affected children diagnosed with autism
    8. Other macrocephalic conditions with overgrowth (Simpson-Golabi-Behmel syndrome, Beckwith-Wiedemann syndrome)
    9. Autism and macrocephaly or autism with no other clinical features: Reported to have germline *PTEN* mutations (Herman et al. 2007)
    10. Timothy syndrome (an autosomal dominant disorder characterized by lethal cardiac arrhythmias, congenital heart disease, webbing of fingers and toes, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism) (Splawski et al. 2004)
    11. Williams syndrome: Individuals with Williams syndrome show an unusually strong interest in people, including strangers, warm and engaging, and highly empathetic toward others versus profound impairments in social functioning, including difficulties interacting with others, attending to people, and decoding nonverbal cures, and impairments in social emotional reciprocity (Caglayan 2010)
    12. Smith-Magenis syndrome: Autistic-type behaviors reported in many affected individuals (Dykens et al. 1997)
    13. Smith-Lemli-Opitz syndrome: ~75% of affected children met the criteria for some variants of ASDs (Sikora et al. 2006)
    14. Cohen syndrome (an autosomal recessive connective tissue disorder caused by COH1 gene mutations): Autistic features may be relatively common (Karpf et al. 2004).
    15. Duchenne muscular dystrophy: 3.1% of patients with ASDs (Hendriksen and Vles 2008).
4. Metabolic cause associated with autism
    1. Mitochondrial cytopathies: 7% of patients with ASDs (Oliveira et al. 2005)
    2. Untreated phenylketonuria: an autism frequency of 2.7–5.6% in affected

individuals (Baieli et al. 2003; Steiner et al. 2003)
3. Sanfilippo syndrome: prominent behavioral disturbance in affected individuals (Neufeld and Muenzer 2001)
4. Adenylosuccinate lyase deficiency: autistic features in about one-third of patients (Spiegel et al. 2006)

2. Idiopathic autism (inherited autism of unknown cause)
1. Family studies indicate genetics plays the major causative role in most individuals with "idiopathic" autism (90–95%).
2. Epidemiologic studies.
1. A prevalence of 5–10 cases of classic autism per 10,000 (3–6 per 1,000 if the entire spectrum of autism is included)
2. A male-to-female ratio of 3:1
1. The preponderance of males suggests an X-linked disorder.
2. Linkage to the X chromosome suggested by recent genome-wide screens, although the data are inconsistent.
3. Male-to-male transmission of autism in multiplex families (families with more than a single affected family member) ruled out X-linkage in these families.
4. No significant associations of autism to Y chromosome based on Y haplotype analysis, although Y chromosome abnormalities have been documented.
3. Classification of idiopathic autism.
1. Essential autism
1. Defined by the absence of physical abnormalities
2. Seen in about 70% of children with idiopathic autism
3. Associated with better outcome overall
4. More likely a male
5. A higher sibling recurrence risk
2. Complex autism
1. Defined by the presence of dysmorphic features (microcephaly and/or a structural brain malformation)
2. Seen in about 30% of children with idiopathic autism
3. Associated with a poorer prognosis
4. A lower male-to-female ratio
5. A lower sibling recurrence risk

4. Evidence suggesting genetic basis of autism without a diagnosable cause.
1. 25% rate of recurrence in siblings of affected individuals from family studies: much greater than the prevalence rate in the general population
2. Greater than 60% rate of concordance for classic autism in monozygotic twins compared with no concordance found between dizygotic twins

5. The identity and the number of genes involved in autistic disorders: remained unknown.
1. Multigenic
1. Similar autistic phenotypes may arise from different genes or gene combinations in different families (single-mutation genetic heterogeneity).
2. Example: tuberous sclerosis caused by *TSC1* on chromosome 9q in some families and *TSC2* on 16p in others.
2. Polygenic
1. Several synergistically acting genes in an affected individual's genome may be required to produce the full autistic phenotype.
2. Lowering of a theoretical threshold by certain sets of genes acting in concert to allow the development of autism, either by themselves or given the right set of environmental or immunologic modifiers.
3. Other related developmental disorders in family members presumed to have inherited some of the susceptibility genes found in the affected family member or to have the same set of

susceptibility genes without exposure to the same environmental "trigger factors" for autism.

3. Search for candidate genes
   1. Cytogenetics: scrutinize the region involved in visible breakpoints, translocations, duplications, inversions, and deletions for the presence of genes that potentially may be involved in the pathogenesis of autistic spectrum disorders.
   2. Whole genome search: microsatellite marker screening in multiplex family uncovers specific chromosomal regions that affected individuals inherit more often than predicted by chance.
4. Genes for a monogenic hereditable form of autism (Caglayan 2010; Lintas and Persico 2009)
   1. Neuroligins (*NLGN3*, *NLGN4*) (located at Xq13 and Xq22.33, respectively): gene mutations noted in 1% of individuals with ASDs (Jamain et al. 2003; Lintas and Persico 2009).
   2. *Shanks3* gene (located at 22q13.3): mutations cause ASDs with phenotype characterized mainly by severe verbal and social deficits (Moessner et al. 2007; Aneja and Tierney 2008).
   3. Neurexins (*NRXN1*) (located at 2p16.3): Exonic deletions involving *NRXN1* have been found in 0.4% of probands with ASD, and rarely in controls, in large-scale genomic screening studies (Devlin and Scherer 2012).
   4. Methyl-CpG-binding protein 2 gene (*MeCP2*) (located at Xq28): de novo mutations occur in 80% of female patients with Rett syndrome.
   5. The homeobox A1 gene (*HOXA1*) (located at 7p15.3): autism noted in some patients (Bosley-Salih-Alorainy syndrome) (Herman et al. 2007).
   6. The phosphatase and tensin homologue gene (*PTEN*) (located at 10q23): reported in individuals with macrocephaly and autism (Butler et al. 2005; Herman et al. 2007; Buxbaum et al. 2007).
   7. Deletions in the X-linked *PTCHD1* gene and in the upstream *PTCHD1AS1* non-coding RNA may be associated with intellectual disability with or without ASD (Pinto et al. 2010; Noor et al. 2010).

Clinical Features

1. Early signs of infants with autism (Miles et al. 2005).
   1. Do not care to be held or cuddled
   2. Do not reach out to be picked up
   3. Often "colicky" and hard to console
   4. Typically quieting more readily when left alone
   5. Avoid and fail to initiate eye contact
   6. Stare into space
   7. Sleep disturbances
   8. Usually do not come to medical attention until after the second year when language delays are evident
2. Natural history.
   1. Onset of autism: prior to age three.
   2. Gradual onset in most children with autism.
   3. "Regressive" onset in about 30% of children with autism.
      1. Initially begin to talk.
      2. Then often precipitously lose language and become distant.
      3. Refuse to make eye contact within a matter of days and no longer respond to his or her name.
      4. Repetitive movements may develop immediately or by 3 or 4 years of age.
   4. About 25% of children who fit diagnostic criteria for autism at age 2 or 3 years.
      1. Subsequently begin to talk and communicate
      2. Blend to varying degrees into the regular school population by 6 or 7 years
   5. Remaining 75% of children with autism continue to have a life-long disability requiring intensive parental, school, and societal support.

6. Fewer than 5% of children with autism completely recover.
3. Mental retardation by nonverbal IQ testing in 50–70% of children with autism.
4. Seizures develop in about 25% of children with autism.
5. Idiopathic autism.
    1. About 30% of children have complex autism, defined by the presence of the following features:
        1. Dysmorphic features
        2. Microcephaly
        3. Structural brain malformation
    2. About 70% of children have essential autism, defined by the absence of physical abnormalities.
6. Behavioral impairments (Bailey et al. 1996; Agency for Healthcare Research and Quality 2014).
    1. Impairments in social interaction: separates individuals with autism from individuals around them
        1. Unable to "read" other people, ignoring them, and often strenuously avoiding eye contact
        2. Do not comfort others or seek comfort and do not share interests with others
        3. Usually prefers to be by himself, engaging in his own, often repetitive, activities at home
        4. Fail to develop friendships with peers and siblings
        5. Demonstrate a marked deficit in imitating other's actions, which may impede the development of interpersonal synchrony, communication, symbolic play, and the learning of new behaviors
    2. Impairments in communication
        1. Fail to develop reciprocal communication either by speech, gestures, or facial expression in most children with autism
        2. Fail to use eye gaze to communicate and direct attention in young children
        3. Display stereotypic speech that may involve echolalia or unusual inflections and intonations when children with autism learn to talk
    3. Restrictive, repetitive, and stereotypic behaviors and activities
        1. Staring or rocking.
        2. Toddlers may have motor "stereotypies."
            1. Movements of fingers
            2. Twirling strings
            3. Flicking pages of books
            4. Licking
        3. Repetitive whole-body movements.
            1. Spinning
            2. Running back and forth
        4. Complex repetitive movements may last for hours.
        5. Develop elaborate rituals in which the order of events, the exact words, and the arrangement of objects must be followed.
    4. Other symptoms
        1. Hyper- and hyposensitivities to sensory stimulation of all types (e.g., visual, auditory, tactile, and pain)
        2. Odd behaviors around foods and their presentation
        3. Abnormal sleep patterns
        4. Tantrums and/or self-injurious and aggressive behaviors brought on by a change in routine, an offending touch, or no apparent reason
        5. Impaired motor development with toe walking early in life and general clumsiness
        6. Total disregard for danger, resulting in high risk of early death, most commonly from drowning
7. Behavioral characteristics/co-occurring diagnoses (Harrington and Allen 2014; Lai et al. 2014).
    1. Developmental
        1. Intellectual disability (~45%)
        2. Language disorders (variable)
        3. Attention-deficit/hyperactivity disorder (28–44%)
        4. Tic disorders (14–38%)
        5. Motor abnormality ($\leq$79%)
    2. General medical
        1. Epilepsy (8–30%)
        2. Gastrointestinal problems (9–70%)
        3. Immune dysregulation ($\leq$38%)

4. Genetic syndromes (~5%)
5. Sleep disorders (50–80%)

3. Psychiatric disorders
   1. Anxiety (42–56%)
   2. Depression (12–70%)
   3. Obsessive-compulsive disorder (7–24%)
   4. Psychotic disorders (12–17%)
   5. Substance use disorders (≤16%)
   6. Oppositional defiant disorder (16–28%)
   7. Eating disorders (4–5%)
4. Personality disorders
   1. Paranoid disorders (0–19%)
   2. Schizoid personality disorder (21–26%)
   3. Schizotypal personality disorder (2–13%)
   4. Borderline personality disorder (0–9%)
   5. Obsessive-compulsive personality disorder (19–32%)
   6. Avoidant personality disorder (13–25%)
5. Behavioral
   1. Aggressive behaviors (≤68%)
   2. Self-injurious behaviors (≤50%)
   3. Pica (~36%)
   4. Suicidal ideation or attempt (11–14%)

8. Diagnostic criteria for autistic disorder (adapted from DSM-V) (American Psychiatric Association 2013; Augustyn 2014).
   1. Persistent deficits in social communication and social interaction in multiple settings; demonstrated by deficits in all three of the following (either currently or by history):
      1. Social-emotional reciprocity (e.g., failure of back-and-forth conversation; reduced sharing of interests and emotions)
      2. Nonverbal communicative behaviors used for social interaction (e.g., poorly integrated verbal and nonverbal communication; abnormal eye contact or body language; poor understanding of gestures)
      3. Developing, maintaining, and understanding relationships (e.g., difficulty adjusting behavior to social setting; difficulty making friends; lack of interest in peers)
   2. Restricted, repetitive patterns of behavior, interests, or activities; demonstrated by ≥2 of the following (either currently or by history):
      1. Stereotyped or repetitive movements, use of objects, or speech (e.g., stereotypes, echolalia, ordering toys, etc.)
      2. Insistence on sameness, unwavering adherence to routines, or ritualized patterns of behavior (verbal or nonverbal)
      3. Highly restricted, fixated interests that are abnormal in strength or focus (e.g., preoccupation with certain objects; perseverative interests)
      4. Increased or decreased response to sensory input or unusual interest in sensory aspects of the environment (e.g., adverse response to particular sounds; apparent indifference to temperature; excessive touching/smelling of objects)
   3. The symptoms must impair function (e.g., social, academic).
   4. The symptoms must be present in the early developmental period. However, they may become apparent only after social demands exceed limited capacity; in later life, symptoms may be masked by learned strategies.
   5. The symptoms are not better explained by intellectual disability or global developmental delay.
9. Differential diagnosis with other pervasive developmental disorders (Cohen and Volkmar 1997).
   1. Asperger disorder (Asperger 1944; Frith 1991, 2004; Miles et al. 2010)
      1. A variant of autism typically occurring in high-functioning individuals without mental retardation.
      2. Whether Asperger syndrome is the expression of the high end of the autism spectrum or a discrete genetic entity is unclear.
      3. Language development.
         1. Develops better than classic autism
         2. Problems with the semantic and pragmatic use of language
      4. Requires all other DSM-IV diagnostic criteria for autism.

5. Other characteristics.
    1. Misdiagnosed early on and in adulthood as odd or eccentric.
    2. Generally loners.
    3. Uncomfortable in groups.
    4. Unable to empathize with others.
    5. Does not chat.
    6. Follow a literal interpretation of speech with no understanding of idioms or jokes.
    7. Maintain a sameness in routine and follow strict rules.
    8. Have an encompassing preoccupation with one domain, such as the weather or computers.
    9. Speech may be pedantic or repetitive with odd intonations.
    10. Clumsiness: common.
    11. IQ must be within the normal range to qualify for the diagnosis.
2. Childhood disintegrative disorder (Heller syndrome)
    1. Behavioral, cognitive, and language regression between ages 2 and 10 years after entirely normal early development.
    2. Lose previously acquired language, social, and play skills.
    3. Cognitive skills usually impaired significantly.
    4. The condition may resemble autism in clinical presentation but differs from autism in the pattern of onset, course, and outcome.
    5. No longer considered one of the pervasive developmental disorders.
3. Pervasive developmental disorder, not otherwise specified (PDD-NOS)
    1. Onset after age 3 years.
    2. Children with autistic symptoms who do not meet full criteria in all three diagnostic domains can be diagnosed with PDD-NOS.
        1. Includes children with milder symptoms of all three autism diagnostic criteria and those meeting full criteria for autism in two of the three domains
        2. Used as an initial or tentative diagnosis for younger children or before diagnostic evaluations are completed

Diagnostic Investigations

1. Cytogenetic studies and molecular genetic analyses (Filipek et al. 2000; Miles et al. 2010; Baker and Jeste 2015)
    1. High-resolution or multi-FISH telomere chromosome studies.
        1. Chromosomal abnormality involving the proximal long arm of chromosome 15 (15q11-q13) observed in more than 1% of autistic individuals. Duplication is usually maternally derived, with one or two extra copies of the area roughly corresponding to the typical Angelman syndrome/Prader-Willi syndrome deletion region:
            1. Pseudodicentric 15 (inverted duplication 15)
            2. Atypical marker chromosomes
        2. Other chromosome abnormality: Cytogenetic abnormalities have been found on virtually every chromosome in individuals with autism.
    2. Chromosome microarray analysis (CMA) (Malhotra and Sebat 2012; Baker and Jeste 2015).
        1. Has replaced high-resolution chromosome analysis as the test of choice for the evaluation of any child with an autism spectrum disorder.
        2. Cytogenetic analysis, in addition to aCGH, is recommended when the family history suggests transmission of a balanced chromosome rearrangement.
        3. Two types of CMA technologies: provide the first opportunity to perform relatively unbiased genome-wide surveys of chromosomal deletions and duplications with much greater resolution.
            1. Array-based comparative genomic hybridization (aCGH)

2. Single nucleotide polymorphism (SNP): advantage of being able to detect specific inheritance patterns, such as uniparental disomy, which cannot be detected by aCGH (Heil and Schaaf 2013)
3. Limitations: cannot detect point mutations and microdeletions

3. Molecular genetic testing (*FMR1*) for full mutations and premutations for fragile X syndrome: unlikely positive in the presence of high-functioning autism.
4. Whole exome and whole-genome sequencing technology: Recent advances in genetic method have led to the identification of contributory mutations in up to 30% of children with ASD (Neale et al. 2012; O'Roak et al. 2012; Sanders et al. 2012; Yu et al. 2013; Baker and Jeste 2015).
    1. Facilitate investigations at the level of the single base pair
    2. Allow analysis of single gene defects
    3. Allow identification of partial loss of gene function
    4. Most large-scale exome-sequencing studies based on data from simplex families, or families with only one affected child leading to a growing appreciation of the role of de novo mutations in the pathogenesis of ASD
        1. More than 500 candidate genes have been identified from these large cohorts of thousands of children.
        2. Each with 50% chance of being contributory or causative.
        3. Network analyses of the functions of the potentially causative genes find genes implicated in synaptic formation and integrity and in chromatin modulation (Pinto et al. 2014; Ronemus et al. 2014).

2. Metabolic studies: positive in probably less than 5% of children with autism
    1. Metabolic evaluation.
        1. Quantitative plasma amino acids
        2. Quantitative urine organic acids
        3. Purines, creatine, and guanidinoacetate in the urine
        4. Serum concentration of lactate, pyruvate, creatine kinase, and uric acid
    2. Increased serum serotonin in about one-third of individuals with autistic disorder.
    3. Toxicologic studies.
    4. Review of child's newborn screening test results.
    5. Further studies are needed to determine the prevalence of mitochondrial respiratory chain disorders in autism, especially those with recurrent setbacks, hypotonia, and failure to thrive.
3. Electrophysiologic studies: epileptiform EEG abnormalities in autistic children with a history of regression and seizures
4. Neuroimaging (MRI) of the brain
    1. Indicated when the history and physical examination or neurologic examination suggests a localized lesion, tuberous sclerosis complex, Joubert syndrome, or an early environmental insult.
    2. Its routine use is controversial because of the expense and need for sedation or anesthesia by an anesthesiologist.
5. Guideline for genetic testing in autism spectrum disorder (Baker and Jeste 2015)
    1. Guidelines on the screening and diagnosis of autism published by the American Academy of Neurology and Child Neurology Society in 2000: High-resolution chromosome studies (karyotype) and DNA analysis for fragile X should be performed in the presence of mental retardation or if dysmorphic features are present (Filipek et al. 2000)
    2. Revised guidelines for testing published by the American College of Medical Genetics in 2003 (Schaefer and Mendelsohn 2013)
        1. All children with ASD
            1. Three generation family history
            2. Detailed physical examination to identify known syndromes

3. Chromosomal microarray oligonucleotide array comparative hybridization or single-nucleotide polymorphism microarray
2. Specific testing
   1. Males: DNA testing for fragile X
   2. Females: MECP2 sequencing
   3. Macrocephaly (>2.5 standard deviation above the mean): PTEN gene sequence analysis
3. Genetic counseling for all families
   1. Negative test (no etiology identified): counseling about recurrence risk (up to 20% based on infant sib studies)
   2. Positive test (etiology identified): counseling about specific mutations and associated clinical features, including comorbidities, treatment, and prognosis

Genetic Counseling

1. Recurrence risk
   1. Patient's sib.
      1. Secondary autism: The recurrence risk is based on information relevant to the primary diagnosis. For example:
         1. Supernumerary isodicentric 15q chromosome: no increased recurrence risk since it is a de novo occurrence
         2. Duplication of proximal 15q: an increased recurrence risk since it may result from segregation of a parental chromosome translocation or a maternally derived interstitial 15q duplication
      2. Idiopathic autism
         1. The empiric aggregate risk to sibs of individuals with autism of unknown cause varies across studies but is generally considered to range from 5% to 10% for autism and 10–15% for milder symptoms, including language, social, and psychiatric disorders (Bolton et al. 1994; Lauritsen et al. 2005; Miles et al. 2005; Landa 2008; Selkirk et al. 2009).
         2. For families with ≥2 children: the recurrence risk approaches 35% (Ritvo et al. 1989).
      3. Essential autism (Miles et al. 2005)
         1. For male sibs (brothers) of a proband with essential autism: a 7% of risk for autism and an additional 7% risk for milder autism spectrum symptoms
         2. For female sibs (sisters) of a proband with essential autism: a 1% risk for autism and an unknown risk for a milder autism spectrum disorder
      4. Complex autism (Miles et al. 2005): the sib recurrence risk of a proband with complex autism
         1. One percentage for autism
         2. An additional 2% for a milder autism spectrum disorder
      5. Half-siblings or third-degree relatives: generally accepted that recurrent risk falls off dramatically with more distant family relationship (Carter and Scherer 2013)
   2. Patient's offspring: unknown but the risk is probably higher than for siblings (Carter and Scherer 2013).
   3. De novo pathogenic mutation or CNV is present in the proband: recurrence risk is typically quoted as 1%, taking account the rare cases of gonadal mosaicism in one of the parents, or the possibility that one parent carries a chromosomal rearrangement that predisposes to the CNV, with much higher recurrent risk (Carter and Scherer 2013).
2. Prenatal diagnosis: may be available for the specific etiology for families at risk of having a child with a chromosomal disorder, copy number variant, or a single gene disorder
3. Management (Agency for Healthcare Research and Quality 2014)
   1. General goals of treatment.
      1. Improve language and social skills
      2. Decrease stereotypic and disruptive behaviors
      3. Support parents and families in their adjustment and to educate their children
      4. Foster independence

2. Early intervention programs focused on developing the following areas:
    1. Language
    2. Cognitive and imitation skills
    3. Social responsiveness
    4. Appropriate behavior
3. Behavior modification programs (Prater 2002).
    1. Structure the environment
    2. Provide consistent responses to behaviors
    3. Reward a desired behavior (positive reinforcement)
    4. No reward for undesirable behavior (negative reinforcement)
    5. Apply an adverse stimulus to deter an unwanted response (punishment)
    6. Reinforcing closer and closer approximations to the desired behavior (shaping)
4. School-aged children with autism (Bennetto and Rogers 2001).
    1. Need a curriculum that is tailored to individual strengths and needs
    2. Effective education programs
        1. Well-structured, systematic teaching routines
        2. Consistency and repetition
        3. Concrete and functional learning objectives
5. Adolescents and adults with autism (Bennetto and Rogers 2001).
    1. Need specific help in vocations and avocations in adult life
    2. Social skills groups
    3. Recreational activities
    4. Individual psychotherapy
    5. Vocational coaching and assistance
6. Pharmacotherapy (Anagnostou et al. 2014; Ji and Findling 2015): No medications are autism-specific.
    1. Antidepressants: Selective serotonin reuptake inhibitors with some success in treating preoccupations, ritualized behaviors, and mood disorders and anxiety.
    2. Stimulant medications: Little or no clinical improvement to decrease the activity levels and to improve the attention span of some children.
    3. Antipsychotic medications: New atypical antipsychotic medications may be useful in treating aggressive and hyperactive behavior with fewer side effects.
    4. Anticonvulsant medications: Used to treat individuals with autism who suffer from seizures and may be effective in decreasing aggressive behavior and episodic behavioral outbursts, particularly in children with seizure disorder.
    5. Risperidone and aripiprazole: The only two FDA-approved medications for irritability (aggression, self-injury, and severe tantrums) in children with ASD.
    6. Methylphenidate, atomoxetine, and alpha-2 agonists for ADHD symptoms.
    7. Melatonin for initial insomnia.
7. Treatments for core symptoms of autism spectrum disorders (Levy et al. 2009).
    1. Socialization
        1. Educational curricula (Myers 2009)
        2. Communication and language (Paul 2008): didactic and intensive training and Milieu teaching
        3. Social skills training (Seida et al. 2009)
        4. Behavioral treatment (Rogers and Vismara 2008): discrete trial instruction, pivotal response training, and relationship development intervention
    2. Communication
        1. Communication intervention (Paul 2008): within a comprehensive program (e.g., pivotal response training or other center), social pragmatics approach, and parent training
        2. Augmentative and assistive communication (Schlosser and Wendt 2008): picture exchange communication system, sign language, and assistive technology (e.g., vocal output devices)
        3. Behavioral (e.g., play, reciprocal communication) (Ospina et al. 2008): floor time/developmental, individual

differences, relationship-based approach, applied verbal behavior
4. Educational (Myers 2009)

3. Behavior
   1. Behavioral intervention (Ospina et al. 2008): discrete trial instruction and other comprehensive programs using applied behavior analysis
   2. Psychopharmacology (King and Bostic 2006): selective serotonin reuptake inhibitors, anticonvulsants, atypical antipsychotics, α-2 agonists

8. Complementary and alternative medical treatments (Hess et al. 2008)
   1. Biological
      1. Supplements – e.g., vitamin B6 or magnesium ion, dimethyl glycine, and cod liver oil
      2. Anti-infectives – e.g., antibiotics, antifungals, and antivirals
      3. Immunoglobulins
      4. Off-label drugs – e.g., secretin
      5. Chelation medications
      6. Gastrointestinal medications
      7. Elimination or special diets – e.g., gluten-free or casein-free
      8. Hyperbaric oxygen administration
   2. Non-biological
      1. Auditory integration training
      2. Chiropractic therapy
      3. Craniosacral manipulation
      4. Facilitated communication
      5. Massage and qigong
      6. Interactive metronome
      7. Reiki
      8. Transcranial stimulation
      9. Yoga

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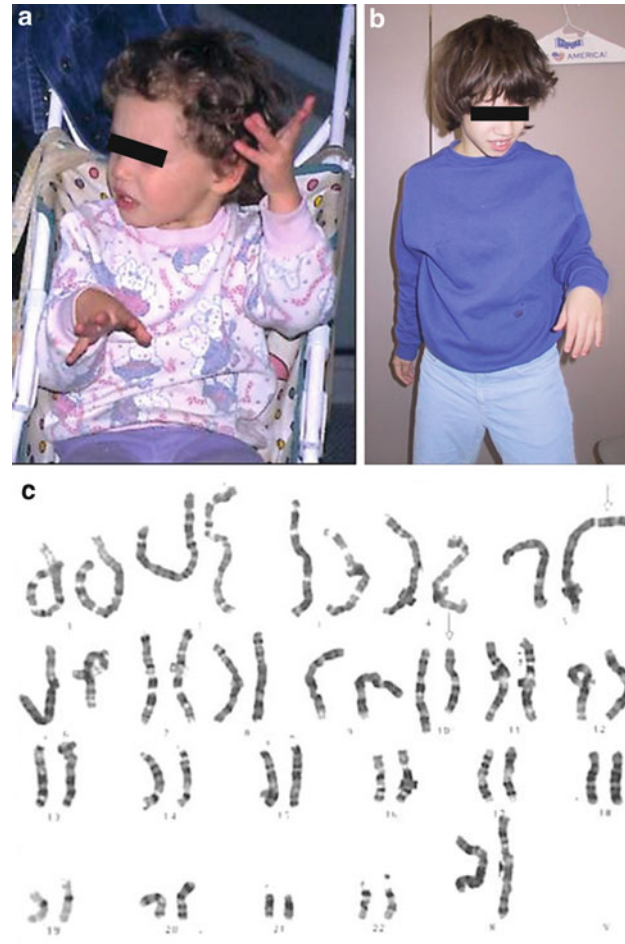

Fig. 1 (**a**–**c**) A girl (at 4 years and 10 years) with autism (**a**, **b**). Her chromosome study showed a balanced translocation between the short arm of chromosome 3 and the long arm of chromosome 10 [t (5;10)(p13;q21)] (karyotype shown) (**c**). Her parents had normal chromosomes

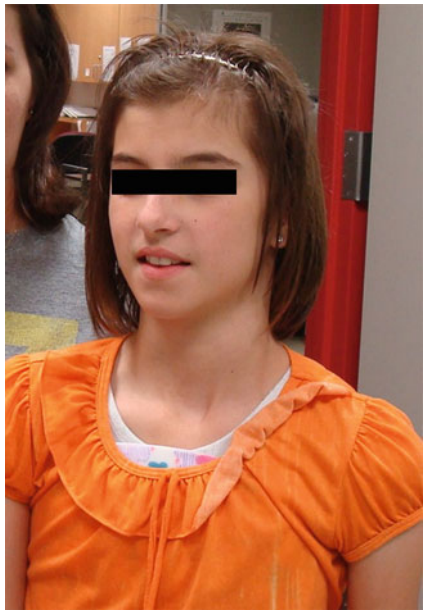

Fig. 2 An 11-year-old girl with autism. During infancy, she did not pay attention to people or environment and was often staring into space. She had echolalia and smiled without reason. She walked in time, but had reported spinning, flapping, and rocking

Bannayan-Riley-Ruvalcaba Syndrome

Contents

In 1960, Riley and Smith described a mother and her four children with macrocephaly and pseudopapilledema due to a mutation in a single autosomal gene (Riley and Smith 1960). In 1971, Bannayan described a 3-year-old girl with macrocephaly and numerous subcutaneous lesions ranging from lipolymphangio-hemangiomas to vascular hamartomas (Bannayan 1971). This syndrome was felt to be related to the one reported earlier by Riley and Smith since both lipomatosis and hemangiomatosis are hamartomatous malformations. In 1980, Ruvalcaba, Myhre, and Smith described two patients with macrocephaly, mental retardation, pigmented spotting of the glans penis and shaft, and multiple polyps of the gastrointestinal tract (Ruvalcaba et al. 1980). The cases described by Bannayan, Riley, Ruvalcaba, Myhre, and Smith were later known as the Bannayan-Riley-Ruvalcaba syndrome (BRRS) when Gorlin and colleagues in 1992 coined the term based on evidence of overlap of these syndromes and later would be linked to mutations in the *PTEN* gene, which also causes Cowden syndrome (CS) (Gorlin et al. 1992).

Currently, BRRS and CS are considered to be a single entity, with a phenotypic spectrum caused by mutations of the *PTEN* gene, referred to as the *PTEN* hamartoma tumor syndrome.

Synonyms and Related Disorders

Cowden syndrome; Proteus-like syndrome; PTEN hamartoma tumor syndrome; PTEN-related Proteus syndrome

Genetics/Basic Defects

1. *PTEN* (Phosphatase and Tensin homolog deleted on chromosome 10), a tumor suppressor gene on 10q23.3 (Zigman et al. 1997), has been identified as the susceptibility gene for two hamartoma syndromes, BRRS and CS (allelic conditions with variable expression and age-related penetrance) (Longy et al. 1998; Lachlan et al. 2007). Although distinct phenotypically, these two disorders display partial clinical overlap (Arch et al. 1997).
2. *PTEN* encodes a dual specificity phosphatase with homology to the focal adhesion molecules tensin and auxilin.
3. Germline mutations in the *PTEN* (Liaw et al. 1997; Celebi et al. 1999) are found in approximately 85% of individuals with classic

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Cowden syndrome and in 65% of individuals with BRRS and in other disorders (20%) (Proteus syndrome, Proteus-like syndrome) which are collectively referred to as the "*PTEN* hamartoma tumor syndrome" (PHTS) (Marsh et al. 1997, 1999; Eng 2000; Merks et al. 2003).
4. These phenotypically diverse disorders share several overlapping clinical features and a common genetic etiology, which has led to their gene-based classification of PHTS (Marsh et al. 1998, 1999). The broad, apparently difficult to predict, clinical manifestations of PHTS mandate thorough and meticulous phenomic analysis to ensure recognition and then proper diagnosis of patients who are at risk of developing neoplasia (Orloff and Eng 2008)

Clinical Features

1. Clinical features (Zonana et al. 1976; Gorlin et al. 1992).
    1. Macrocephaly with a normal ventricular system is common to all BRRS patients.
    2. Downslanting of the palpebral fissures (60%).
    3. Strabismus or amblyopia (15%).
    4. Schwalbe lines (35%).
    5. Birth weight above the mean and body length above the 97th percentile in most cases.
    6. Hypotonia, mild mental retardation, gross motor delay, autism spectrum disorder, and speech delay (50%).
        1. Motor delay is, for the most part, transient and improves with time.
        2. Irreversible myopathic disease in 60% of patients.
        3. Speckling of the glans penis and shaft, cutaneous angiolipomas, lymphangiomyomas, angiokeratomas, joint hyperextensibility, pectus excavatum, scoliosis, and accelerated growth of the metacarpals and of the first and second phalanges (50%).
    7. Subcutaneous lipomas (75%).
    8. Hemangiomas and café au lait spots of the trunk and lower extremities (10%).
    9. Hamartomatous polyps (45%): limited to the ileum and colon leading to rectal bleeding and intussusception.
    10. Posterior subcapsular congenital cataract due to altered function of the PTEN protein (Boccone et al. 2008).
2. Several clinical features common to CS (Marsh et al. 1999).
    1. Hashimoto's thyroiditis
    2. Vascular malformations
    3. Mental retardation
    4. Main differential features with BRRS
        1. Pigmented macules of the glans penis and shaft and delayed motor development: seen in BRRS but not seen in CS patients
        2. Lipomatosis common in BRRS: rarely seen in patients with CS
3. No agreed international criteria for the diagnosis of BRRS exist.
    1. Criteria of diagnosis by Marsh et al. (1999) with at least the following four features:
        1. Macrocephaly
        2. Lipomatosis
        3. Hemangiomas
        4. Speckled penis in males
    2. Criteria by Parisi et al. (2001) with at least two of the following three features:
        1. Macrocephaly
        2. Hamartomas (including at least one lipoma, hemangioma, or intestinal polyp)
        3. Penile macules in males
4. Differential diagnosis (Calva and Howe 2008; Eng 2014).
    1. Cowden syndrome (Lloyd and Dennis 1963; Starink et al 1986; Pilarski et al. 2011)
        1. A complex disorder with malignant and benign (hamartomatous) lesions affecting derivatives of all three germ cell layers, affecting the breast, thyroid, uterus, brain, and mucocutaneous tissues.
        2. Lhermitte-Duclos disease (adult) (dysplastic cerebellar gangliocytoma) (Zhou et al. 2003b; Riegert-Johnson et al. 2010): pathognomonic.
        3. By the third decade, 99% of affected individuals develop the mucocutaneous

stigmata (primarily trichilemmomas and papillomatosis papules) as well as acral and plantar keratoses: pathognomonic (Eng 2000).
4. Thyroid abnormalities (50–67%).
    1. Goiter
    2. Adenoma
    3. Thyroid cancer (typically follicular, but occasionally papillary) (approximately 10%), while the risk for endometrial cancer, although not well established, has been estimated to be 5–10%
5. Breast lesions.
    1. Fibroadenomas/fibrocystic disease (76% of affected females)
    2. Adenocarcinoma (25–50% of affected females), with an average age of diagnosis between 38 and 46 years old
6. Gastrointestinal lesions: hamartomatous polyps (40%).
7. Macrocephaly (38%).
8. Genitourinary abnormalities (44% of females).
9. Uterine leiomyoma (multiple, early onset).
10. Associated with germline mutations in *PTEN* (80% in Cowden syndrome probands ascertained by the strict operational diagnostic criteria for Cowden syndrome).

2. Proteus syndrome and Proteus-like syndrome
    1. A highly variable disorder involving congenital malformations, hamartomatous overgrowth of multiple tissues, connective tissue and epidermal nevi, and hyperostoses which affect patients in a mosaic pattern.
    2. Consensus diagnostic criteria available (Biesecker et al. 1999).
    3. While initially thought to be unrelated to Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome, at least two independent reports have identified germline *PTEN* mutations in approximately 20% of patients with Proteus syndrome (Zori et al. 1998; Smith et al. 2002).
    4. Furthermore, approximately 50% of patients with a Proteus-like syndrome (with significant features of Proteus syndrome, but not meeting diagnostic criteria) were also found to have germline *PTEN* mutations (Zhou et al. 2001).
    5. Thus, at least a subset of Proteus syndrome and Proteus syndrome-like conditions are allelic to Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome and are part of the *PTEN* hamartoma tumor syndrome spectrum.
3. Juvenile polyposis syndrome (JPS)
    1. An autosomal dominant disorder.
    2. Characterized by predisposition for hamartomatous polyps in the gastrointestinal tract, specifically in the stomach, small intestine, colon, and rectum.
    3. Untreated polyps lead to bleeding and anemia.
    4. Malignant transformation can occur though most juvenile polyps are benign.
    5. Approximately 20% of individuals with JPS have mutations in the *MADH4* gene, and approximately another 20% of individuals with JPS have mutations in the *BMPR1A* gene (Howe et al. 1998; 2001).
4. Peutz-Jeghers syndrome (PJS)
    1. An autosomal dominant disorder
    2. Characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation
    3. Characteristics of polyps
        1. Most prevalent in the small intestine but also occur in the stomach and large bowel.
        2. Often symptomatic with intussusception and rectal bleeding.
        3. The pigmentation of the perioral region is pathognomonic, particularly if it crosses the vermilion border.

4. Hyperpigmented macules on the fingers are also common.
5. Molecular genetic testing of *STK11/LKB1* reveals disease-causing mutations in approximately 70% of individuals who have a positive family history and 20–70% of individuals who have no family history of PJS.

Diagnostic Investigations

1. A yearly hemoglobin test from early infancy for the early detection of intestinal hamartomas (Hendriks et al. 2003)
2. Imaging studies to define extent of the neoplasms
3. *PTEN* molecular genetic diagnosis by full sequencing available on clinical basis (Eng 2014)
    1. Diagnosis of PHTS made only when a *PTEN* mutation is identified
    2. Detectable *PTEN* gene mutation
        1. Up to 65% of individuals meeting the diagnostic criteria of BRRS (Marsh et al. 1999; Zhou et al. 2003a).
        2. Up to 85% of individuals meeting the diagnostic criteria for CS (Marsh et al. 1998; Zhou et al. 2003a).
        3. Preliminary data available suggest that up to 50% of individuals with a Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have *PTEN* mutations.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. 50% if one parent is affected
        2. Recurrent risk probably negligible if neither parent has the *PTEN* mutation found in the proband since germline mosaicism has not been reported
    2. Patient's offspring: 50%
2. Prenatal diagnosis (Eng 2014)
    1. Possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15–18 weeks' gestation or chorionic villus sampling at approximately 10–12 weeks' gestation if the disease-causing allele of an affected family member has been identified.
    2. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member.
3. Management
    1. Cancer surveillance: the most important aspect of management of an individual with a *PTEN* mutation
        1. Annual physical examination from age 18 years
        2. Annual urinalysis
        3. Baseline colonoscopy at age 50 years
    2. Molecular testing of asymptomatic at-risk relatives to identify those who have a family-specific *PTEN* mutation and ensure appropriate surveillance

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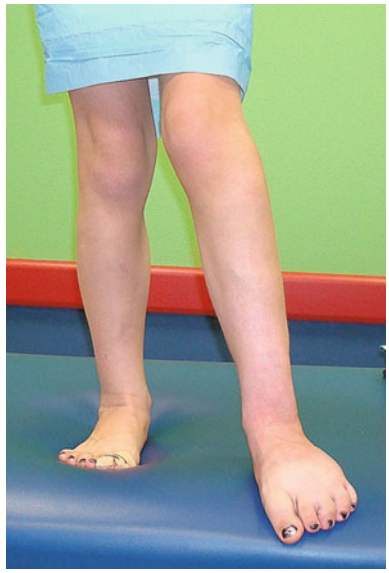

Fig. 1 The patient, a 6-year-old Caucasian female, was seen for difficulty in walking. She complained significant pain in the *left* lower leg with prominent veins associated with intermittent swelling for the past 4 years. The physical examinations and various imaging studies revealed *left* lower extremity vascular malformation causing significant pain syndrome, swelling, limb dysfunction and gait disturbance, and multiple lipomas. The patient was found to have a PTEN deletion which was performed at other institution. The molecular testing confirmed the clinical diagnosis of Bannayan-Riley-Ruvalcaba syndrome. The family history revealed multiple family members affected with lipomatosis (mother, maternal great aunt, and a first cousin)

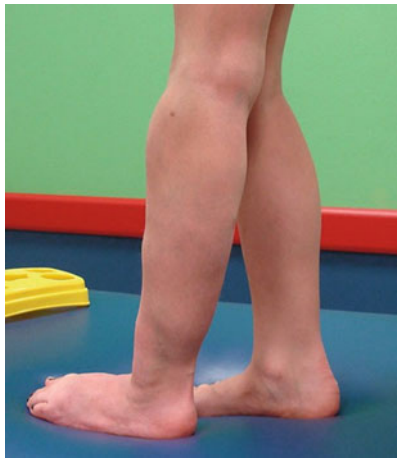

Fig. 2 Note the vascular malformation affecting *left* lower extremity

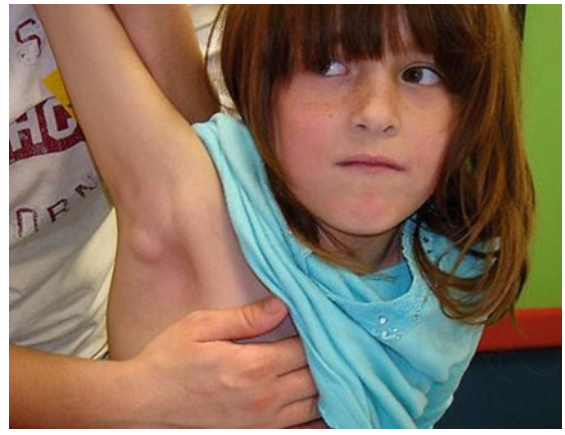

Fig. 3 A lipoma noted on the *right* axillary region

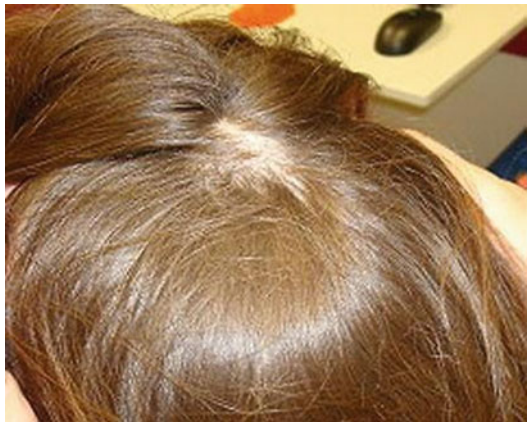

Fig. 4 A lipoma noted on the scalp

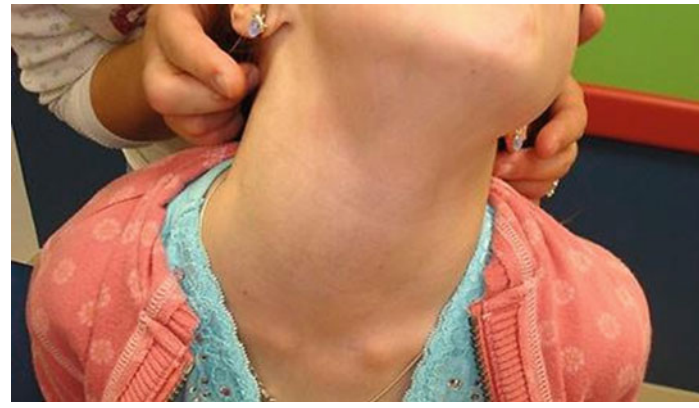

Fig. 5 A diffuse lipoma noted on the *right* side of the anterior neck

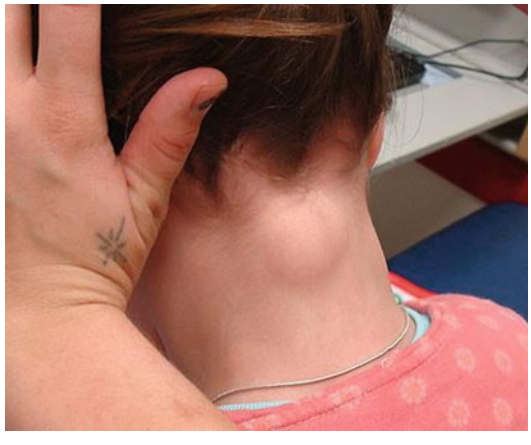

Fig. 6 A lipoma noted on the back of the neck

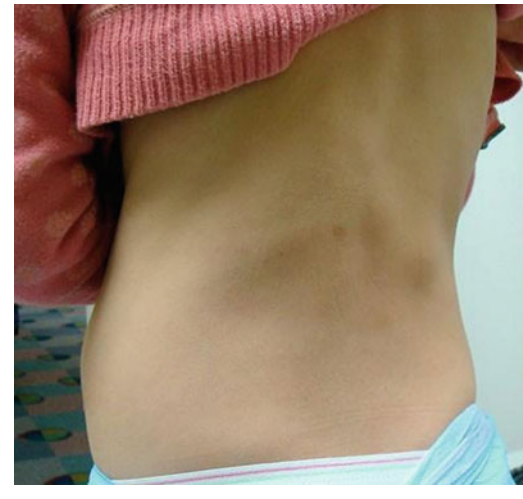

Fig. 7 A diffuse lipoma noted on the *left* side of the back

Beckwith-Wiedemann Syndrome

Contents

The Beckwith-Wiedemann syndrome (BWS) is the most common and the best-known congenital overgrowth syndrome. It was named after Beckwith who, in 1963, described three unrelated patients with exomphalos, hyperplasia of the kidneys and pancreas, and adrenal cytomegaly (Beckwith 1963). Wiedemann in 1964 (Wiedemann 1964) reported a familial form of omphalocele with macroglossia. The incidence is estimated to be about one in 13,700 births.

Synonyms and Related Disorders

Exomphalos-macroglossia-gigantism syndrome; Wiedemann-Beckwith syndrome

Genetics/Basic Defects

1. Genetics of BWS: complex (Engel et al. 2000)
    1. Pedigree data (Engstrom et al. 1988; Elliott et al. 1994)
        1. Sporadic (85%)
        2. Familial (15%): autosomal dominant inheritance with variable expressivity, incomplete penetrance (Pettenati et al. 1986), and preferential maternal transmission
    2. Karyotypic data
        1. Chromosome rearrangements influenced by the parent of origin (2%)
            1. Paternally derived 11p15.5 duplications exhibiting atypical clinical features as well as a significant risk of developmental delay
            2. Maternally derived translocations and inversions exhibiting typical features of Beckwith-Wiedemann syndrome
        2. Normal karyotype (98%)
    3. Molecular data: BWS is caused by alterations in growth regulatory genes on chromosome region 11p15.5, which is subjected to genomic imprinting (an epigenetic mechanism in which gene expression is altered according to the parental origin of the allele)
2. Pathogenesis (Li et al. 1997, 1998; Maher and Reik 2000; Ferry 2010; Soejima and Higashimoto 2013)
    1. Imprinted genes have been implicated in the pathogenesis of both familial and sporadic BWS (Hatada and Mukai 2000)
    2. A subgroup of BWS patients has loss of methylation at a differentially methylated region (KvDMR1) within the *KCNQ1* gene centromeric to the *IGF2* and *H19* genes

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Maternally expressed 11p genes
    1. *CDKN1C* (also known as *P57KIP2*) (Hatada et al. 1996; Lam et al. 1999): a member of the cyclin-dependent kinase inhibitor family: a candidate for a maternally expressed growth inhibitory gene in BWS
        1. Germline mutations detected in >40% of familial cases
        2. Mutations infrequent (<5%) in sporadic cases
    2. *H19*: a maternally expressed gene encoding a biologically active nontranslated mRNA that may function as a tumor suppressor. Deletion of *H19* or transposition from its usual position relative to *IGF2* disrupts normal imprinting.
    3. *KCNQ1* (also known as *KvLQT1*): serves as an imprinting center, disruption of which could affect transcription and DNA replication through an effect on chromatin structure.
4. Paternally expressed 11p genes
    1. *IGF2* (the gene for insulin-like growth factor-2): a paternally expressed and maternally imprinted embryonic growth factor. Many sporadic cases show loss of imprinting of *IGF2* resulting in biallelic expression.
    2. *KCNQ1OT1* gene (also known as *LIT1*): The unmethylated paternal allele of *KvDMR1* permits transcription of the antisense transcript *KCNQ1OT1* and silencing of the *KCNQ1* and *CDKN1C* genes (Murrell et al. 2004).
5. Effect of multiple genes: combination of increased expression of paternally expressed growth promoter genes such as *IGF2* and loss of maternally expressed growth suppressor genes in some patients with paternal uniparental disomy of 11p15
6. Uniparental disomy (mosaic paternal isodisomy) for the band 11p15.5 (10–20% of sporadic cases)
    1. Two paternally derived copies of chromosome 11p15 and no maternal contribution for that chromosome region
    2. Resulting from postzygotic mitotic recombination and mosaic paternal isodisomy
    3. All patients with uniparental disomy exhibit somatic mosaicism
7. Opposite methylation defects, gain of methylation and loss of methylation, at H19DMR are known to cause clinically opposite disorders: BWS and Silver-Russell syndrome, respectively. Loss of function or gain of function of CDKN1C also causes clinically opposite disorders, BWS and IMAGe (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies) (Soejima and Higashimoto 2013)
8. Recent clinical studies have suggested a relationship between assisted reproductive technology and the risk of imprinting disorders, along with the existence of trans-acting factors that regulate multiple imprinted differentially methylated regions (Soejima and Higashimoto 2013)

3. Clinical findings relevant to molecular etiology (Weksberg et al. 2010)
    1. Tumor development
        1. Individuals with UPD of 11p15.5 or gain of methylation at the H19. Imprinting center (IC) carry the highest risk to develop Wilms tumor or hepatoblastoma.
        2. Individuals with loss of maternal methylation at IC2 carry a lower tumor risk; as well, the tumors in this molecular subgroup do not include Wilms tumor.
        3. Individuals with mutations in *CDKN1C* seem to have the lowest risk with only a small number of cases reported. In cases with *CDKN1C* mutation, only neuroblastoma has been reported to date.
    2. Hemihyperplasia in cases of BWS: Alterations have included mosaicism for UPD 11p15.5 with hemihyperplasia and or molecular alterations at IC2 or IC1.
    3. Positive family history: associated with mutations in *CDKN1C* or microdeletions of IC1 and very rarely IC2.

4. Omphalocele: associated with an IC2 defect or *CDKN1C* mutation.
5. Developmental delay: associated with cytogenetically detectable duplications involving the paternal copy of chromosome 11p15.5.
6. A severe BWS phenotype
    1. This seems to be associated, at least in certain cases, with very high levels of paternal chromosome 11p15.
    2. An increased frequency of female monozygotic twins discordant for BWS has been reported. These females usually show loss of methylation at IC2.
    3. In contrast, the less frequently observed male monozygotic twins show a broad spectrum of BWS-associated molecular alterations.
7. Sterility/assisted reproductive technologies (ART)
    1. This seems to be associated with an increased risk of BWS cases with loss of methylation at IC2.
    2. No specific aspect of subfertility or its treatment has been specifically associated with the increased risk of epigenetic defects associated with BWS after ART.

Clinical Features

1. Variable phenotypic expression (Shuman et al. 2010; Ibrahim et al. 2014)
2. Prenatal and postnatal overgrowth (gigantism) (cardinal feature)
    1. Fetus grows at an increased rate during the latter half of pregnancy
    2. Large or above normal size baby at birth
    3. Eventual somatic gigantism in most cases
    4. Advanced bone age
    5. Hemihyperplasia or hemihypertrophy (13%)
3. Performance
    1. Development
        1. Usually normal unless there is chromosome 11p15.5 duplication or serious perinatal complications such as prematurity or uncontrolled hypoglycemia.
        2. Mild-moderate mental retardation from undetected hypoglycemic episodes during infancy
    3. Hypoglycemia
        1. Reported in 30–50% of babies with BWS
        2. Likely caused by islet cell hyperplasia and hyperinsulinemia
    2. Seizures in some cases
4. A recognizable facial gestalt: common but often normalizes across childhood (Elliot and Maher 1994)
    1. Macroglossia (cardinal feature)
        1. Chronic alveolar hypoventilation
        2. Anterior open bite
    2. Earlobe grooves or indented ear lesions on the posterior rim of the helix or concha
    3. Facial nevus flammeus
    4. Midfacial hypoplasia
    5. Prominent eyes with infraorbital creases
    6. Maxillary hypoplasia
    7. Full lower face with a prominent mandible
    8. Prominent occiput
    9. Ear creases/pits
5. Abdominal wall defect
    1. Omphalocele (cardinal feature)
    2. Umbilical hernia
    3. Diastasis recti
6. Gastointestinal anomalies
    1. Malrotation anomalies
    2. Dome-shaped defect of the diaphragm
7. Visceromegaly
    1. Fetal adrenocortical cytomegaly: pathognomonic finding for BWS
    2. Hepatomegaly (frequent)
    3. Nephromegaly (frequent)
    4. Cardiomegaly that resolves spontaneously
    5. Occasional clitoromegaly
    6. Hyperplastic pancreas, bladder, uterus, and thymus
8. Neoplasms: overall risk for tumor development in children with BWS estimated at 7.5%
    1. Benign tumors
        1. Adrenal adenoma
        2. Carcinoid tumor
        3. Fibroadenoma
        4. Fibrous hamartoma

5. Ganglioneuroma
6. Myxoma

2. Malignant tumors: predisposition to embryonal malignancies
    1. Wilms tumor (most frequent) (3.7% incidence) (Borer et al. 1999)
    2. Hepatoblastoma: can be associated with elevated serum alpha-fetoprotein levels (Everman et al. 2000)
    3. Adrenocortical carcinoma
    4. Rhabdomyosarcoma
    5. Neuroblastoma
    6. Glioblastoma
    7. Malignant lymphoma
    8. Pancreatoblastoma
    9. Teratoma
3. Clinical findings associated with higher risks of tumor development
    1. Hemihyperplasia
    2. Nephromegaly
    3. Nephrogenic rests

9. Additional features
    1. Polyhydramnios
    2. Prematurity
    3. Enlarged placenta
    4. Hemangioma
    5. Congenital heart defects
    6. Other renal anomalies
        1. Medullary dysplasia
        2. Duplicated collecting system
        3. Nephrocalcinosis
        4. Medullary sponge kidney
        5. Cystic changes
        6. Diverticula
10. Adult phenotype
    1. Hemihyperplasia
    2. Prominent jaw
    3. Enlarge tongue
    4. Ear creases and pits
    5. Enlarged kidneys and other abdominal organs
    6. Normal height
11. Major and minor findings associated with BWS (Weksberg et al. 2010)
    1. Major findings
        1. Abdominal wall defect: omphalocele (exomphalos) or umbilical hernia
        2. Macroglossia
        3. Macrosomia (traditionally defined as height and weight >97th percentile)
        4. Anterior ear lobe creases and/or posterior helical pits (bilateral or unilateral)
        5. Visceromegaly of intra-abdominal organ(s); for example, liver, kidney (s), spleen, pancreas, and adrenal glands
        6. Embryonal tumor in childhood
        7. Hemihyperplasia
        8. Cytomegaly of adrenal fetal cortex, usually diffuse and bilateral
        9. Renal abnormalities, including medullary dysplasia and later development of medullary sponge kidney (MSK)
        10. Positive family history of BWS
        11. Cleft palate
    2. Minor findings
        1. Pregnancy-related findings of polyhydramnios, enlarged placenta, and/or thickened umbilical cord, premature onset of labor and delivery
        2. Neonatal hypoglycemia
        3. Nevus flammeus
        4. Cardiomegaly/structural cardiac anomalies/cardiomyopathy
        5. Characteristic facies
        6. Diastasis recti
        7. Advanced bone age
12. Simpson-Golabi-Behmel syndrome (clinical overlap with BWS) (Knopp et al. 2015)
    1. Clinical features overlap with BWS
        1. Pre- and postnatal overgrowth
        2. Macroglossia
        3. Umbilical hernia
        4. Organomegaly
        5. Ear lobe creases
        6. Occurrence of embryonic tumors
    2. Other features
        1. Distinctive craniofacial features (a wide mouth with an everted and thickening below the lower lip, epicanthal folds, and others)
        2. Supernumerary nipples
    3. A rare X-linked condition caused by glypican3 (GPC3) which encodes for a

membrane-associated heparan sulfate proteoglycan

Diagnostic Investigations

1. Transitory neonatal hypoglycemia (spontaneous regression during the first 4 months of life) (63%)
2. Neonatal polycythemia (20%)
3. Hypercholesterolemia, hyperlipidemia, hypothyroidism, thyroxine-binding globulin deficiency: rare occurrence
4. Periodic abdominal ultrasonography for organomegaly and embryonal tumors, followed by MRI or CT if indicated
5. Radiography
    1. Advanced bone age
    2. Chest radiography to rule out rare neural crest tumors such as thoracic neuroblastoma
6. Echocardiography for suspected cardiac abnormality
7. Chromosome analysis (high resolution and FISH studies)
    1. Normal chromosomes in most patients
    2. Chromosome abnormalities involving 11p15 in $\leq$1% of cases
        1. Partial duplication of chromosome 11p (Waziri et al. 1983)
        2. Paternally derived 11p15.5 duplication (Slavotinek et al. 1997)
        3. Maternally derived translocations and inversions
8. Molecular analysis (Shuman et al. 2010)
    1. Paternal uniparental disomy (UPD) of 11p15 in multiple tissues (10–20%)
        1. Restriction fragment length polymorphism (RFLP) analysis of multiple 11p15 loci
        2. Methylation studies of multiple imprinted genes on 11p15
    2. Mosaicism for paternal uniparental isodisomy of chromosome 11p15.5 om 28% of informative sporadic BWS patients (Slatter et al. 1994)
    3. Mutation analysis: *P57 KIP2* (5–10%) (screen for mutation by heteroduplex/SSCP analysis, followed by sequence of *P57 KIP2* exons)
    4. Molecular testing is typically not indicated for parents or other family members when UPD is found, as these cases arise through postzygotic somatic recombination.
    5. Parental studies are recommended if genomic alterations are found, that is, karyotype abnormalities, *CDKN1C* mutations, or microduplications or microdeletions of the 11p15.5 region (Weksberg et al. 2010).
    6. *CDKN1C* sequencing (after 11p15 methylation analysis) should be performed for (Brioude et al. 2015):
        1. Apparently sporadic cases in patients with abdominal wall defects (umbilical hernia or exomphalos), a cleft palate or a hypospadias, and without hemihyperplasia, or
        2. In familial cases of BWS even if the abdominal wall is normal
9. Molecular genetic results and relationship to clinical indications for referral (a total of 1,091 referrals) (Ibrahim et al. 2014)
    1. 46.5% had abnormal methylation profile at IC1 (distal imprinting centers) and/or IC2 (centromeric imprinting centers)
        1. 4.3% had hypermethylation at IC1 only
        2. 29.4% had isolated IC2 hypermethylation
        3. 12.4% had isolated IC1 and IC2 methylation from paternal UPD
    2. Low-level mosaicism may be missed
    3. Some cases with normal BWS methylation profiles may have *CDKN1C* mutations

Genetic Counseling

1. Recurrence risks (Shuman et al. 2010)
    1. Patient's sib: The risk to the sibs of a child with BWS depends on the genetic basis for BWS in the proband
        1. Probably a low recurrence risk in cases of negative family history, normal karyotype, and absence of identifiable molecular etiology

2. Up to 50% of recurrence risk in cases of positive family history and normal karyotype
3. Up to 50% recurrence risk in cytogenetically detected maternal 11p15 translocation or inversion
4. An undetermined recurrence risk in cytogenetically detected paternal 11p15 duplication
5. A low recurrence risk in cases of paternal 11p15 uniparental disomy as this event arises from a postzygotic somatic recombination
6. 50% recurrence risk if a *CDKN1C* mutation is present in a parent (usually maternally transmitted)
7. Four clinically relevant categories identified for approximately 85% of individuals with BWS who have a negative family history and a normal karyotype (Shuman et al. 2010):
    1. Proband with *KCNQ1OT1* hypomethylation (∼50–60%): very low recurrence risk since no recurrences of loss of methylation at *KCNQ1OT1* have been reported in first-degree relatives of individuals with BWS who have this molecular lesion.
    2. Proband with paternal uniparental disomy for 11p15 (∼10–20%): the recurrence risk is empirically very low because the UPD appears to arise from a postzygotic somatic recombination.
    3. Proband with a *CDKN1C* mutation (∼510%): Both parents should be tested for mutations. Several instances of transmission of *CDKN1C* mutations from clinically unaffected mothers to affected offspring have been reported as well as two instances of paternal transmission from clinically unaffected fathers. The recurrence risk for such parents may be as high as 50%.
    4. Proband with no identifiable primary etiology (∼13–15%): The risk to members in these families is unknown but empirically low.
    2. Patient's offspring (Shuman et al. 2010)
        1. Negative family history (10–20% of individuals with BWS and no known family history of BWS have paternal uniparental disomy of 11p15) and normal karyotype (5–10% of all individuals with BWS with a normal karyotype have identifiable mutations in *CDKN1C*): ∼85% of individuals with BWS
            1. *KCNQ1OT1* hypomethylation: a low recurrence risk
            2. Uniparental disomy for 11p15: likely a very low risk
            3. Identified *CDKN1C* mutation: The risk to offspring of a female with a *CDKN1C* mutation is 50%; the risk to offspring of a male with a *CDKN1C* mutation is <50%, but too few cases have been reported to generate a risk figure
        2. Positive family history and normal karyotype: ∼10–15% of individuals with BWS
            1. ∼50% if transmitting parent is female
            2. <50% if transmitting parent is male
        3. Monozygous twins (<1% of individuals with BWS): theoretically low
2. Prenatal diagnosis
    1. Indications (Weksberg et al. 2010)
        1. Families having a child with severe manifestations of BWS.
        2. If a cytogenetic or genomic abnormality (e.g., microdeletion, *CDKN1C* mutation) has been identified, prenatal testing may be indicated by CVS or amniocentesis. If such abnormalities are *de novo*, gonadal mosaicism remains a possibility. Epigenetic analysis of amniocytes can be undertaken by methylation-sensitive multiplex ligation probe analysis (MS-MLPA).
        3. Families, for whom UPD or methylation alterations have been detected in the absence of a transmissible genomic alteration, may also wish to consider

prenatal diagnostic testing even though the recurrence risk would be very low. Of note, a recent follow-up study of apparently isolated fetal omphalocele reported BWS in 20% of cases based on clinical or molecular findings (Wilkins-Haug et al. 2009).

2. Maternal serum screening (Kagan et al. 2015)
    1. Maternal serum alpha-fetoprotein: may be elevated in a fetus with omphalocele
    2. An excessive beta-hCG levels: may be related to the placentamegaly
3. Prenatal Ultrasonography (Weng et al. 1995a, b; Eckmann-Scholz and Jonat 2011; Kagan et al. 2015)
    1. Fetal overgrowth (macrosomia)
    2. Polyhydramnios
    3. Enlarged (hydropic) placenta
    4. A long umbilical cord
    5. Macroglossia
    6. Cleft palate
    7. Distended abdomen
    8. Abdominal wall defects including omphalocele (Winter et al. 1986)
    9. Organomegaly (hepatomegaly)
    10. Renal anomalies
    11. Cardiac anomalies
4. Cytogenetic studies
    1. Possible if a cytogenetic abnormality has been identified in the proband and one parent
    2. To identify translocations, deletions, inversions (Norman et al. 1992), and duplications involving 11p15 (Reish et al. 2002)
5. Molecular analysis
    1. Uniparental disomy
    2. Mutation analysis of *CDKN1C*, provided the mutation has been documented in the previously affected child

3. Management
    1. Early detection and close monitoring for hypoglycemia to reduce the risk of central nervous system complications
    2. Partial tongue resection for cosmetic purpose and to relieve severe airway obstruction
    3. Surgical risks related to hypoglycemia or difficulty in intubation secondary to macroglossia
    4. Management of abdominal wall defects, gastrointestinal malformations, and renal anomalies
    5. Orthopedic follow-up of hemihyperplasia
    6. Management of structural renal abnormalities
    7. Persistent congenital hyperinsulinism in BWS/11p overgrowth appears to be exclusive due to paternal UPD11p and may present to be either diazoxide-responsive or diazoxide-unresponsive. In cases of UPD-11p overgrowth that have also had a paternally transmitted KATP mutation, congenital hyperinsulinism may be particularly severe and difficult to control. Recognition of UPD-11p overgrowth in patients with congenital hyperinsulinism is of particular importance because of the need to monitor for potential tumors (Kalish et al. 2016).
    8. Management of embryonal neoplasms

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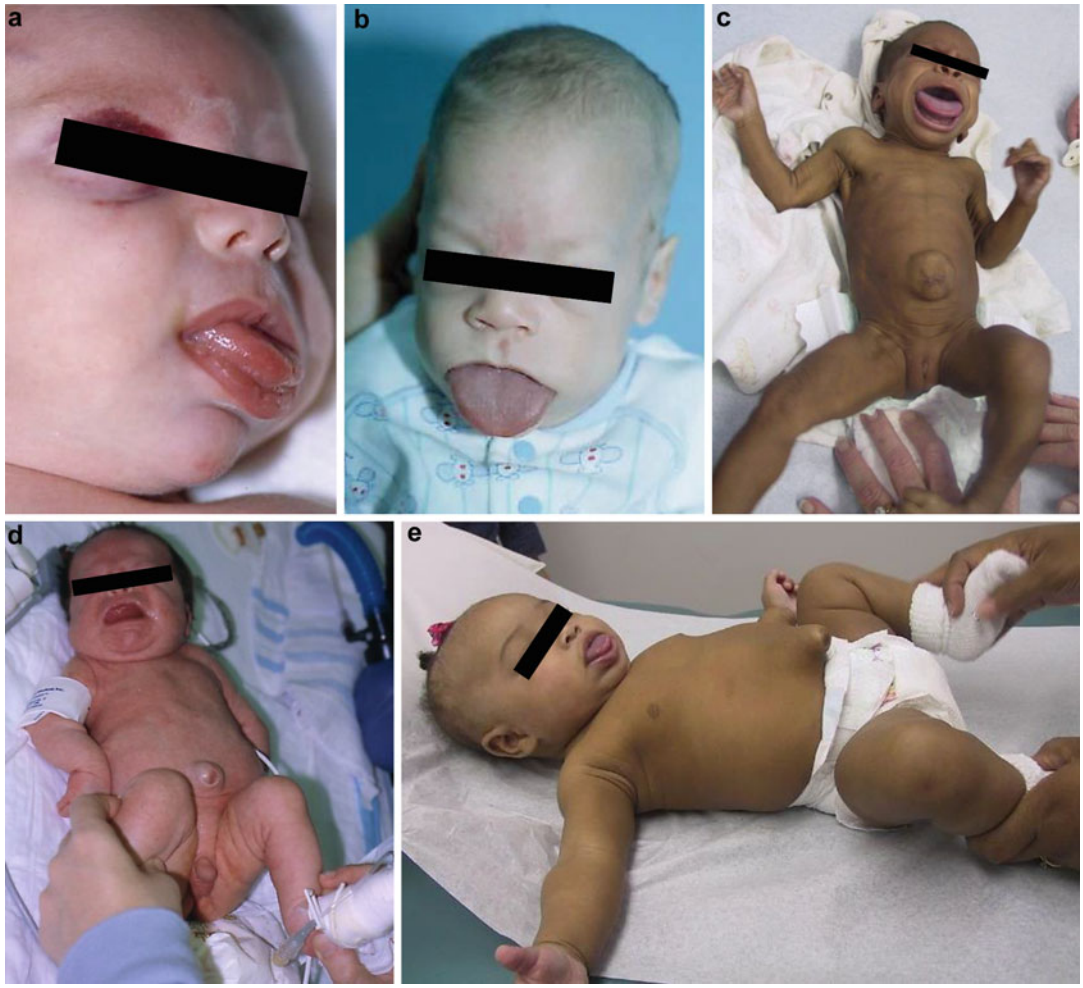

Fig. 1 (**a**–**e**) Five infants with Beckwith-Wiedemann syndrome showing hemangioma, macroglossia, and umbilical hernia

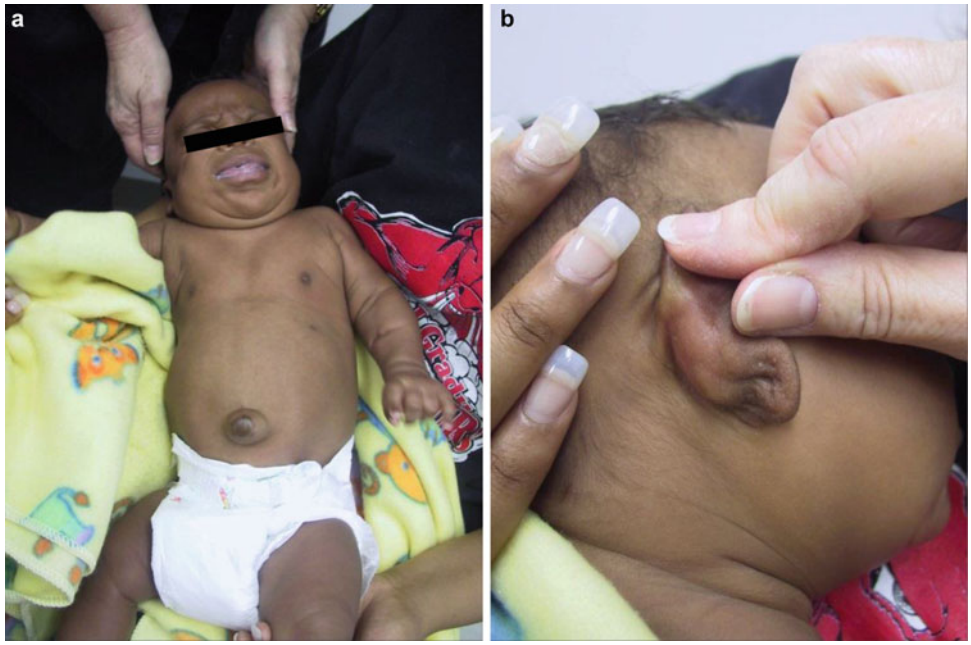

Fig. 2 (**a**, **b**) An infant with Beckwith-Wiedemann syndrome showing macroglossia, ear crease, and umbilical hernia

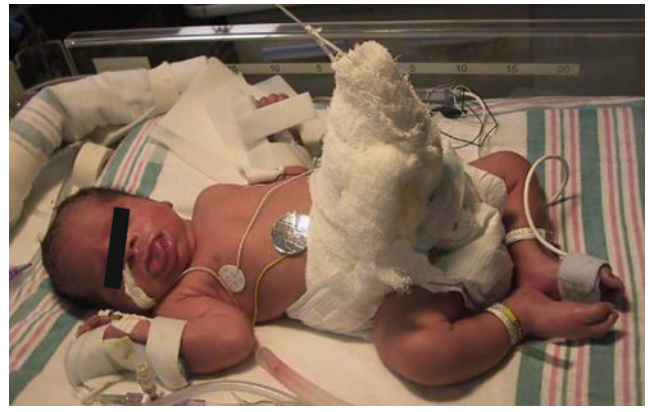

Fig. 3 An infant with Beckwith-Wiedemann syndrome and a large omphalocele requiring surgical intervention

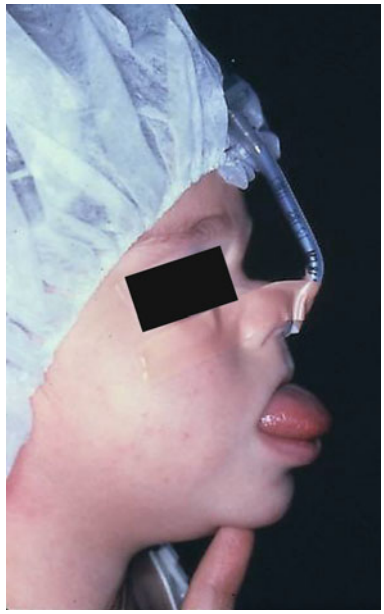

Fig. 4 An infant with Beckwith-Wiedemann syndrome prior to partial glossectomy

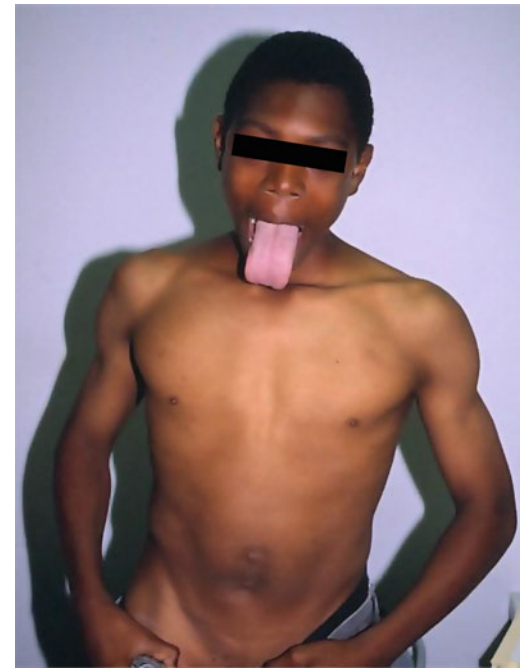

Fig. 5 A young adult with Beckwith-Wiedemann syndrome showing macroglossia and postsurgical status of umbilical and inguinal hernia repairs

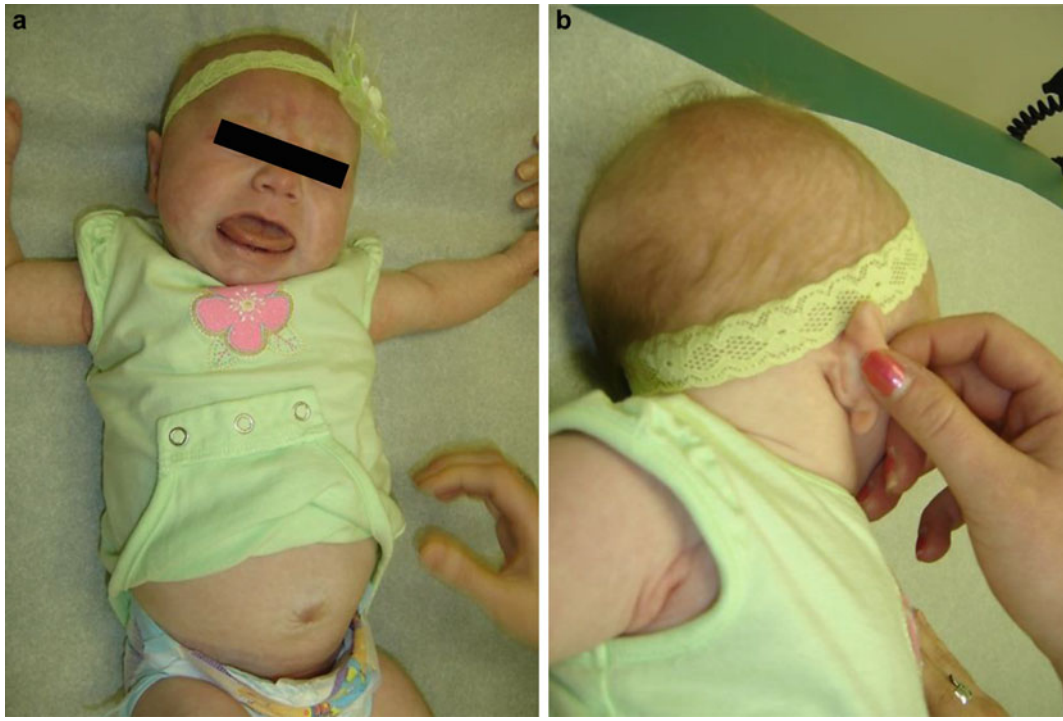

Fig. 6 (**a**, **b**) A 2-month-old infant with macroglossia and posterior ear creases, suspected of having Beckwith-Wiedemann syndrome clinically. Southern blot analysis was utilized to detect abnormal methylation in the imprinting center DMR2, which is located within the BWS critical region on chromosome 1p15. The DNA probe LIT1 was used for the analysis. Hypomethylation of LIT1 was detected. The methylation index was 0.21 (Reference range: 0.40–0.58). The results are consistent with a diagnosis of Beckwith-Wiedemann syndrome

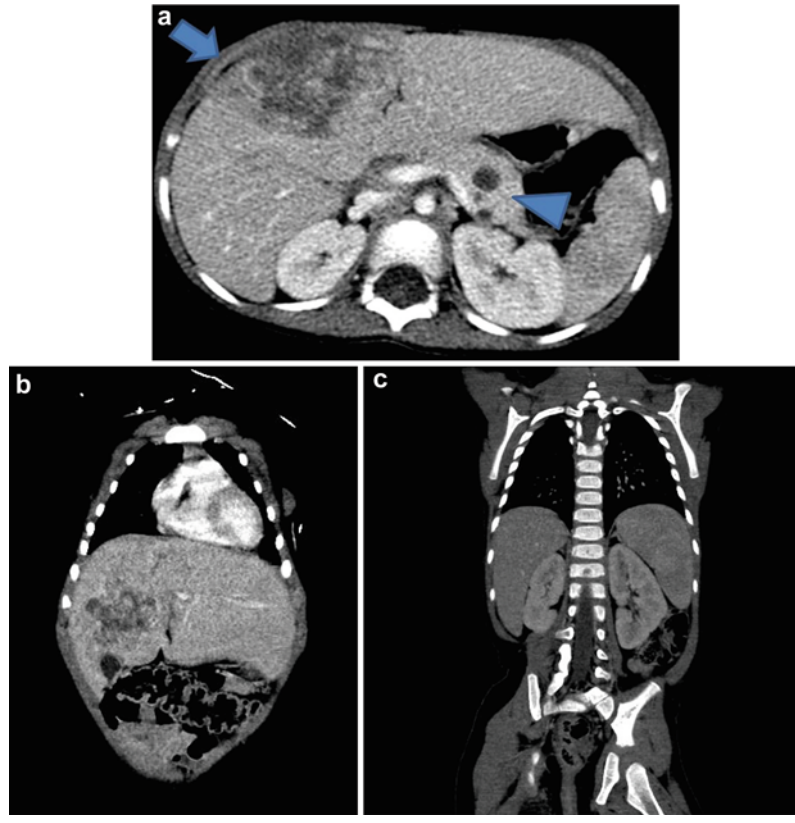

Fig. 7 (**a**–**c**) A 2-year-old girl with a diagnosis of Beckwith-Wiedemann syndrome. Enhanced axial CT image (**a**) demonstrated a large, heterogeneous hepatoblastoma (*arrow*) and multiple cystic lesions in the pancreas (*arrowhead*). The large, heterogeneous hepatoblastoma was also demonstrated in the second image (**b**). There was asymmetric enlargement of the left kidney with symmetric enhancement (**c**) (Courtesy of Dr. Grace Guo)

Behçet Disease

Contents

In 1937, Behçet (1937) first described three patients with oral and genital ulceration and hypopyon. It is most common in the Middle and Far East with a prevalence of 7–8 per 100,000 people, whereas in the USA the prevalence is estimated at 4 per 1,000,000 people.

Synonyms and Related Disorders

Behçet syndrome

Genetics/Basic Defect

1. A complex multisystem inflammatory disease of unknown cause
2. Considered a relapsing and remitting vasculitis of the small- to medium-sized vessels with following protean manifestations:
    1. Aphthous stomatitis
    2. Genital ulceration
    3. Uveitis
    4. Synovitis
    5. Gastrointestinal lesions
    6. Cutaneous lesions
    7. Central nervous system lesions
    8. Cardiac lesions
    9. Vessel lesions
3. Immunopathogenic aspects of Behçet disease (Direskeneli 2001; Krause and Weinberger 2008; Dalvi et al. 2012)
    1. Vascular injuries, hyperfunction of neutrophils, and autoimmune (Yazici 1997) responses: characteristics of Behçet disease (Sakane et al. 1999)
    2. Cellular and humoral immunity
    3. Antigenic stimuli
        1. Herpes simplex virus
        2. Streptococci and superantigens
        3. Heat shock proteins (65 kDa, αβ-crystallin)
    4. Genetic risk factor: most strongly associated with Behçet disease: human leukocyte antigen (HLA-B51) allele
        1. Genetic predisposition to HLA-B51 and antigen presentation
        2. Retinal-S antigen and HLA-B51 as autoantigens
    5. Vascular disease and antiendothelial cell antibodies
    6. Severity and sex: more severe in men
    7. Tumor necrosis factor-α-1031C allele: associated with disease susceptibility

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_23

8. Polymorphisms in interleukin-10 and CD28 genes: also associated with Behçet disease
9. Association with endothelial nitric oxide synthase gene polymorphism: ethnic related

Clinical Features

1. Highly variable clinical course with recurrences and remissions (Chajek and Fainaru 1975; Rizzi et al. 1997)
2. More prevalent in regions along the Silk Road from the Mediterranean to the Far East (Verity et al. 1999)
3. Recurrent attacks of oral, genital, ocular, and skin lesions (Kurokawa and Suzuki 2004; Alpsoy et al. 2007; Dalvi et al. 2012; Alnaimat 2015)
    1. Oral aphthous ulcers
        1. Keystones to diagnosis of Behçet disease according to the classification criteria
        2. Often an initial presenting sign
        3. Occurring on the buccal mucosa, tongue, gingiva, and the soft palate area
        4. Minor aphthous ulcers: superficial with a diameter of 2–6 mm, appearing as multiple lesions, and developing within 1–2 days. They heal without scarring within 7–10 days and recur at various frequencies.
        5. Major aphthous ulcers: deeper and painful lesions leaving scars after healing
        6. Herpetiform aphthous ulcers: numerous lesions grouped as small ulcers
    2. Genital ulcers
        1. Women: located on the vulva, vagina, and cervix uteri
        2. Men: located on the prepuce and scrotum
        3. Lesions resembling the oral aphthae but tend to be deeper and leaving scars
        4. Differential diagnosis from other genital ulcers (herpes simplex, syphilis, tropical ulcers, and skin infestations)
    3. Ocular lesions (70–85%) (Bashour 2014)
        1. Generally follow the genital and oral ulceration by a few years
        2. Characterized by severe vasculitis with arterial and venous occlusions
        3. Iridiocyclitis with hypopyon (presence of leukocytes in the anterior chamber of the eye) (one third of cases)
        4. Uveitis
        5. Retinal vasculitis (classic fundus findings) affecting both arteries and veins in the posterior pole
        6. Hemorrhagic and exudative retinal lesions (retinitis)
        7. Marked vitritis
        8. Choroiditis
        9. Bilateral nongranulomatous inflammation of the iris and ciliary body
        10. Intermittent blurring of vision and loss of vision
    4. Skin lesions
        1. Pustular vasculitic cutaneous lesions: may evolve as lesions of small vessel necrotizing vasculitis from a neutrophilic vascular reaction to a lymphocytic perivascular reaction
        2. Erythema nodosum-like lesions: usually occurring on the lower extremities but can be seen on the arms, neck, and face
        3. Pseudofolliculitis
        4. Papulopustular lesions: neutrophil-induced, vessel-based reaction
        5. Acneiform nodules
4. Myositis (Lang et al. 1990; Zen-nyoji et al. 2000)
    1. Pediatric onset of Behçet disease with myositis with calf pain and swelling
    2. Intestinal Behçet disease associated with generalized myositis
5. Articular manifestations
    1. Recurrent seronegative arthritis
        1. Common findings

    2. A nonspecific synovitis
  2. Monoarthritis
  3. Polyarthritis
6. Gastrointestinal manifestations (about 70% of patients) (Ebert 2009)
  1. Ulcerative lesions most frequently occurring in the terminal ileum, cecum, stomach, and intestine
  2. Symptoms
    1. Abdominal pain
    2. Diarrhea
    3. Melena
    4. Perforation
7. CNS manifestations (about 1% of patients)
  1. Headaches
  2. Meningitis
  3. Meningoencephalitis
  4. Cranial nerve palsies
  5. Peripheral nerve involvement with vasculitis
  6. Cerebellar ataxia
  7. Hemiplegia
  8. Benign intracranial hypertension
  9. Neurologic deficits
  10. Cerebral aneurysm
  11. Cerebral vasculitis and ischemic stroke (Krespi et al. 2001): unusual
  12. Personality changes and depression
  13. Dementia
  14. Hearing and vestibular disturbances
8. Pulmonary manifestations
  1. Tracheobronchial ulcerations
  2. Pleurisy
  3. Embolism
  4. Pulmonary arterial aneurysms
  5. Pneumonitis
  6. Fibrosis
9. Renal involvement: rare
  1. Glomerulonephritis
  2. Systemic amyloidosis
10. Cardiac manifestations
  1. Intracardiac thrombosis (Mogulkoc et al. 2000)
  2. Myocardial infarction
  3. Pericarditis
  4. Endocarditis
11. Vascular manifestations
  1. Superficial thrombophlebitis
  2. Deep thrombophlebitis
  3. Small- and large-vessel vasculitis
  4. Pulmonary artery aneurysms (PAI) (Seyahi and Yazici 2015)
    1. Strongly associated with venous thrombosis such as deep vein thrombosis of the legs, dural sinus thrombosis, and vena cava inferior thrombosis
    2. Thrombi on the right side of the heart occur in about one third of patients with PAI
12. Pregnancy in Behçet disease (Noel et al. 2013; Iskender et al. 2014)
  1. A higher rate of vascular complications during pregnancy
  2. The disease course: improves during pregnancy, mostly in patients who are treated with colchicine
  3. Rate for other obstetric complications: not increased
  4. Neonatal outcomes: not negatively influenced by Behçet disease
13. Neuro-Behçet disease (Serdaroglu 1998; Diri and Espinoza 2006)
  1. Defined as a constellation of neurologic manifestations with characteristic neuropathologic findings, usually confirmed by ancillary investigations, in patients who meet the diagnostic criteria for Behçet disease
  2. Neurologic involvement
    1. One of the most serious manifestations of Behçet disease
    2. More common in male patients and have been reported to occur in anywhere from 5% to 50% of Behçet disease patients, depending on their geographical region
  3. Two types of CNS involvement
    1. Primary parenchymal (neuro-Behçet disease; 82% of cases): pathological process within the CNS parenchyma (worse prognosis)
    2. Secondary or nonparenchymal (vascular-Behçet disease; 18% of cases):

pathological process resulting from a major vasculopathy (better prognosis if occluded)
4. Predominantly motor/mental picture
5. Peripheral neuropathy and myopathy: rare
6. MRI lesion extending from brain stem to basal ganglia
7. Immunosuppression: widely used for treatment

14. Prognosis (Ebert 2009)
    1. Runs a chronic, unpredictable course with exacerbations and remissions which decrease in frequency and severity over time
    2. Death: mainly due to major vessel disease and neurological involvement
    3. Prognosis for Behçet disease: worst for young males
    4. Prognosis for intestinal Behçet disease
        1. Complete remission: 38% of patients with intestinal Behçet disease after 8 weeks of medical treatment
        2. Rate of recurrence after surgery: 40–56%
        3. Recurrence: 49% of patients at 5 years, especially those with intestinal perforation or fistula formation
    5. Visual acuity: significantly improved after early treatment with chlorambucil (Pivetti Pezzi et al. 1985)
15. Criteria for clinical diagnosis of Behçet disease, proposed by O'Duffy and Goldstein in 1976, require the presence of recurrent oral or genital aphthae along with two additional systemic findings for diagnosis and only one for the diagnosis of the incomplete form (O'Duffy and Goldstein 1976):
    1. Criteria
        1. Aphthous stomatitis
        2. Aphthous genital ulceration
        3. Uveitis
        4. Cutaneous "pustular" vasculitis
        5. Synovitis
        6. Meningoencephalitis
    2. Diagnosis: At least three criteria present, one being recurrent aphthous ulceration
    3. Incomplete form: Two criteria present, one being recurrent aphthous ulceration
    4. Exclusion
        1. Inflammatory bowel disease
        2. Systemic lupus erythematosus
        3. Reiter's disease
        4. Herpetic infections
16. The International Study Group criteria (1990) included positive pathergy test as one of the criteria to establish the diagnosis of Behçet disease (Ghate and Jorizzo 1999):
    1. Recurrent oral ulceration: minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times in one 12-month period
    2. *Plus 2 of the following criteria* (findings applicable only in absence of other clinical explanations)
        1. Recurrent genital ulceration: aphthous ulceration or scarring observed by physician or patient
        2. Eye lesions: Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
        3. Skin lesions: erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by physician in postadolescent patients not receiving corticosteroid treatment
        4. Pathergy test (a nonspecific pustule that is an inflammatory reaction to needle pricks in approximately 40% of patients, especially during the exacerbation period): Pathergy test is positive when pricking a sterile needle into the patient's forearm results in an aseptic erythematous nodule or pustule that is more than 2 mm in diameter at 24–48 h.
17. Differential diagnosis (Dalvi et al. 2012)
    1. Reactive arthritis
        1. Conjunctivitis
        2. Urethritis
        3. Sacroiliitis
        4. Keratoderma blennorrhagicum

2. Inflammatory bowel disease
    1. Lesions seen in all parts of gastrointestinal tract, perianal, and rectal disease
    2. Fistula formation
3. Sarcoidosis
    1. Bilateral hilar lymphadenopathy
    2. Interstitial lung disease
4. Seronegative arthropathies
    1. Sacroiliitis
    2. Psoriatic skin lesions
    3. Aortic insufficiency
    4. Axial disease
5. Other systemic vasculitides
    1. Antineutrophilic cytoplasmic antibodies
    2. Mononeuritis multiplex
6. Sweet syndrome
    1. Moderate to high fever or upper respiratory infection preceding the skin lesions
    2. Neutrophilia

Diagnostic Investigations

1. Positive skin pathergy test
2. Laboratory findings (Önder and Gürer 2001)
    1. Acute-phase response
        1. Raised erythrocyte sedimentation rate
        2. Increased serum levels of C-reactive protein
        3. Elevated plasma complement components, such as C3, C4, C9, and factor B
    2. Disease exacerbations
        1. Elevated IgG, IgA, and IgM
        2. Elevated C-reactive protein
        3. Elevated 2-globulin
    3. Interleukin (IL)-8 as a serological marker
    4. Increased serum leptin concentration: correlated with disease activity (Evereklioglu et al. 2002)
3. HLA typing
4. Ultrasonography of lower extremity: to evaluate vein thrombosis (Seyahi et al. 2015)
5. Echocardiography: to detect valve vegetations and ventricular thrombi
6. Endoscopy of the GI tracts: to detect GI ulcerations
7. Radiography: show a wide spectrum of radiologic abnormalities (Chae et al. 2008; Rabinovich 2014)
    1. Barium studies with a double-contrast technique: demonstrate small ulcers in the bowel loop more effectively than do those with a single-contrast technique
    2. Fluorescein angiography, color Doppler imaging, and fundoscopic examination to detect retinal features
    3. Angiography: shows area of aneurysm formation and thrombosis
    4. CT scan (Ceylan et al. 2010)
        1. Effectively demonstrates vascular system involvement that is the main cause of mortality in these patients
        2. Also effective in detecting mediastinal, pleural, and pulmonary parenchymal findings related to the disease
    5. MRI and CT scan
        1. To identify cerebral vasculopathy and areas of acute/subacute ischemia
        2. Thorax CT: may disclose ground glass lesions, nodules, and pleural lesions, other than arterial lesions (Seyahi and Yazii 2015)
        3. Brainstem involvement with meningoencephalitis (T2-weighted images) (Rabinovich 2014)
    6. Electrocardiograph-gated cardiac CT and cardiac MRI: easily demonstrate periaortic pseudoaneurysms with their possible rupture into the cardiac chamber, as well as provide the detailed three-dimensional information required for surgery
    7. Single-photon emission computed tomography (SPECT): to identify areas of cerebral hypoperfusion
    8. Angiography: to evaluate aneurysms
8. Whole exome sequencing: identification of two rare putative protein-damaging genetic variants (*LIMK2* and *NEIK1*) associated with this disease (Ognenovski et al. 2015)
9. Neuropsychologic testing (Rabinovich 2014)
    1. Reveals memory impairment or personality changes
    2. Useful in monitoring neuropsychologic status

10. Histopathological features
    1. Pathergy lesions
        1. Leucocytoclastic vasculitis
        2. Neutrophilic vascular reaction
        3. Polymorphonuclear leucocyte infiltration
    2. Erythema nodosum-like lesions
        1. Neutrophilic vascular reaction or vasculitis in the dermis and subcutaneous tissue
        2. Perivascular lymphocytic dermal inflammation
    3. Common histopathological lesions in all organ systems
        1. Vasculitis
        2. Thrombosis
        3. Perivascular infiltrates of lymphomononuclear cells
        4. Neutrophilic vascular reaction
    4. Early cutaneous lesions: neutrophilic vascular reaction or leucocytoclastic vasculitis (Chen et al. 1997)
    5. Late cutaneous lesions: lymphocytic perivasculitis

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased
    2. Patient's offspring: not increased
2. Prenatal diagnosis: no prenatal diagnosis reported
3. Management (Alpsoy and Akman 2009; Dalvi et al. 2012; Saleh and Arayssi 2014)
    1. Mucocutaneous lesions (Mangelsdorf et al. 1996)
        1. Topical corticosteroids: useful for oral and genital ulcers
        2. Colchicine
            1. Beneficial effects on the mucocutaneous symptoms, presumably by inhibiting neutrophil function
            2. The first choice for treatment of genital ulcers and/or erythema nodosum, especially in female patients
            3. Combination with benzathine penicillin: for patients who are ineffective with colchicine alone, or a male patient, or in the presence of oral ulcers with or without other mucocutaneous lesions
        3. Treatment with thalidomide in severe, refractory Behçet disease (Hamuryudan et al. 1998; Shek et al. 1999; Brik et al. 2001): effective for oral and genital ulcers, gastrointestinal manifestations, and pseudofolliculitis
        4. Dapson, zinc sulfate, and rebamipide can be other choices
        5. Immunosuppressive agents, such as azathioprine and cyclosporine, and biologicals, such as Interferon (IFN)-alpha (Georgiou et al. 1998) and antitumor necrosis factor (TNF)-α agents: to control the patients with severe mucocutaneous disease or unresponsive to the respected treatments
        6. Methotrexate
        7. Systemic corticosteroids: prescribed for erythema nodosum that is refractory to treatment with colchicine
    2. Ocular lesions
        1. Require special attention and aggressive treatment because of its highest morbidity
        2. About 25% of patients eventually develop blindness despite therapeutic intervention
        3. Topical mydriatic agents and corticosteroid drops: given for acute attacks of anterior uveitis
        4. Colchicine: prescribed to prevent both anterior and posterior uveitis because of its high degree of efficacy and relatively low toxicity
        5. Topical injection of corticosteroids, with systemic administration in some cases: used for acute attacks of posterior uveitis
        6. Cytotoxic agents (azathioprine, chlorambucil, and cyclophosphamide): help prevent ocular attacks in approximately 50–75% of patients; however, loss of useful visual acuity occur in 74% of eyes after intensive follow-up

and treatment (Benezra and Cohen 1986)
7. Cyclosporine: beneficial in 70–80% of patients with ocular lesions that have been refractory to the conventional therapies
8. Subcutaneous human recombinant interferon alpha: an effective and fairly well-tolerated therapy for Behçet disease
9. Systemic corticosteroids: generally given in acute attacks of posterior uveitis, panuveitis, and retinal vasculitis
10. Results from therapies: improved vision and decreased pain, saving the individual a potential enucleation
11. Retinal vasculitis: successfully treated with rituximab (Sadreddini et al. 2008)
12. Panuveitis or retinal vasculitis: effectively treated with gevokizumab or canakinumab (recombinant humanized anti-IL-1β antibody) (Gul et al. 2012; Ugurlu et al. 2012)

3. Arthritis
   1. Nonsteroidal anti-inflammatory drugs and colchicine: the first choice and are effective for most cases of arthritis
   2. Additional use of benzathine penicillin: the next step
   3. Low dose corticosteroids and azathioprine: used in patients whose arthritis is resistant to treatment with nonsteroidal anti-inflammatory drugs, colchicine, or sulfasalazine
   4. Interferon alfa: also highly effective
4. Gastrointestinal lesions (Skef et al. 2015)
   1. Goal of treatment
      1. Keeps patients in remission
      2. Reduces relapses
      3. Prevents surgical intervention
   2. Sulfasalazine, corticosteroids, and azathioprine: the principal drugs
   3. Anti-TNF-α treatments, especially infliximab: a new and effective alternative for more severe and/or refractory intestinal disease
   4. Bowel rest: obligatory in patients with an acute abdomen and bleeding
   5. Surgery: considered for patients with bowel perforation and intractable bleeding
5. CNS lesions
   1. High doses of corticosteroids
   2. Supplemented with cytotoxic agents
6. While the recurrence rate for PAI is about 20%, PAI may disappear in about 70% of the cases with immunosuppressive treatment. Yet, the disease can still be fatal in one fourth of patients despite all efforts (Seyahi and Yazici 2015)
7. Large-vessel lesions
   1. Treated with a combination of corticosteroids and cytotoxic agents
   2. Anticoagulants and antiplatelet agents: used for deep venous thrombosis
   3. Surgery for refractory large-vessel disease

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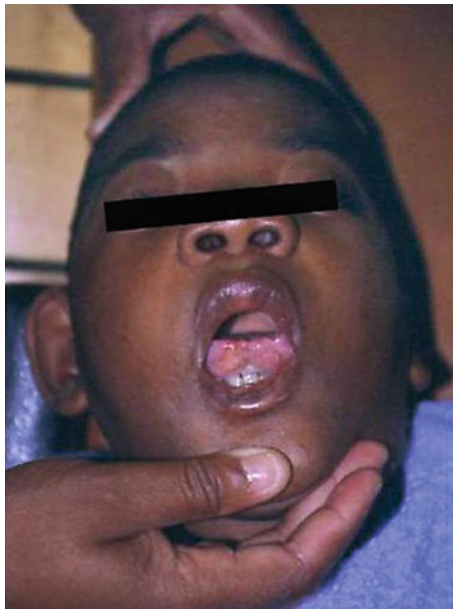

Fig. 1 Aphthae on the tongue, buccal mucosa, and gums of a child with Behçet disease

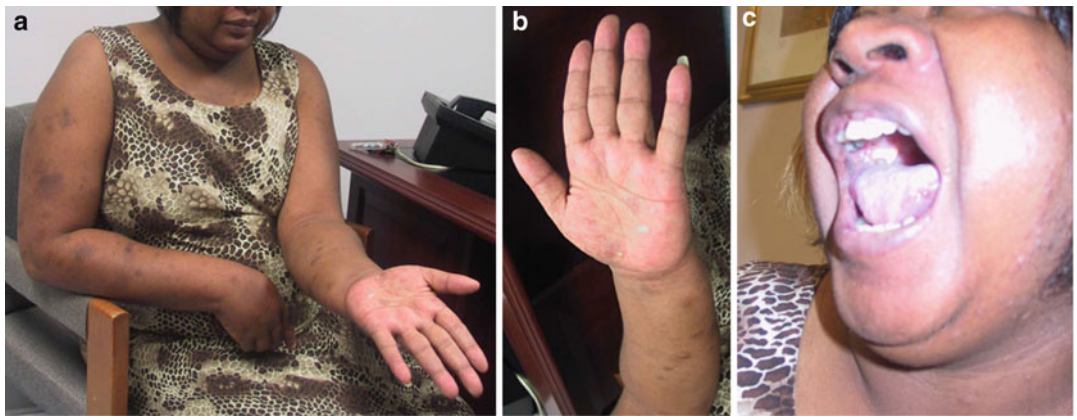

Fig. 2 (**a**–**c**) A female patient with Behçet disease showing generalized scars from blisters on the buccal mucosa, trunk, arms, legs, and palms

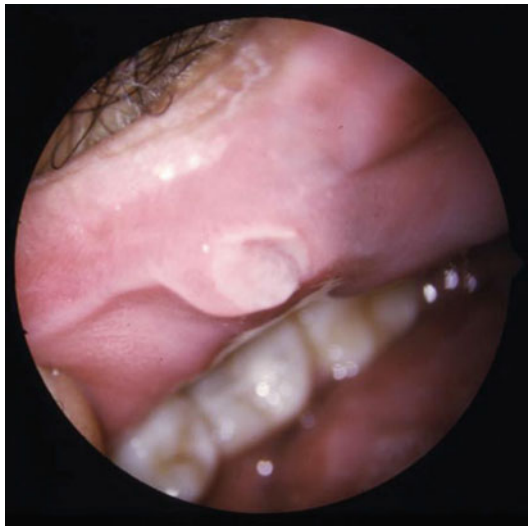

Fig. 3 A large aphthous ulcer on mucosal membrane of the lower lip of a patient with acute exacerbation of Behçet disease

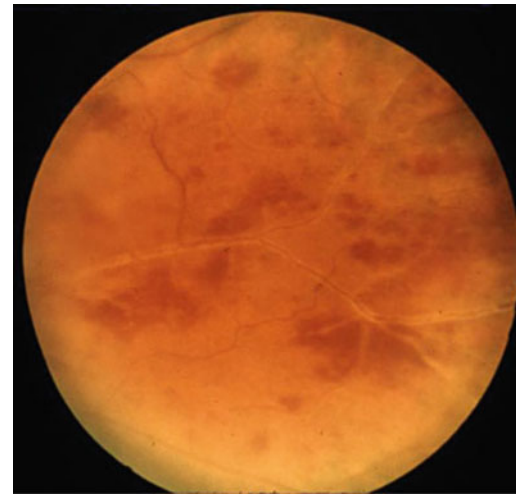

Fig. 4 Occluded retinal vessels and retinal hemorrhage with arterial and venous occlusive vasculitis in a patient with Behçet disease

Biotinidase Deficiency

Contents

In 1971, Gompertz and colleagues (1971) first described multiple carboxylase deficiency responsive to biotin administration. Wolf and colleagues (1981) further characterized the infantile form of multiple carboxylase deficiency as biotinidase deficiency (BTD) in 1981.

Based on the results of worldwide screening of biotinidase deficiency (Wolf 1991), the incidence of the disorder is one in 137,401 for profound biotinidase deficiency, one in 109,921 for partial biotinidase deficiency, and one in 61,067 for the combined incidence of profound and partial biotinidase deficiency. Carrier frequency in the general population is approximately one in 120.

Synonyms and Related Disorders

Juvenile-onset multiple carboxylase deficiency; Late-onset multiple carboxylase deficiency

Genetics/Basic Defects

1. An autosomal recessive disorder affecting the endogenous recycling and release of biotin (vitamin H) from dietary protein: consecutive biotin depletion resulting in low activities of biotin-dependent carboxylases and urinary excretion of organic acids characteristic of multiple carboxylase deficiency
2. Classification of biotinidase deficiency according to residual enzyme activity (Baumgartner and Suormala 1997; Wolf 2001)
    1. Profound biotinidase deficiency (residual activity $<10\%$ of mean normal value)
    2. Partial biotinidase deficiency (residual activity 10–30% of mean control value)
3. Caused by complete or partial absence of the enzyme biotinidase
4. The gene that encodes biotinidase is mapped at 3p25.
5. *BTD* (the gene encoding biotinidase) mutations
    1. 98-104del7ins3: the most common *BTD* mutation (about 50% of symptomatic children)
    2. Arg538 R → C: less common
    3. P.D444H (Wolf 2013)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_24

Clinical Features

1. Natural history (Wolf 2013)
    1. Biotinidase deficiency: a readily treatable inherited disorder (Wolf 2003)
    2. Individuals with biotinidase deficiency, diagnosed by newborn screening, who are treated with biotin before developing symptoms: develop normally
    3. Individuals with biotinidase deficiency who have recurrent symptoms and metabolic compromise prior to biotin treatment: develop neurologic problems
    4. Early onset of symptoms is predicted by the presence of zero residual activity as measured by sensitive assays and by homozygosity for the G98:d7i3 mutations (Mühl et al. 2001; Möslinger et al. 2003)
    5. Subtle neurologic abnormalities may appear as early as at 2 months of age and that developmental abnormalities may occur even in the absence of episodes of overt metabolic decompensation (Wolf et al. 1985a)
2. Untreated profound biotinidase deficiency
    1. Symptoms usually develop between ages 1 week and 10 years
    2. Clinical features, also observed in children with many other inherited metabolic disorders, include:
        1. Seizures (either alone or with other neurological or cutaneous findings): the most frequent initial symptoms (Wolf et al. 1985b)
        2. Hypotonia
        3. Developmental delay
        4. Breathing abnormalities
            1. Hyperventilation
            2. Laryngeal stridor
            3. Apnea
    3. More specific features
        1. Sensorineural hearing loss
        2. Optic atrophy
        3. Cutaneous symptoms
            1. Eczematous skin rash
            2. Alopecia
        4. Conjunctivitis
        5. Chronic and possibly lethal fungal infections (e.g., candidiasis)
        6. Ataxia
    4. Symptoms encountered by older children and adolescents
        1. Limb weakness
        2. Rare spastic paraparesis
        3. Scotomata
3. Children with untreated partial biotinidase deficiency: usually have mild symptoms which occur only when the child is stressed (e.g., prolonged infection, illness, fasting)
4. Prognosis for individuals diagnosed with biotinidase deficiency: good, provided they are treated before symptoms occur (Szymańska et al. 2015)

Diagnostic Investigations

1. New born screening (Wolf 2013)
    1. Utilizes a small amount of blood obtained from a heel prick for a colorimetric test for biotinidase activity (Heard et al. 1984, 1986; Wolf et al. 1985a; Wolf 1991)
    2. Detect virtually 100% of affected infants
    3. False positive test results in:
        1. Premature infants
        2. Samples placed in plastic prior to sufficient drying
    4. Measure biotinidase activity in serum/plasma in infants whose initial screening tests are abnormal
    5. Newborns should be screened for profound and partial biotinidase deficiency (Wolf 2015)
2. Other laboratory findings
    1. Decreased or low normal plasma biotin concentrations in individuals with profound biotinidase deficiency
    2. In most individuals
        1. Metabolic ketolactic acidosis
        2. Organic aciduria
        3. Metabolic ketoacidosis

3. Specific tests
    1. Biotinidase levels: Carriers (heterozygotes) usually have serum enzyme activity levels intermediate between those of affected and those of normal individuals (Wolf et al. 1983)
    2. Serum ammonia
    3. Urine organic acids
    4. Plasma amino acids
    5. Urine ketones
    6. Blood gas
    7. Serum chemistries
    8. Carnitine and acylcarnitine profiles
3. Imaging studies: MRI of the brain (Desai et al. 2008)
    1. Cerebral edema
    2. Low attenuation of white matter signal
    3. Cerebral atrophy
    4. Compensatory ventricular enlargement
4. Other tests
    1. Ophthalmologic testing
        1. Dilated fundoscopy to detect optic atrophy
        2. Visual field testing and visual evoked potentials to detect degree of optic nerve injury
    2. Audiologic testing
        1. To detect hearing deficits in symptomatic children which can be persistent after treatment
        2. Brainstem auditory evoked potentials to delineate the abnormality in younger children or in developmentally delayed patients
    3. EEG for seizure activities
5. Molecular Genetic testing: clinically available
    1. Targeted mutation analysis
        1. Real-time PCR of DNA from the blood spot of a newborn screen card can be used to identify a panel of common *BTD* mutations (p.Cys33PhefsX36, p.Gln456His, p.Arg538Cys, p.Asp444His, and p.Ala171Thr).
        2. These five mutations that cause profound biotinidase deficiency comprise approximately 60% of the abnormal alleles found in symptomatic individuals and in children identified by newborn screening.
    2. Sequence analysis
        1. Direct sequencing of *BTD* and its intron/exon junctions is available clinically.
        2. Almost all individuals with partial biotinidase deficiency have the mutation p.Asp444His in one allele of *BTD* in combination with a mutation for profound deficiency in the other allele.
    3. Deletion/duplication analysis: Although deletion testing is offered clinically, no large deletions have been reported in *BTD*.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25%
    2. Patient's offspring: not increased unless the spouse is also a carrier
2. Prenatal diagnosis possible for pregnancies at increased risk
    1. Biochemical testing (measurement of biotinidase enzyme activity in cultured amniotic fluid cells and in amniotic fluid obtained by amniocentesis) (Secor McVoy et al. 1984; Chalmers et al. 1994)
    2. Molecular genetic testing (analysis of DNA extracted from fetal cells obtained by amniocentesis or CVS), provided both disease-causing alleles of an affected family member have been identified
    3. Request for prenatal diagnosis or preimplantation genetic diagnosis is not common since biotinidase deficiency can be treated and does not affect intellect.
3. Management
    1. Biotin treatment with supplementation with oral biotin in free form
        1. Children with biotinidase deficiency identified by newborn screening: remain asymptomatic with compliance to lifelong biotin therapy

2. Children with profound biotinidase deficiency should be treated with biotin regardless of their residual enzyme activity or genotype (Wolf 2002)
3. Effective in preventing symptoms (Möslinger et al. 2001; Weber et al. 2004)
4. Compliance with biotin therapy: improves symptoms in symptomatic individuals
5. Three children with partial deficiency discontinued biotin for varied lengths of time. Two of whom became symptomatic with abnormal gait, alopecia, skin rashes, and developmental delay (Gannavarapu et al. 2015)

2. Medical care for developmental delay, hypotonia, spasticity, and bulbar dysfunction

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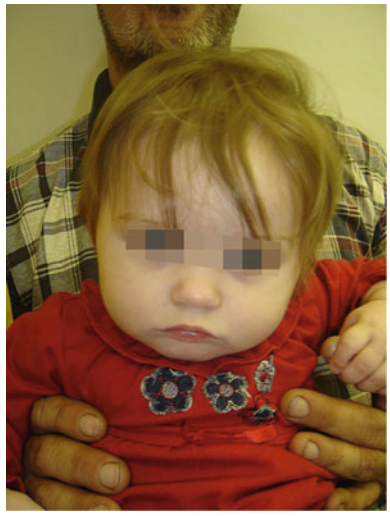

Fig. 1 A 11-month-old girl with biotinidase deficiency (0.41 nmol/mL/min) (normal, 3.66–9.21) detected by newborn screening. Her growth and development have been normal with oral biotin supplementation

Fig. 3 A 12-week-old infant boy was found to have a borderline biotinidase activity by newborn screening. DNA analysis showed a heterozygous D444H mutation and, therefore, he is a carrier

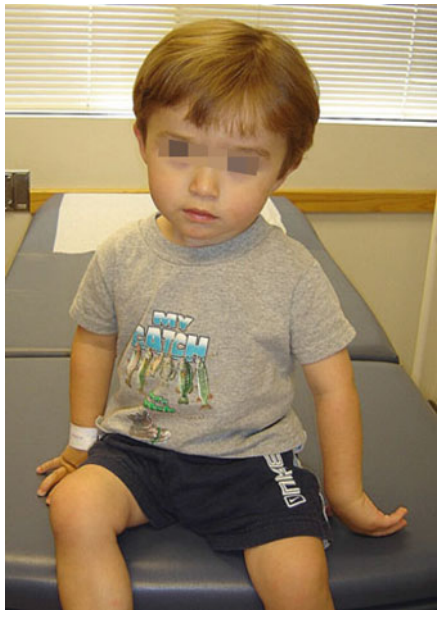

Fig. 2 A 26-month-old boy was found to have partial biotinidase deficiency by newborn screening with a biotin level of 6.3 (normal: >16). DNA analysis showed one copy of D444H mutation and one copy of G68:d7i3 mutations. His growth and development have been normal with oral biotin supplementation

Bladder Exstrophy

Contents

Bladder exstrophy is a rare developmental anomaly occurring as an isolated defect in about 1/25,000–1/40,000 births (Cacciari et al. 1999).

Synonyms and Related Disorders

Bladder exstrophy and epispadias complex

Genetics/Basic Defects

1. Genetics
    1. Usually an isolated defect
    2. Most likely a multifactorial trait (Messelink et al. 1994)
    3. Pure terminal 1q deletion [del(1)(q43q44)] in a patient with bladder exstrophy and extreme genital anomaly (Zaki et al. 2012)
    4. Microduplications at 22q11.21: associated with nonsyndromic classic bladder exstrophy (Draaken et al. 2010)
    5. Microduplication at 22q11.2: reported in two patients with bladder exstrophy and hearing impairment (Lundin et al. 2010)
2. Basic defects (Ives et al. 1980)
    1. Probably failure of fusion of the secondary mesoderm (from the primitive streak) in the midline of the anterior abdominal wall, with subsequent rupture of the thin wall consisting only of the ectoderm and endoderm
    2. Early rupture (fifth week) resulting in exstrophy of the cloaca and later rupture (seventh week) resulting in exstrophy of the bladder

Clinical Features

1. Classical bladder exstrophy (Higgins 1962; Ben-Chaim et al. 1996)
    1. Diagnosis easily made at birth
    2. Occupy 60% of the patients with the exstrophy-epispadias complex
    3. Bladder plate protruding just beneath the umbilical cord
    4. Posterior bladder wall is exposed through a midline abdominal wall defect
    5. Inferiorly displaced umbilicus located close to the superior margin of the exstrophic bladder
    6. Rectus muscles divergent on either side of the bladder

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Leading to the separated pubic bones
2. Separation of the pubic bones caused by an outward rotation of the innominate bones and eversion of the pubic rami

7. Male patients (Pierre et al. 2014)
   1. A short epispadiac phallus with a dorsal urethral plate
      1. Caused by separation of the pubic bones
      2. Possibly caused by a true deficiency of corporeal tissue
   2. A splayed glans
   3. Dorsal chordee
   4. Exposed urethra
   5. Exposed bladder
   6. Umbilical stump
8. Female patients (Pierre et al. 2014)
   1. Genital defect analogous to the male but more easily reconstructed
   2. Separated mons pubis (both the hemiclitoris and labia and split clitoris and exstrophic vagina)
   3. Exposed urethra
   4. Exposed bladder
   5. Umbilical stump
   6. Predisposing to uterine prolapse (Burbige et al. 1986), especially after pregnancy and delivery, secondary to pelvic floor defect
9. Urinary tract abnormalities
   1. Generally normal upper urinary tract
   2. Occasional abnormalities
      1. Unilateral renal agenesis
      2. Horseshoe kidney
      3. Hydronephrosis
      4. Other renal anomalies
10. Internal genitalia: usually normal
11. Fertility and childbearing/pregnancy (Ledfors et al. 1966; Krisiloff et al. 1978)
    1. Documented in both sexes but less common in the males
    2. C-section advised to avoid injury to continence mechanism
    3. Postpartum uterine prolapse common because of aggravation of preexisting abnormal pelvic support
    4. Successful pregnancy and delivery (Bildircin et al. 2012)
12. Inguinal hernias
    1. Incidence: very common
       1. Fifty six to eighty two percent in boys
       2. Eleven to fifteen percent in girls
    2. Incidence of bowel incarceration below 1 year of age: 10–53%
    3. Causes
       1. Large internal and external inguinal rings
       2. Lack of obliquity of the inguinal canal
13. Anus
    1. Anteriorly placed
    2. Fecal continence adversely affected by the divergence of the pelvic musculature
14. Rectal prolapse
    1. Virtually always disappears after bladder closure or cystectomy
    2. Represents an indication for surgical management of the exstrophied bladder
15. Spinal abnormalities (6.7%) (Cadeddu et al. 1997)
    1. Myelomeningocele
    2. Lipomeningocele
    3. Scimitar sacrum
    4. Posterior laminal defects
    5. Vertebral fusion
    6. Hemivertebrae
16. Malignancies (Pierre et al. 2014)
    1. Rare late complication of bladder exstrophy, especially in untreated patients whose bladders are left exstrophic for many years
    2. Types of malignancies
       1. Adenocarcinoma: the most common type, arising from the precursor cystitis glandularis, a consequence of chronic irritation and inflammation of exposed bladder mucosa.
       2. Squamous cell carcinoma and rhabdomyosarcoma.
       3. Adenocarcinoma developing adjacent to the ureterointestinal anastomoses in patients with urinary

diversions that mix the urinary and fecal streams.
4. The risk of developing colon adenocarcinoma is increased 7,000-fold after ureterosigmoidostomy among patients younger than 25 years of age than the general population.

17. Psychological impact on children and on the lives of families (Stjernqvist and Kockum 1999)
18. Behavioral, social, and school competency problems observed in 70% of adolescents and 33% of school-aged children
19. Seventy percent of parents express concern about the children's sexual function or sexual disfigurement
20. Consider all patients with exstrophy-epispadias complex to be latex sensitive

2. Variants of exstrophy (Cerniglia et al. 1989)
   1. Pseudoexstrophy (exstrophic abdominal wall defect without bladder exstrophy)
   2. Duplicate exstrophy
   3. Superior vesical fistula and fissure
   4. Covered exstrophy and visceral sequestration
3. Exstrophy of the bladder and exstrophy of the cloaca: two different expressions of a primary developmental field (Martinez-Frias et al. 2001; Canning 2003)

Diagnostic Investigations

1. General assessment
2. Cardiopulmonary assessment
3. Renal ultrasound for baseline examination of the kidneys since increased bladder pressure after bladder closure can lead to hydronephrosis and upper urinary tract deterioration (Yerkes 2014).
4. Voiding cystourethrogram (Yerkes 2014)
   1. To rule out bilateral vesicoureteral reflux which is present in nearly all patients with classic bladder exstrophy
   2. Performed in early childhood to assess bladder capacity in preparation for continence reconstruction
5. Imaging of complications following bladder exstrophy repair (Pierre et al. 2014)
   1. Fluoroscopy for urethrocutaneous fistula, urethral stricture, bladder rupture/perforation, and complications of bladder augmentation
   2. Ultrasound for renal scarring and stone formation
   3. MRI: primarily utilized in a research capacity to evaluate pelvic anatomy changes following repair
   4. Combined high-end 2D and 3D MRI: the technique of choice for the evaluation of pediatric pelvic floor in the presurgical planning and for the postoperative evaluation of the various surgical approaches applied for repair of classic bladder exstrophy (Tekes et al. 2014)

Genetic Counseling

1. Recurrence risk (Ben-Chaim et al. 1996)
   1. Patient's sib: The risk of recurrence of exstrophy or epispadias in a given family is 1 of 275 births. Risk to sibs is low, probably $<1\%$ (Ives et al. 1980).
   2. Patient's offspring: The risk of a parent with exstrophy producing a child with exstrophy or epispadias is up to 1 of 70 or 500 times the risk of the general population.
2. Prenatal diagnosis
   1. Ultrasonography (Barth et al. 1990; Gearhart et al. 1995; Goldstein et al. 2001)
      1. Absence of bladder filling in the presence of normal kidneys (bladder never demonstrated on the ultrasound) (71%)
      2. A protuberance on the lower abdomen representing the exstrophied bladder (47%)
      3. A diminutive penis with anteriorly displaced scrotum (57% of the males)
      4. A low-set umbilical insertion (29%)
      5. Abnormal widening of the iliac crests (18%)
      6. Separation of the pubic rami
      7. Difficulty in ascertaining the sex of the fetus

2. Fetal MRI (Goldman et al. 2012)
    1. Shows a detailed scenario of the abnormality with advantages over the ultrasound evaluation in regard to excluding cloacal anomalies
    2. Allowed accurate sexual differentiation
3. Management (Megalli and Lattimer 1973; Mesrobian et al. 1988; Inouye et al. 2014)
    1. Supportive management
        1. Ligate umbilical cord with suture to avoid bladder mucosal damage by an umbilical clamp.
        2. Protect bladder
            1. With clear plastic wrap.
            2. Irrigate the bladder surface with sterile saline each time diaper is changed and the wrap replaced.
        3. Initiate prophylactic antibiotics
    2. Goals of the reconstruction of bladder exstrophy (Grady et al. 1999)
        1. Preservation of the kidney function
        2. Creation of urinary continence
        3. Reduction in the urinary tract infections
        4. Creation of functionally and cosmetically acceptable external genitalia
    3. Initial bladder closure
        1. Begin with closure of the bladder and abdominal wall by either the modern staged repair of exstrophy or complete primary repair of bladder exstrophy (combination of epispadias repair often performed at the time of primary bladder closure).
        2. Closure of the pelvic ring
            1. Important for the initial closure
            2. Important for the eventual attainment of urinary continence
        3. Pelvic osteotomy
            1. Two main approaches: posterior iliac osteotomy and the anterior innominate osteotomy
            2. Reduce the tension on the suture lines to help securing the bladder closure
            3. To restore the pelvic anatomy and thus increase the chances of eventual continence and reduce the likelihood of uterine prolapse
    4. Epispadias repair
        1. Usually performed at 2–3 years of age before the continence procedure
        2. Contributing significantly to the development of bladder capacity
        3. Goals
            1. Reconstruction of the urethra and glans penis
            2. Encourage the potential of penile length
            3. Correction of the dorsal chordee
            4. Achieving adequate skin coverage
        4. Penis is generally reconstructible to cosmetically and functionally acceptable form, despite a short phallus
    5. Bladder neck reconstruction
        1. Usually performed at age of 4–5 years (when toilet training is possible).
        2. Require anti-reflux procedure since all exstrophy patients have vesicoureteral reflux.
        3. Complete urinary drainage achieved with ureteral stents and suprapubic cystostomy tubes.
    6. Ureteral reimplantation
    7. Bladder augmentation and continent diversion for patients who have failed bladder neck reconstruction and have an inadequate bladder capacity
    8. Alternatives for exstrophy reconstruction
        1. For patients with very small bladder plates or hydronephrosis
        2. Ureterosigmoidostomies
            1. Allow children to achieve continence
            2. Protect upper urinary tracts
            3. Potential complications: recurrent acute and chronic pyelonephritis, urolithiasis, hyperchloremic hypokalemic metabolic acidosis, ureteral obstruction, and the late development of colonic malignancy
    9. Repair of inguinal hernias at the time of primary closure of bladder exstrophy
    10. Specialized experience in management allow demonstrable improvement in bladder exstrophy outcomes (Dickson 2014)

11. Professional mental health guidance with a developmental and family perspective and establishment of patient and parent support groups and family information services and seminars (Diseth et al. 1999)

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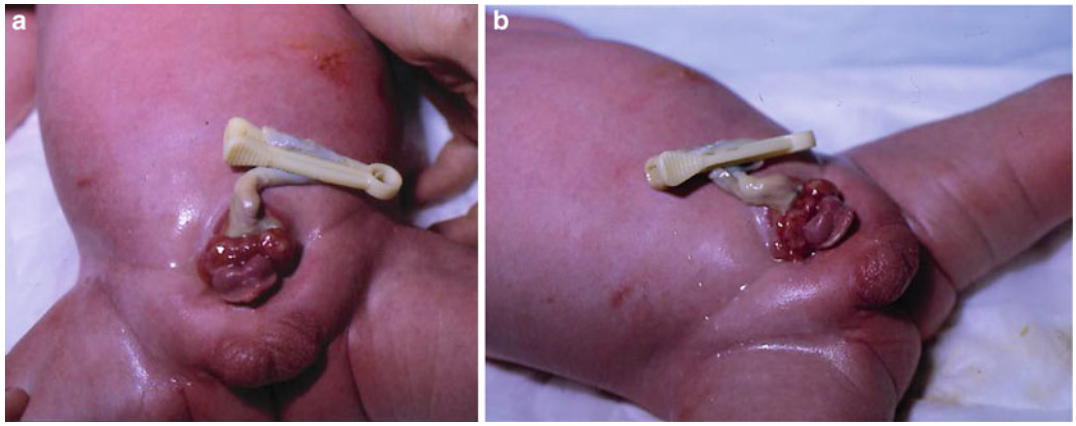

Fig. 1 (**a**, **b**) A newborn male with classic bladder exstrophy showing low insertion of the umbilical cord, a bulging mass of exstrophic bladder, and grossly abnormal external genitalia

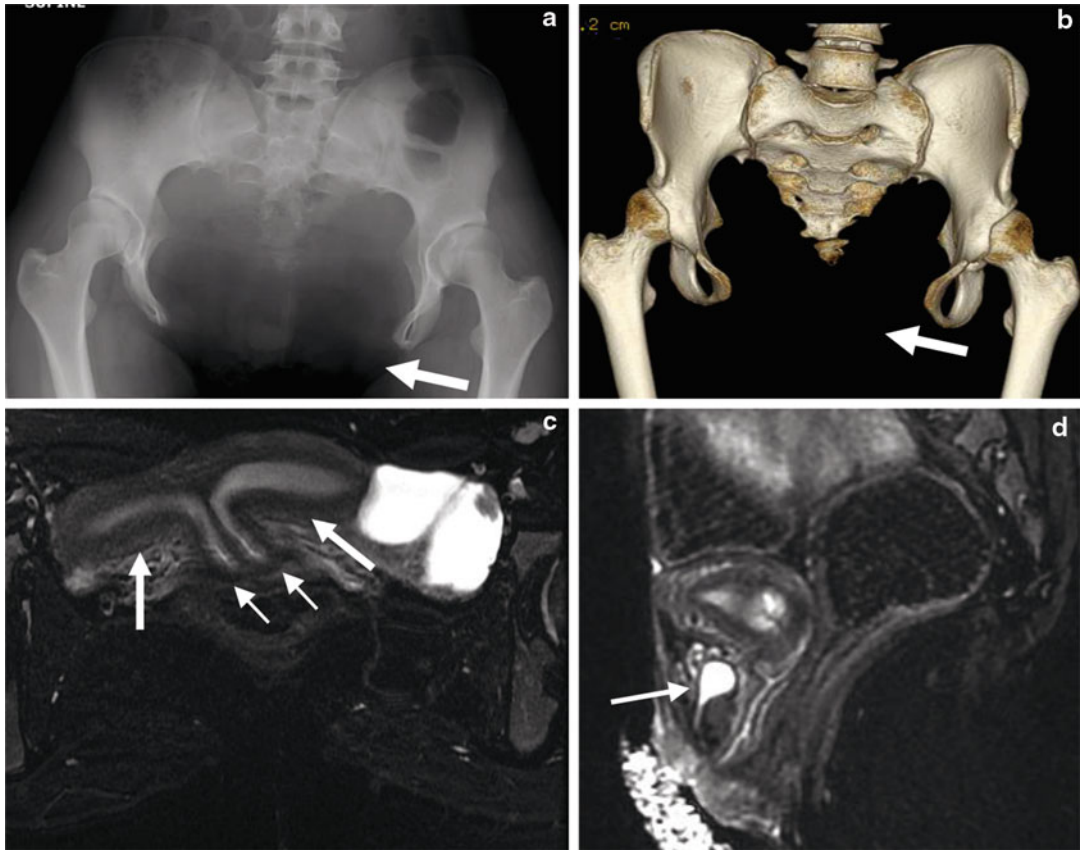

Fig. 2 (**a**–**d**) A 16-year-old female was evaluated for previous history of bladder exstrophy. The pelvic radiography (**a**) and 3D CT reconstruction image (**b**) showed the previous site of bladder exstrophy with substantial widening of the pubic rami and ischium (*arrows*). MRI image (**c**) demonstrated uterus didelphys (*large arrows*) with vaginal duplication (*small arrows*). The structures in the pelvis (**d**) (the bladder (*arrow*), the uterus, and the rectum) appear more anterior on the perineum than normally expected. No past medical history was available (Courtesy of Dr. Grace Guo)

Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome

Contents

In 1921, Komoto reported the first case known today as blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES), with the triad of wide set eyes, ectropion, excessive brow hair, and hypoplasia of the caruncle and relatives with similar phenotypic features. Later that year, Dimitry described a family with the above triad and traced the pedigree of "blepharophimosis syndrome," apparently transmitted in an autosomal dominant manner for the first time. In 1971, Kohn and Komoto (1971) added telecanthus to the triad of this syndrome.

Synonyms and Related Disorders

BPES plus; BPES with Duane retraction syndrome; BPES with/without ovarian failure

Genetics/Basic Defects

1. An autosomal dominant disorder
    1. No known affected family members in about one quarter of cases
        1. New mutation cases
        2. Minimal expression in affected relatives
    2. A significant number of patients with no identifiable family history of BPES
2. BPES gene *FOXL2*
    1. Mapped to chromosome 3q23 (Amati et al. 1995)
    2. Recently mutation of *FOXL2* has been described as a cause of BPES
3. Two forms of BPES (Zlotogora et al. 1983; Krastinova and Jasinski 2003)
    1. BPES type I
        1. Characterized by hypogonadism and infertility in affected females
        2. Complete penetrance
        3. Transmission by males as fertility in affected females is reduced
    2. BPES type II
        1. Not associated with female infertility
        2. Incomplete penetrance
        3. Transmission occurs in both males and females
4. *FOXL2*
    1. The only gene known to be associated with BPES (Verdin and De Baere 2015)

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2. Encodes for a transcription factor that is expressed predominantly in the developing eyelid and in the ovary (Mari et al. 2006)
5. Mutations of *FOXL2*: detected in patients with both type I and type II BPES (De Baere et al. 2001)
6. Genotype-phenotype correlation
    1. BPES type I: predicted to be the result of a truncated protein either lacking or containing the forkhead domain (Crisponi et al. 2001)
    2. BPES type II: predicted to be the result of duplications, within or downstream of the forkhead domain, or other mutations resulting in an extended protein
7. MRI studies of BPES type I patients demonstrate the possible role of *FOX2* in the differentiation of the superior levator muscle of the eyelid

Clinical Features

1. Clinical triad (Oley and Baraitser 1988; Allen and Rubin 2008)
    1. Blepharophimosis (profound small and narrow horizontal palpebral fissure): morphologically defined as reduction of both the horizontal and vertical dimensions of the palpebral fissure
    2. Ptosis of the eyelids: severe, bilateral, and symmetric (Beaconsfield et al. 1991)
    3. Epicanthus inversus (a small skinfold which arises in the lower lids and runs upward)
2. Other ocular associations (Choi et al. 2006)
    1. Patients often assume a chin up, head tilt backward position to clear their visual axis.
    2. Patients often present with raised arched eyebrows because of recruitment of frontalis muscle to compensate for ptosis and visual field defect.
    3. Associated with telecanthus (normal interpupillary distance with abnormally wide intercanthal distance).
    4. Abnormalities of the eyelid margin and lacrimal drainage apparatus.
    5. A high incidence of amblyopia in BPES (39–56%) than general population (3.2%) (Beckingsale et al. 2003).
    6. Strabismus: much higher incidence in BPES (20–27%) than general population (2–4%) (Dawson et al. 2003).
    7. Microphthalmos/optic disc colobomas (Lee and Sullivan 1995).
3. Non-ocular associations (Cunniff et al. 1998)
    1. Infertility in women with type I BPES due to premature ovarian failure which is defined as the onset of menopause before the age of 40 years
        1. Normal menarche followed by oligomenorrhea and later amenorrhea in most women with BPES type I
        2. Fertile in early reproductive years
        3. Soon leading to either ovarian resistance to gonadotrophins or true premature ovarian failure
        4. Usually with normal secondary sexual characteristics
    2. Broad flat nasal bridge
    3. High-arched palate
    4. Protruding or cup-shaped ears
    5. Cardiac defects
    6. Mental retardation: microdeletions leading to contiguous gene syndrome, including mental retardation (De Baere et al. 2003)
4. Natural history of BPES
    1. Epicanthal folds and telecanthus: improve significantly with time
    2. Ptosis and blepharophimosis: do not improve with time
5. Differential diagnosis (Verdin and De Baere 2015)
    1. BPES plus (Yu et al. 2014)
        1. Facial anomalies: blepharophimosis, ptosis, and epicanthus inversus
        2. Neurological anomalies: global developmental delay
        3. Musculoskeletal anomalies: widely-spaced nipples, slight 2–3 syndactyly
        4. Genital anomalies: cryptorchidism, hydrocele
        5. Associated with *KAT6B* mutation

2. Blepharophimosis
    1. As an isolated clinical finding
    2. As part of a number of congenital syndromes
3. Ohdo blepharophimosis syndrome (Ohdo et al. 1986)
    1. Presumably an autosomal dominant condition
    2. Blepharophimosis
    3. Blepharoptosis
    4. Dental hypoplasia
    5. Partial deafness
    6. Congenital heart defects
    7. Intellectual disability
4. Michels syndrome (3MC syndrome 1)
    1. Presumably an autosomal dominant condition
    2. Blepharophimosis
    3. Blepharoptosis
    4. Epicanthus inversus
    5. Ophthalmic anterior segment (cornea) defects
    6. Cleft lip/palate
    7. Minor skeletal abnormalities
5. Ptosis with external ophthalmoplegia
    1. An autosomal recessive condition
    2. Ptosis
    3. Ophthalmoplegia
    4. Miosis
    5. Decreased accommodation
    6. Strabismus
    7. Amblyopia
6. Schwartz-Jampel syndrome (please see the chapter of Schwartz-Jampel syndrome)
    1. An autosomal recessive condition
    2. Intermittent ptosis
    3. Blepharophimosis
    4. Telecanthus
    5. Cataract
    6. Short stature
    7. Cartilage and skeletal anomalies
    8. Muscle hypertrophy
7. Dubowitz syndrome
    1. An autosomal recessive syndrome
    2. Ptosis
    3. Blepharophimosis
    4. Lateral telecanthus
    5. Short stature
    6. Intellectual disability
    7. Immunologic deficiencies
8. Smith-Lemli-Opitz syndrome (please see the chapter of Smith-Lemli-Opitz syndrome)
    1. Ptosis
    2. Epicanthus
    3. Cataract
    4. Growth retardation
    5. Intellectual disability
    6. Others: severe genitourinary, cardiac, gastrointestinal anomalies
9. KANSL1-related intellectual disability syndrome (Gijsbers et al. 2008)
    1. A 17q21.31 microdeletion syndrome
    2. Developmental delay with mild-to-moderate intellectual disability
    3. Characteristic facies: long face, high forehead, ptosis, blepharophimosis, large low-set ears, bulbous nasal tip, pear-shaped nose
    4. Nasal speech
    5. Friendly disposition
    6. Others: cardiac septal defects, seizures, cryptorchidism
10. Observed in several aneuploidies such as chromosome 3p deletion (blepharophimosis, ptosis, mental retardation) (Moncla et al. 1995)
11. Fetal alcohol effects (ocular involvement) (Stromland 1987)

Diagnostic Investigations

1. Diagnosis based on clinical findings which are present at birth
2. Detection of premature ovarian failure (Verdin and De Baere 2015)
    1. Secondary amenorrhea
    2. Endocrinologic evaluation of hypergonadotrophic hypogonadism
        1. Elevated follicle-stimulating hormone
        2. Elevated luteinizing hormone
        3. Decreased serum concentration of estradiol and progesterone
    3. Ultrasound studies
        1. Small hypoplastic uterus
        2. Streak ovaries

3. Early on, normal presence of primordial follicle but without normal follicular development
4. Later on, presence of scars in place of primordial follicles when progress into true premature menopause

3. Cytogenetic testing for chromosome rearrangement involving 3q23
   1. Unbalanced translocations and interstitial deletions (De Baere et al. 1999)
   2. Estimated to occur in a very small fraction of individuals with BPES (Beysen et al. 2005)
4. Molecular genetic testing of *FOXL2* gene mutations (Verdin and De Baere 2015)
   1. Sequence analysis
   2. Deletion/duplication analysis
   3. *FOXL2* mutations detectable in up to 75% of affected individuals (Beysen et al. 2005)
   4. Individuals with BPES without a *FOXL2* mutation should be tested for *KAT6B* mutations (Yu et al. 2014)

Genetic Counseling

1. Recurrence risk: autosomal dominant inheritance (Verdin and De Baere 2015)
   1. Patient's sib
      1. Low recurrence risk when parents are not affected and do not have a *FOXL2* mutation. However, Germline mosaicism has been observed in BPES and demonstrated at the molecular level.
      2. Fifty percent risk if a parent is also affected.
      3. Germline mosaicism: observed in autosomal BPES and demonstrated at the molecular level (Beysen et al. 2005): incidence unknown.
   2. Patient's offspring
      1. A 50% recurrence risk for an affected individual to have an affected offspring
      2. Affected female individuals with type I BPES may have infertility: crucial to distinguish the two types of BPES to address the infertility issues with patients and for genetic counseling of female patients of child-bearing age (Fokstuen and Antonarakis 2003)
      3. Possible presence of offspring risks to unaffected members of the families because of the presence of nonpenetrance or very minimal expression of BPES (Temple and Baraitser 1989)
2. Prenatal diagnosis (Verdin and De Baere 2015)
   1. Available by DNA analysis from fetal cells obtained via amniocentesis (during 15–18 weeks of gestation) and chorionic villus sampling (10–12 weeks of gestation).
   2. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
   3. Preimplantation genetic diagnosis may be available for some families in which the pathogenic variant has been identified.
   4. These tests, however, are not commonly done for BPES.
3. Management
   1. Crucial to distinguish two types of BPES to address the infertility issues with patients and for genetic counseling of female patients of child-bearing age
   2. Endocrine and gynecologic evaluation and management recommended in affected females
      1. Hormone replacement therapy as needed
      2. Need to address concerns of infertility such as adoption or ovum donation for premature ovarian failure
      3. Referral to a clinical geneticist for an appropriate genetic workup and counseling
   3. Complex and requires coordination among several specialists, including pediatric ophthalmologist, oculoplastic surgeon, pediatric endocrinologist,

reproductive endocrinologist, gynecologist, and genetic counselor
4. Treatment goals for an ophthalmologist
    1. Promote normal visual development
    2. Improve cosmesis
    3. Alleviate abnormal chin-up posture
5. A comprehensive ophthalmic examination
    1. Visual acuity
    2. Refraction
    3. Ocular movements
6. Diagnosis and treatment of amblyopia and strabismus crucial
7. Ptosis repair: usually addressed after medial canthoplasty
8. Medial epicanthoplasty using the skin redraping for treatment of epicanthus inversus and telecanthus in patients with BPES (Sa et al. 2012)
9. Modified staged surgical intervention (Song et al. 2015)
    1. Medial canthoplasty
    2. Lateral canthoplasty
    3. Blepharoptosis correction surgery
10. Timing of surgery for congenital ptosis: controversial
    1. Weighing the balance of early surgery to prevent amblyopia
    2. Late surgery to allow for more reliable ptosis measurement, which provides a better surgical outcome

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Fig. 1 A father and a daughter. Both have blepharophimosis, ptosis, and epicanthus inversus of both eyes

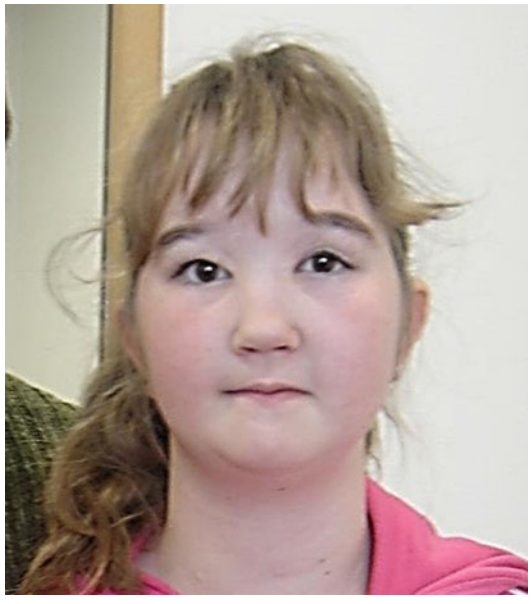

Fig. 2 A postsurgically repaired 15-year-old girl who had bilateral blepharophimosis, bilateral ptosis, and bilateral epicanthus inversus at birth

Body Stalk Anomaly

Contents

Body stalk anomaly, sometimes also called limb body wall complex, is a rare abdominal wall defect due to failure of the development of the body stalk. Prevalence is estimated to be 0.32 per 10,000 births.

Synonyms and Related Disorders

Limb body wall complex

Genetics/Basic Defects

1. Sporadic occurrence in most cases, although concordance in twins has been reported
2. Failure in body folding in cranial, caudal, and lateral axes during the embryonic stage of development (Hiett et al. 1992)
    1. Abnormalities of cranial folding leading to pentalogy of Cantrell et al. (1958) consisting of the following:
        1. Cardiac abnormalities
        2. Sternal cleft
        3. Upper abdominal defect
        4. Anterior diaphragmatic hernia
        5. Deficiency of the diaphragmatic pericardium
    2. Abnormalities of caudal folding leading to the following:
        1. Cloacal exstrophy
        2. Hypogastric omphalocele
        3. Imperforate anus
        4. Partial colonic agenesis
        5. Agenesis of one umbilical artery (Craven et al. 1997)
    3. Abnormalities of lateral folding leading to midline omphalocele
    4. Abnormalities of folding along all three axes resulting in a body stalk anomaly
        1. Failure to obliterate the extraembryonic cavity that continues to communicate with the intraembryonic cavity
        2. Creation of a large ventral wall defect that is covered by an amnioperitoneal membrane which contains the abdominal viscera and inserts directly into the chorionic plate
        3. The fetus appearing to be directly attached to the placenta as the umbilical cord is significantly shortened or absent.
        4. Frequent kyphoscoliosis due to limited truncal flexion
3. Possible causes of the anomaly (Becker et al. 2000):

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_27

1. Early amnion rupture before obliteration of the extraembryonic coelom
2. Abnormal splitting of the embryo at the fourth gestational week
3. Disturbance of the blood flow due to vascular rupture, as described in cocaine users (Martinez et al. 1994)
4. Monozygotic twinning: early cleavage disorder (Shih et al. 1996)
5. Maternal uniparental disomy of chromosome 16 in a fetus with body stalk anomaly suggesting placental insufficiency or imprinting effects as cause of this anomaly (Chan et al. 2000)

4. Pathogenesis (de Silva et al. 2001)
   1. The umbilical cord, derived from a small mass of mesoderm (body stalk), attaches the embryo to the wall of the blastocysts.
   2. Extreme maldevelopment of embryonic body folding resulting in incomplete fusion of the amnion to the chorion and failure to form an umbilical cord (Lockwood et al. 1986)
   3. Abnormal development of the body stalk resulting in an absent or rudimentary umbilical cord
   4. Vascular disruption during 4–6 weeks' gestation as an etiology for limb body wall complex (Van Allen et al. 1987)
   5. Consequences
      1. Direct attachment of fetus to the placenta
      2. Abdominal viscera lying in a sac outside the abdominal cavity covered by amnion
   6. OEIS (omphalocele, exstrophy of cloaca, imperforate anus, and spinal defect) and limb body wall complex (LBWC) (Mandrekar et al. 2014)
      1. Share congenital talipes equinovarus, hydroureter, and body stalk anomaly
      2. OEIS and LBWC may represent a continuous spectrum of abnormalities rather than separate conditions and may share a common etiology and pathogenetic mechanism as proposed by several authors.

Clinical Features

1. A large anterior abdominal wall defect with a large omphalocele
   1. Outside the abdominal cavity containing thoracic and/or abdominal organs
   2. Covered by amnion
   3. Appears continuous with (adherent to) the placental membranes
2. Absent, rudimentary, or extremely short umbilical cord. A severe type of short umbilical cord syndrome may be a variant of the body stalk anomaly.
3. Two-vessel cord
4. Severe kyphoscoliosis
5. Placenta directly attached to the amnioperitoneal sac
6. Extensive associated anomalies (Giacoia 1992)
   1. Hypoplasia of the lungs
   2. Anal atresia (imperforate anus)
   3. Agenesis of the colon
   4. Intestinal atresia
   5. Exstrophy of the cloaca
   6. Vaginal atresia
   7. Agenesis of uterus and gonads
   8. Absence of external genitalia
   9. Hypoplastic kidneys
   10. Absence of diaphragm
   11. Diaphragmatic hernia
   12. Spina bifida
   13. Dysplastic thorax
   14. Occasional coexistence of the syndrome with limb malformations (mostly lower extremities) and amniotic bands (Martínez-Frías et al. 2000)
7. Fetal death caused by abruptio placentae
8. Live-born infant dies shortly afterward

Diagnostic Investigations

1. Radiography to document skeletal anomalies
2. Cytogenetic analysis
   1. No specific anomaly

2. Placental karyotyping: report of a case with placental trisomy 16 and maternal uniparental disomy (UPD)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased
   2. Patient's offspring: not surviving to reproductive age
2. Prenatal diagnosis
   1. High maternal serum alpha-fetoprotein
   2. Ultrasonography (Goldstein et al. 1989; Daskalakis et al. 1997; Jauniaux et al. 1990; Takeuchi et al. 1995; Paul et al. 2001; Daskalakis and Nicolaides 2002; Smrcek et al. 2003; Rovida et al. 2014; Kocherla et al. 2015)
      1. Can be diagnosed as early as the first trimester by transvaginal sonography (Shalev et al. 1995; Ginsberg et al. 1997)
      2. A large abdominal anterior wall defect with abdominal organs in a sac outside the abdominal cavity in apparent continuity with (adherent to) the placental membranes
      3. An extremely short or absent umbilical cord
      4. Severe kyphoscoliosis
      5. Polyhydramnios
      6. Oligohydramnios
      7. Two-vessel cord
      8. Ectopic cordis (Shibata et al. 2014)
      9. Deformed lower limbs
      10. Sonographic signs alone expect an unequivocally poor prognosis.
   3. Amniocentesis
      1. Elevated amniotic fluid alpha-fetoprotein level
      2. Abnormal acetylcholinesterase
      3. Normal chromosomes
3. Management: newborn with the body stalk anomaly, uniformly fatal

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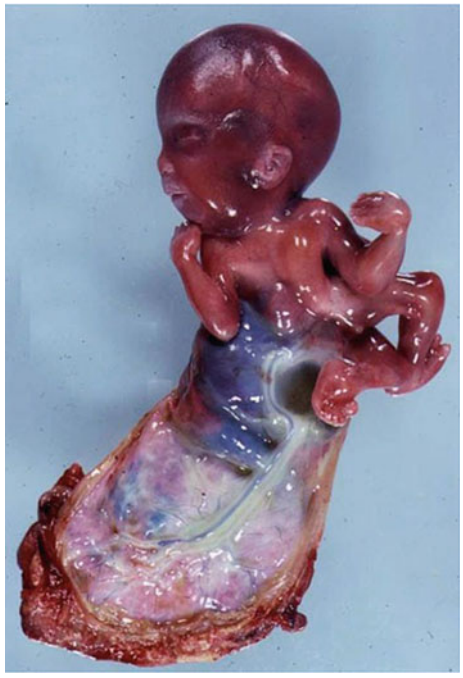

Fig. 1 An extremely premature neonate with body stalk anomaly. Short umbilical cord (7.5 cm with 5 cm fused with placenta) and a large amnioperitoneal sac between the abdomen and the placenta are evident. The sac was filled with internal viscera. In addition, there were anal and urethral atresia, rectovesical fistula, left renal agenesis, lumbosacral meningomyelocele, severe scoliosis, and lumbosacral hypoplasia

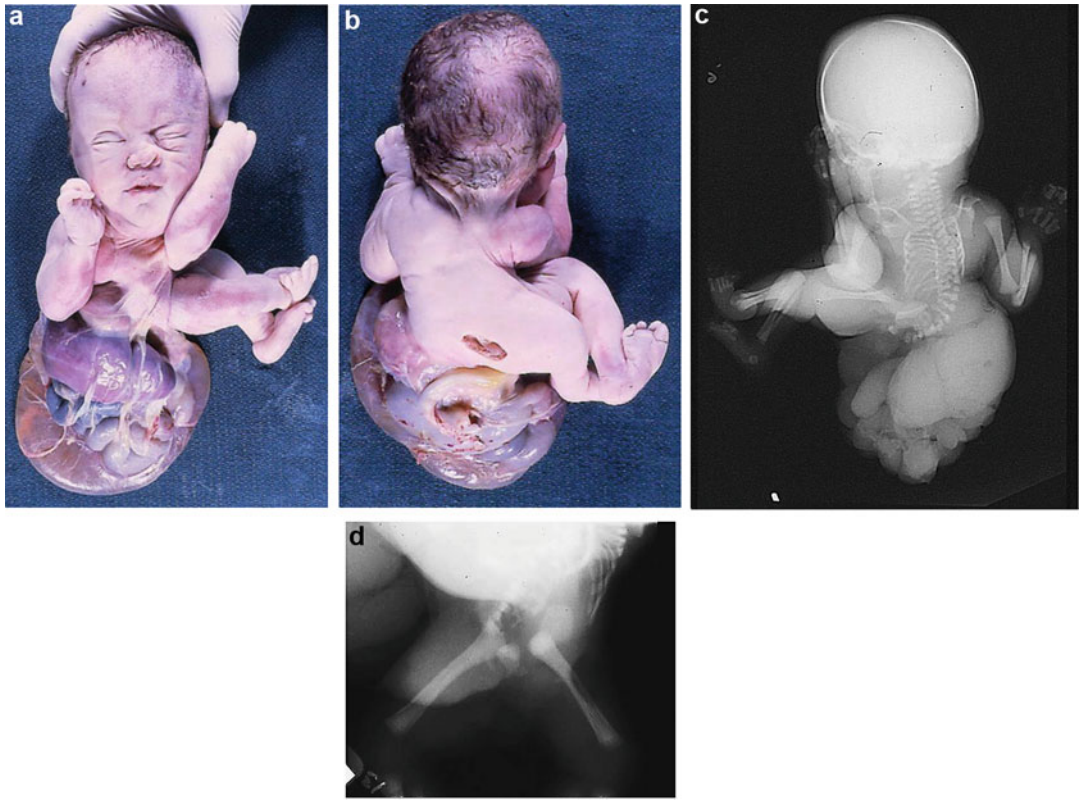

Fig. 2 (**a**–**d**) An infant with body stalk anomaly showing Potter facies, severe kyphoscoliosis, and a large amnioperitoneal sac outside the body. The sac contained abdominal organs. The umbilical cord was absent. Limb and vertebral defects illustrated in the radiographs

Fig. 3 (**a**, **b**) Another infant with body stalk anomaly showing anterior abdominal wall defect with a large sac containing abdominal organs, exstrophy of the bladder, and clubfeet

Brachydactyly

Contents

Brachydactyly, a general term for short digit, refers to disproportionately short fingers and toes and forms part of the group of limb malformations characterized by bone dysostosis. Dysostoses refer to abnormalities of individual bones, either in isolation or in combination with various abnormally formed bones. Dysostosis are usually static and arise during blastogenesis (first 8 weeks of embryonic life) versus osteochondrodysplasias that usually present at a later stage of development, typically affect the skeleton in general, and may continue to evolve as a result of continuous gene functioning throughout life.

Brachydactyly can occur either as an isolated malformation or as a part of a complex malformation syndrome. To date, many different forms of brachydactyly have been identified. Some forms also result in short stature. In isolated brachydactyly, subtle changes elsewhere may be present. Brachydactyly may also be accompanied by other hand malformations, such as syndactyly, polydactyly, reduction defects, or symphalangism.

Synonyms and Related Disorders

"Angel-shaped phalanx" brachydactyly; Brachydactyly type A1 (Farabee type); Brachymetatarsus IV; du Pan syndrome; Kirner deformity (dystelephalangy); Sugarman brachydactyly; Type 2 (Mohr-Wriedt type); Type A3 (brachydactyly-clinodactyly); Type A4 (Temtamy type); Type A5; Type B; Type C (Haws type); Type D (stub thumb); Type E

Genetics/Basic Defects

1. Isolated brachydactyly: the inheritance is mostly autosomal dominant with variable expressivity and penetrance.
2. Causative gene defect identified in the majority of isolated brachydactylies and some syndromic forms of brachydactyly.
3. Genomics of isolated brachydactyly (Hall 2002):
    1. Brachydactyly type A1 BDA1.
        1. Caused by mutations in the Indian hedgehog (*IHH*) gene located on chromosome 2q35-36 (Yang et al. 2000; Gao et al. 2001; Giordano et al. 2003). This supports the hypothesis that *IHH* plays a pivotal role in normal human skeletogenesis.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Another locus for this phenotype, designated *BDA1B*, has been identified on chromosome 5p13.3-p13.2 (Armour et al. 2002; Kirkpatrick et al. 2003).

2. Brachydactyly type A2 (BDA2).
    1. Caused by mutation in the human bone morphogenetic protein receptor 1B gene (*BMPR1B*) (Majewski et al. 2003; Lehmann et al. 2006) on chromosome 4q21-q20, which affects cartilage formation in a dominant-negative manner.
    2. Sparing of the fourth finger distinguishes the Mohr-Wriedt type BDA2 from BDA2 caused by mutations in *BMPR1B* and concludes that the growth and differentiation factor 5 gene (*GDF5*) on chromosome 20q11.2 is a novel BDA2 causing gene (Kjaer et al. 2006; Ploger et al. 2008). Mutations in *GDF5* alter the receptor-binding affinities and can also cause symphalangism (Seemann et al. 2005).
3. Brachydactyly type A3 (BDA3): no gene or locus has yet been identified.
4. Brachydactyly type A4 (BDA4) (*HOXD13*, mapped on 2q31-q32).
    1. Mutations in the homeobox-containing gene (*HOXD13* on chromosome 2q31-q32) can give rise to limb malformations with variable expressivity and a wide spectrum of clinical manifestations including synpolydactyly and brachydactylies types D and E.
    2. The term "HOXD13 limb morphopathies" for the spectrum of limb disorders caused by *HOXD13* mutations was suggested based on a link between *HOXD13* and two additional limb phenotypes – syndactyly type V and brachydactyly type A4.
5. Brachydactyly type B (BDB) (Huang et al. 2014).
    1. Brachydactyly type B1 (Gong et al. 1999; Schwabe et al. 2000; Huang et al. 2014): caused mutations in the receptor kinase-like orphan receptor 2 gene (*ROR2*) on 9q22 in the majority of cases.
    2. Patients affected with the distal mutations have a more severe phenotype than those with the proximal mutations.
    3. Homozygous *ROR2* mutations are associated with an extreme form of brachydactyly, with extensive hypoplasia of the phalanges and metacarpals/metatarsals and absence of nails. In addition, there are vertebral anomalies, brachymelia of the arms, and ventricular septal defect, making up the manifestations of the Robinow syndrome, which also has been shown to be caused by mutations in *ROR2* (Stickler et al. 2006).
    4. Brachydactyly type B2: different mutations in the bone morphogenetic protein (*BMP*) antagonist *NOGGIN* (*NOG*, mapped on chromosome 4q23-q24) were identified in a subset of *ROR2*-negative patients with BDB and additional occurrence of proximal symphalangism and carpal synostosis (Lehmann et al. 2007).
    5. The BDB phenotype, as well as the location and nature of the BDB mutations, suggests a specific mutational effect that cannot be explained by simple haploinsufficiency.
6. Brachydactyly type C (BDC) (Baraitser and Burn 1983) (*CDMP1*, mapped on 20q11.2).
    1. Caused by heterozygous mutations of cartilage-derived morphogenetic protein 1 (*CDMP1*) (Polinkovsky et al. 1997), also known as growth/differentiation factor-5 (*GDF5*) gene, resulting in loss of function (Everman et al. 2002).
    2. Homozygous missense mutations in the GDF5 gene cause brachydactyly type C (Al-Qattan et al. 2015).

3. Factors other than locus heterogeneity, such as genetic modifiers and/or environmental factors, must play a role in phenotypic variability.
4. Non-penetrance in a mutation carrier of heterozygous mutations was identified in additional families with BDC.
5. A novel missense mutation was described in the prodomain of *CDMP1* indicating an important function of the prodomain for the folding, secretion, and availability of biologically active *CDMP1*.
6. Homozygous mutations of *CDMP1* cause the Hunter-Thompson form of chondrodysplasia, a recessive condition that is characterized by severe acromesomelic limb shortness.
7. A novel mutation in CDMP1, confirming that BDC and angel-shaped phalanx brachydactyly are part of the CDMP1 mutational spectrum (Gutiérrez-Amavizca et al. 2012).

7. Brachydactyly type D (BDD): associated with mutations in *HOXD13* (mapped on 2q31-q32) (Johnson et al. 2003).
8. Brachydactyly type E (BDE) (*HOXD13*, mapped on 2q31-q32).
    1. Mutations in parathyroid hormone-like hormone (*PTHLH*) (the gene coding for parathyroid hormone-related protein (PTHrP)): cause BDE (Thomas-Teinturier et al. 2015).
    2. The occurrence of brachydactyly type E was one feature of what appeared to be a contiguous gene syndrome due to a cytogenetically visible de novo deletion of 2q37.
    3. Missense and nonsense mutations (Jamsheer et al. 2012) in *HOXD13* with distinctive limb phenotypes exhibiting overlap with BDD and BDE have been described.
9. Brachymetatarsus IV: no gene or locus for Kirner deformity has yet been identified.
10. Sugarman brachydactyly: no gene or locus for Kirner deformity has yet been identified.

Clinical Features

1. Types of isolated brachydactyly (Temtamy and Aglan 2008)
    1. Brachydactyly type A: shortening is confined to middle phalanges.
        1. Brachydactyly type A1 (BDA1) (Farabee-type brachydactyly)
            1. Variable short or rudimentary middle phalanges of all digits which are occasionally fused with terminal phalanges
            2. Short proximal phalanges of the thumbs and big toes
            3. An autosomal dominant trait with significant intrafamilial phenotypic heterogeneity among the affected individuals (McCready et al. 2002)
        2. Brachydactyly type A2 (BDA2) (Mohr-Wriedt-type brachydactyly)
            1. Characterized by hypoplasia/aplasia of the second middle phalanx of the index finger and sometimes little finger
            2. Characteristic triangular-shaped middle phalanx ("delta phalanx") in the index fingers and second toes
            3. Radially curved index finger in severely affected cases
            4. Malformation of the proximal phalanx of big toes resulting in fibular deviation of the distal phalanx, while all other toes have rudimentary middle phalanges causing tibial deflection of their distal phalanges
            5. An autosomal dominant trait
        3. Brachydactyly type A3 (BDA3) (brachymesophalangy V, brachydactyly-clinodactyly)
            1. Characterized by shortening of the middle phalanx of the little finger.

2. Slanting of the distal articular surface of the middle phalanx leads to radial deflection of the distal phalanx.
3. Not always associated with clinodactyly. A single flexion crease of the little finger indicates a short or absent middle phalanx.
4. This type should be differentiated from other types of crooked little fingers, namely, Kirner deformity and camptodactyly; in the former, there is radial bowing of the terminal phalanx due to curving of its shaft. Camptodactyly is a flexure contracture deformity of the interphalangeal joints.
5. An autosomal dominant trait with reduced penetrance.

4. Brachydactyly type A4 (BDA4) (brachymesophalangy II and V, Temtamy-type brachydactyly)
   1. Brachymesophalangy affecting mainly the second and fifth digits.
   2. When the fourth digit was affected, it showed an abnormally shaped middle phalanx leading to radial deviation of the distal phalanx.
   3. The feet also showed absence of middle phalanges of the lateral four toes.
   4. Rare autosomal dominant trait.
5. Brachydactyly type A5 (BDA5) (absent middle phalanges of digits 2–5 with nail dysplasia):
   1. Absence of the middle phalanges and nail dysplasia with duplicated terminal phalanx of the thumb.
   2. This type can be included in type B brachydactyly.

2. Brachydactyly type B (BDB) (Gong et al. 1999)
   1. Absence or hypoplasia of the terminal parts of the index to little fingers with complete absence of fingernails
   2. Intact thumbs frequently showing flattening, splitting, or duplication of the distal phalanges
   3. Less severely affected digits on the radial side of the hand compared to those on the ulnar side
   4. Similarly but less severely affected feet
   5. Symmetric deformity
   6. Accompanied by soft tissue syndactyly, symphalangism, carpal and/or tarsal fusions, and shortening of metacarpals and/or metatarsals
   7. A rare hand malformation
   8. An autosomal dominant trait with variable severity (expressivity)
3. Brachydactyly type C (BDC) (brachydactyly with hyperphalangism, Haws-type brachydactyly)
   1. Characterized by brachymesophalangy of the index, middle, and little fingers and shortening of the first metacarpal
   2. The ring finger: usually the longest digit, longer than the index finger (hyperphalangism detected on radiological examination)
   3. The proximal phalanx of the index finger: an anomalous configuration resulting in its ulnar deflection
   4. Short metacarpals and symphalangism: occasionally present
   5. The feet: either normal or show ordinary brachydactyly
   6. Inheritance: autosomal dominant with variable expressivity
   7. Presence of considerable intra- and interfamilial variation (Debeer et al. 2001)
4. Brachydactyly type D (BDD) (stub thumb)
   1. Distal phalanx of the thumb alone: characteristically shortened.
   2. Various degrees of thumb shortening, either unilaterally or bilaterally.
   3. Base of the distal phalanx is broader than the surface of the proximal phalanx to which it articulates, and that the distal end of the bone often shows some hyperplasia.
   4. Short distal phalanx of the thumb results from early closure of its epiphyses.

5. An autosomal dominant trait with reduced penetrance.

5. Brachydactyly type E (BDE)
   1. Variable shortening of the metacarpals with more or less normal length of phalanges.
   2. Occasional shortening of the metatarsals, resulting from hypoplastic and partially fused metacarpal epiphyses, visible on radiographs.
   3. Often presence of short terminal phalanges.
   4. Hyperextensibility of the hand joints: frequently a striking feature.
   5. Often relatively high axial triradius.
   6. Mild short stature in affected individuals.
   7. An isolated type E brachydactyly is inherited as an autosomal dominant trait with variable expressivity and variable involvement of the metacarpals and/or metatarsals, with frequent bilateral asymmetry.
   8. Brachydactyly type E as a feature of a syndrome (Pereda et al. 2013):
      1. Pseudohypoparathyroidism
      2. Acrodysostosis with or without multihormonal resistance
      3. Bilfinturan BD or hypertension with brachydactyly syndrome
      4. BDE with short stature, parathyroid hormone-like hormone gene (*PTHLH*) type
      5. Brachydactyly mental retardation syndrome
      6. Trichorhinophalangeal syndrome
      7. Turner syndrome
6. Brachymetatarsus IV (metatarsus IV, short, toes, fourth, short)
   1. Short fourth metatarsi resulting in unilateral or bilateral short fourth toes were observed in 206 persons in Northeastern India with no instance of short metacarpals, distinguishing this form from BDE.
   2. An autosomal dominant trait with approximately 27% penetrance.
   7. Sugarman brachydactyly (brachydactyly with major proximal phalangeal shortening) (Sugarman et al. 1974)
      1. A new form of brachydactyly of which a conspicuous feature was a non-articulating great toe which was set dorsal and proximal to the usual position. The great toes were amputated.
      2. Very short fingers without motion at the proximal interphalangeal joints.
      3. The consanguinity in the family and the presence of seven other affected members among the patient's relatives made autosomal recessive inheritance likely.
   8. Kirner deformity (dystelephalangy) (David and Burwood 1972)
      1. Malformed little finger consists of radial bowing of the terminal phalanx.
      2. Tip of the little finger points toward the thenar eminence.
      3. Usually bilateral malformations.
      4. An autosomal dominant trait with incomplete penetrance.
2. Brachydactyly as part of a syndrome
   1. Angel-shaped phalango-epiphyseal dysplasia (ASPED) (Gutiérrez-Amavizca et al. 2012)
      1. An autosomal dominant skeletal abnormality.
      2. Characterized by a typical angel-shaped phalanx, brachydactyly, abnormal dentition, hip dysplasia, and delayed bone age.
      3. Brachydactyly and ASPED: both result from mutations in the *CDMP1* gene and are part of the CDMP1 mutational spectrum.
   2. Brachyphalangy, polydactyly, and tibial aplasia/hypoplasia syndrome (Shafeghati et al. 2010) (please see the chapter of Tibial Hemimelia)
   3. Autosomal recessive Robinow syndrome (see the chapter of Robinow Syndrome) (Stickler et al. 2006)
   4. "► Rubinstein-Taybi Syndrome" (see the chapter) (Roelfsema and Peters 2007)

5. Albright hereditary osteodystrophy (Davies and Hughes 1993)
6. Brachydactyly type E with hypertension
7. Du Pan syndrome (Faiyaz-Ul-Haque et al. 2002)

3. Prognosis
   1. Strongly dependent on the nature of the brachydactyly
   2. May vary from excellent to severely influencing hand function
   3. Often depends on the nature of the associated anomalies if brachydactyly forms part of a syndromic entity

Diagnostic Investigations

1. Radiographic studies (Temtamy and McKusick 1978)
   1. Brachydactyly type A1
      1. Short middle phalanges involving most digits bilaterally with absent middle phalanges in severely affected individuals
      2. Proximal phalanx of thumb: short in some patients
      3. Flattening of articular surface of metacarpals and short metacarpals in severely affected individuals
      4. Occasional small ossicles at metacarpocarpal joints and at metacarpophalangeal joints
      5. Short proximal phalanx of great toe and absent middle phalanges of the toes in some cases
   2. Brachydactyly type B (Gong et al. 1999)
      1. Middle and distal phalanges: shortened or missing.
      2. Cleft distal phalanx of the great toe.
      3. A single distal phalanx, in some instances, appears to articulate with the proximal phalanx.
      4. Metacarpal and proximal phalanges appear normal.
      5. Mild cutaneous syndactyly in the hands and feet may be present.
   3. Brachydactyly type C (Castriota-Scanderbeg et al. 2005)
      1. Striking shortening of several metacarpals (especially the thumb) and phalanges
      2. Absence ossification of the middle phalanges of the index, middle, ring, and little fingers
      3. "Angel-shaped" phalanges in the proximal phalanges of the index and middle fingers
      4. Ovoid thumb metacarpals
      5. Shortening of the ring and little finger metacarpals
   4. Brachydactyly type D
      1. Broad thumb without associated clinical findings
      2. More common in females than males
      3. Bilateral in about 75%
   5. Brachydactyly E
      1. Shortening of metacarpals and metatarsals due to premature closure of the growth plate, often symmetrical
      2. Often short distal phalanx of the thumb and less commonly of other distal phalanges
2. Mutation studies

Genetic Counseling

1. Recurrence risk: The nature of genetic counseling depends both on the pattern of inheritance of the type of brachydactyly present in the family and on the presence or absence of accompanying symptoms. In autosomal dominant inheritance, variability in severity and incomplete penetrance are common in several types of brachydactyly. In autosomal recessive inheritance, variability is usually smaller although variable symptoms may still be present in affected sibs. Clinically, the presence of a relatively long ring finger in a patient with brachydactyly should bring the attention to testing of candidate genes responsible for endochondral bone formation (Al-Qattan 2014). It is also important to realize that

brachydactyly type C may be inherited as either autosomal dominant or recessive. The dominant mutation may present as a "de novo mutation" (an alteration in a gene that is present for the first time in one family member). Hence, if apparently normal parents had a baby born with brachydactyly type C, genetic testing should include both the baby and parents to determine the risk in the next baby (autosomal recessive inheritance gives a 25% risk in each newborn).

1. Patient's sib
    1. Autosomal dominant inheritance
        1. Recurrence risk of 50% if a parent is affected
        2. Low recurrence risk if both parents are normal
    2. Autosomal recessive inheritance: risk of recurrence 25%
2. Patient's offspring
    1. Autosomal dominant inheritance: a 50% risk of offspring affected
    2. Autosomal recessive inheritance: low recurrence risk unless the spouse is affected or a carrier of brachydactyly mutation

2. Prenatal diagnosis
    1. Usually not indicated for isolated forms of brachydactyly, but may be appropriate in syndromic forms.
    2. Molecular studies of chorionic villus samples at 11 weeks of gestation and by amniocentesis after the 14th week of gestation can provide antenatal diagnosis if the causative mutation in the family is known.
    3. Prenatal diagnosis of a family affected by brachydactyly type A1 with a mutation in IHH (Palka et al. 2012).
3. Management
    1. No specific management or treatment applicable to all forms of brachydactyly.
    2. Plastic surgery:
        1. Only indicated if the brachydactyly affects hand function or for cosmetic reasons
        2. Typically not ordered
    3. Physical therapy and ergotherapy may ameliorate hand function.

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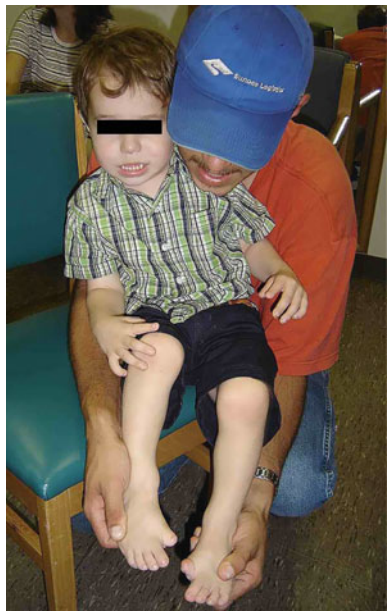

Fig. 1 A 2-year-and-6-month-old boy was evaluated for brachydactyly and abnormal shaped thumbs and great toes. He had hitchhiker-shaped thumbs and great toes with short fingers and toes including clinodactyly of the fifth fingers. His sister, mother, and maternal grandmother are similarly but less severely affected. The brachydactyly present in this kindred is consistent with brachydactyly type A1

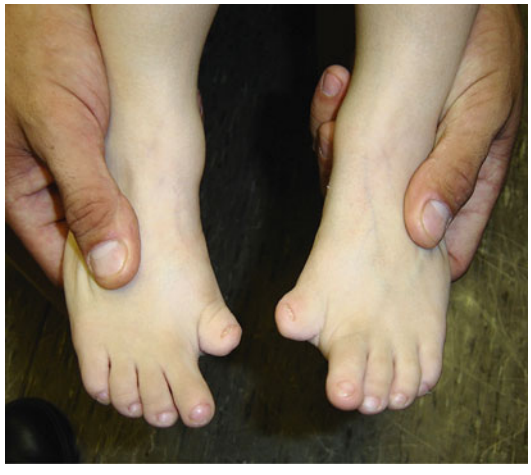

Fig. 2 His great toes showed hitchhiker-shaped deformities

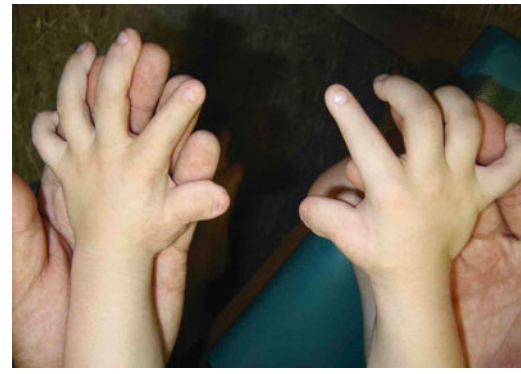

Fig. 3 His thumbs showed hitchhiker-shaped deformities

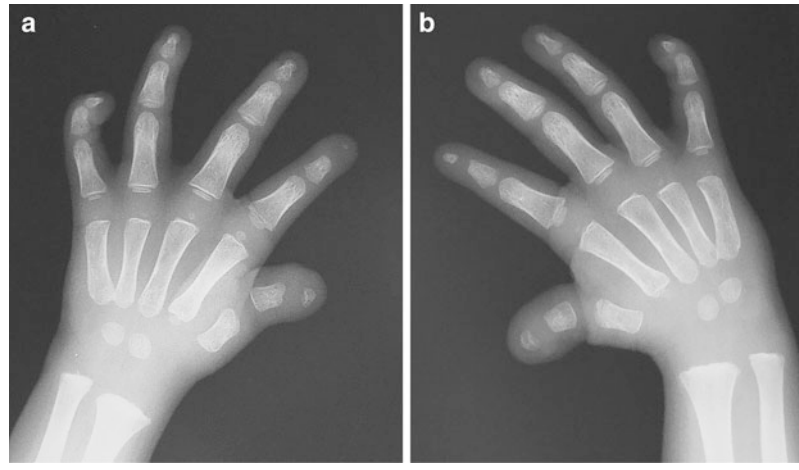

Fig. 4 (**a** and **b**) Radiographs of both hands showed short phalanges, especially short middle and distal phalanges in addition to deformities of the thumbs

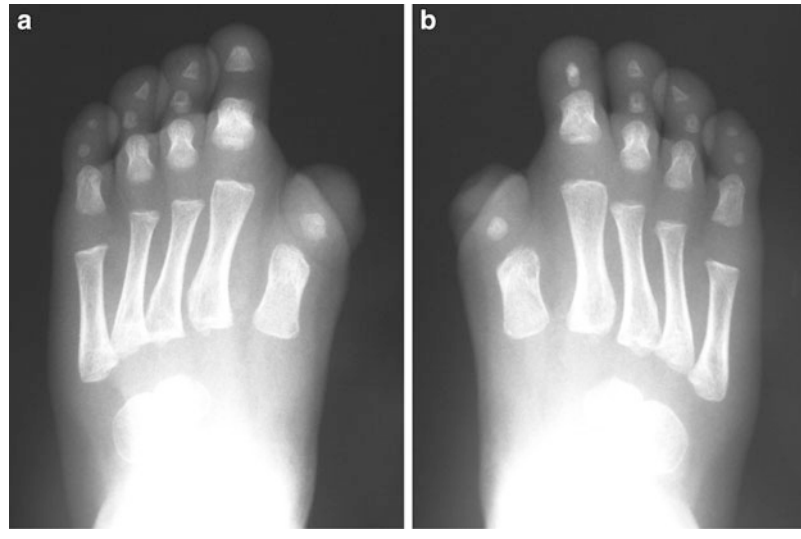

Fig. 5 (**a** and **b**) Radiographs of both feet showed short phalanges, especially middle and distal phalanges, in addition to deformities of the great toes

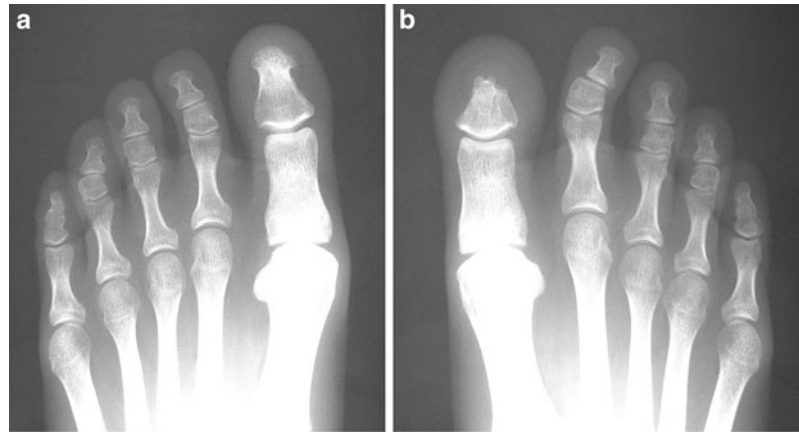

Fig. 6 (**a** and **b**) Radiographs of the feet of his mother

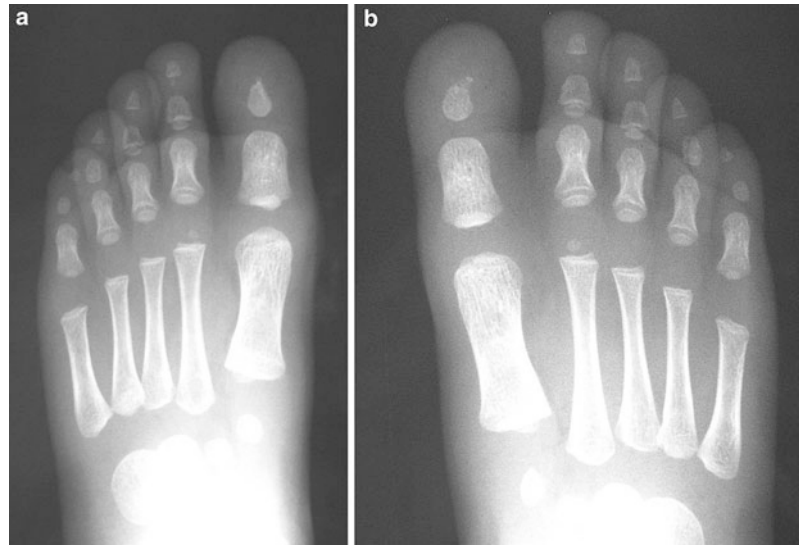

Fig. 7 (**a** and **b**) Radiographs of the feet of his sister

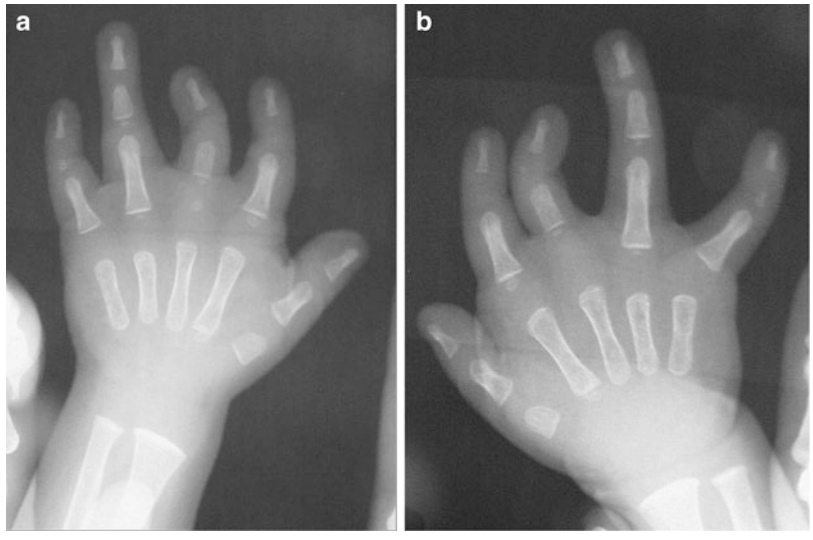

Fig. 8 (**a** and **b**) Radiographs of the hands of a 21-month-old boy, who was evaluated for hand anomalies, showed shortening of thumb metacarpals, ulnar deviation of the second to third fingers with deficient ossification of the middle phalanges, relatively normal fourth finger (the longest digit and longer than the middle finger), and clinodactyly of the fifth finger with hypoplastic middle phalanges. No carpal bones were apparent. The brachydactyly in this child appears to represent brachydactyly type C

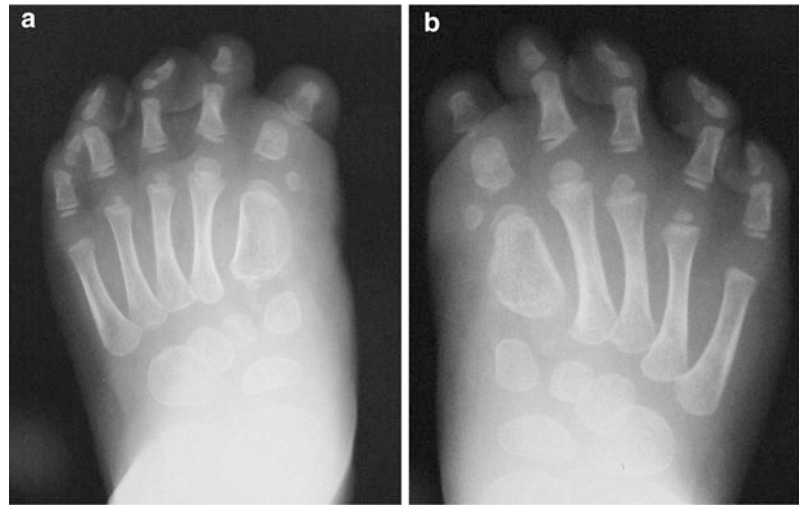

Fig. 9 (**a** and **b**) Radiographs of the feet showed abnormal shaped first metatarsals and short toes with absent or hypoplastic middle phalanges

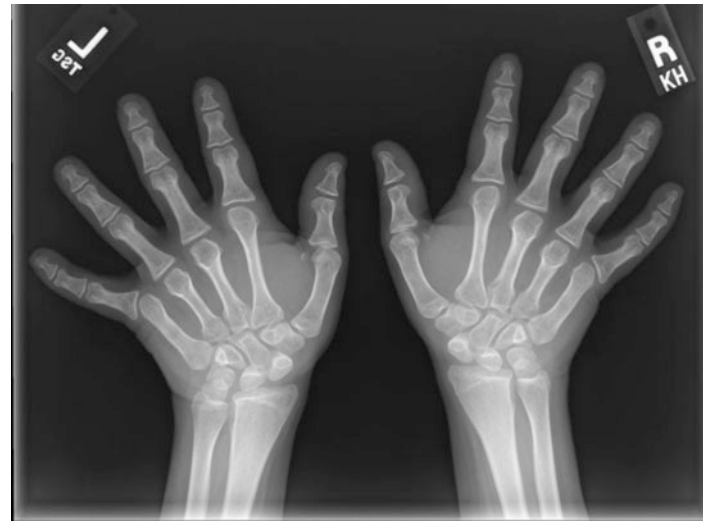

Fig. 10 A 17-year-old female was evaluated for severe scoliosis and status post corrective surgery. She and her mother were noted to have brachydactyly. In the hands, there was evidence of brachydactyly with symmetric shortening of the bilateral 3rd and 4th metacarpals. The bilateral proximal and middle phalanges of the second digit and possibly the distal phalanges appeared also shortened (Courtesy of Dr. Grace Guo)

Branchial Cleft Anomalies

Contents

Abnormal persistence of branchial apparatus remnants results in branchial anomalies. Branchial cleft anomalies are the second most common head and neck congenital lesions seen in children (Bajaj et al. 2011).

Synonyms and Related Disorders

Branchial cyst; Branchial fistula; Branchial remnant presenting as skin tag; Branchial sinus

Genetics/Basic Defects

1. Embryology of the fetal branchial apparatus
    1. A derivative of a foregut, developed during the second fetal week
    2. Consisting of five paired pharyngeal arches, separated internally by four endodermal pouches and externally by four ectodermal clefts
2. Embryology of the branchial clefts (Benson et al. 1992; Prosser and Myer 2015)
    1. First branchial cleft (Arndal and Bonding 1996)
        1. Giving rise to the Eustachian tube, tympanic cavity, and mastoid antrum.
        2. Contributing to the formation of the tympanic membrane.
        3. The only cleft to contribute to the adult structure is the external auditory canal.
        4. Type I: thought to arise from the duplication of the membranous external ear canal and are composed of ectoderm only.
        5. Type II: composed of the ectoderm and mesoderm (Al-Mahdi et al. 2013).
    2. Second, third, and fourth branchial clefts
        1. Known as the cervical sinus of His (part of an ectodermally lined depression)
        2. Obliteration of the cervical sinus as the second and fifth branchial clefts merge
    3. Second branchial pouch
        1. Lined by the ectoderm
        2. Contributing to the palatine tonsil and tonsillar fossa
    4. Third branchial pouch: forming the following structures
        1. Inferior parathyroid gland
        2. Thymus
        3. Pyriform sinus
    5. Fourth branchial pouch: forming the following structures

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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    1. Superior parathyroid gland
    2. Apex of the pyriform sinus
3. Pathogenesis of branchial cleft anomalies: remains controversial
    1. Arising from incomplete obliteration of the cervical sinus of His
    2. Arising from buried epithelial cell rests
4. Genetics: autosomal dominant inheritance in some families (Wheeler et al. 1958; Anand et al. 1979; Clevens and Weimert 1995)

Clinical Features

1. Manifestation of branchial cleft anomalies (Muckle 1961; Maran and Buchanan 1978; Chandler and Mitchell 1981; Howie and Proops 1982; Doi et al. 1988; Ford et al. 1992; Choi and Zalzal 1995; Koeller et al. 1999)
    1. Cyst
        1. An epithelial-lined structure without an external opening
        2. Most common branchial cleft anomalies (75%)
    2. Sinus
        1. A blind tract with an opening externally through the skin on the side of the neck representing persistence of a branchial groove
        2. A blind tract with an opening internally into the foregut representing persistence of a branchial pouch
    3. Fistula
        1. A tract communicating between the skin externally (a patent abnormal canal opening externally on the neck surface) and the foregut internally (within the pharyngeal mucosa)
        2. Representing persistence of a branchial groove with its corresponding pouch and without branchial membrane between them
    4. Skin tag: a branchial remnant presenting in the lateral neck
    5. Bilateral branchial cleft anomalies
        1. Occurring in 2–3% of cases
        2. Often familial
2. First branchial cleft cyst (Triglia et al. 1998)
    1. Accounting for only 5–8% of all branchial cleft defects
    2. Most commonly seen in middle-aged women
    3. Usually manifesting as recurrent abscesses or other inflammation (sinus tract) either around the ear or at the angle of the mandible
    4. History of recurrent parotid abscesses unresponsive to antibiotics and drainage
    5. Cystic drainage into the external auditory canal
        1. Aural fistulas
        2. Auricular swelling
        3. Otitis
        4. Otorrhea
        5. A cervical skin tag at birth
    6. Occasional sinus tract extending to the hyoid bone
    7. Cyst related to the parotid gland
        1. Forming abscess and produce parotitis
        2. May be associated with facial nerve palsy
3. Second branchial cleft cyst (Ramirez-Camacho et al. 2001)
    1. Most common developmental anomalies arising from the branchial apparatus
    2. Cysts
        1. Accounting for at least three fourths of branchial cleft anomalies
        2. Typically occurring between 10 and 40 years of age
    3. Location of the cysts
        1. Most commonly in the submandibular space
        2. Anywhere along a line from the oropharyngeal tonsillar fossa to the supraclavicular region of the neck
    4. Signs and symptoms of second branchial cleft cyst
        1. Usually appearing as painless, fluctuant masses in the lateral portion of the neck adjacent to the anteromedial border of the sternocleidomastoid muscle at the mandibular angle.
        2. Enlarge slowly over time.
        3. Painful and tender if secondarily infected.

    4. Highly suggestive in a young patient with a history of recurrent inflammation in the region of the mandibular angle.
    5. Ostium usually noted at birth just above the clavicle in the anterior neck if a fistula is present.
  5. Fistulas and sinuses
    1. Almost always present at birth
    2. With a small pinpoint external opening
    3. May go unnoticed for years if there is no drainage
    4. Symptoms consisting of continuous or intermittent mucoid drainage and recurrent attacks of inflammation that often follow mild trauma or an infection of the upper respiratory tract
    5. Occasional formation of cellulitis and abscess
    6. Probing of the track producing irritation of the vagus nerve
    7. Usually unilateral
    8. Found in several members of the same family
4. Third branchial cleft cyst
  1. Extremely rare
  2. Most cysts located in the posterior cervical space posterior to the sternocleidomastoid muscle
  3. Constituting the second most common congenital lesion of the posterior cervical space of the neck after cystic hygroma
  4. Usually manifesting as a painless, fluctuant mass in the posterior triangle area of the neck
  5. Mass usually distending during a viral infection of the upper respiratory tract
5. Fourth branchial cleft cyst
  1. Extremely rare
  2. Usually manifesting as a sinus tract rather than a cyst or fistula
  3. Majority of the lesions occurring on the left side

Diagnostic Investigations

1. CT scans/MRI imagings (Koeller et al. 1999)
  1. First branchial cleft cyst
    1. Appearing as a cystic mass either within, superficial to, or deep to the parotid gland
    2. Variable wall thickness and enhancement: increase with recurrent infections
    3. Difficult to differentiate from other cystic mass of the parotid gland
  2. Second branchial cleft cyst
    1. Typically well-circumscribed, homogeneously hypoattenuated masses surrounded by a uniformly thin wall
    2. Increased mural thickness after infection
    3. "Beaked sign" (a curved rim of tissue or "beak" pointing medially between the internal and external carotid arteries) considered a pathognomonic imaging feature of a second branchial cleft cyst
  3. Third branchial cleft cyst
    1. Most commonly appearing as a unilocular cystic mass centered in the posterior cervical space
    2. Cyst fluid varying in signal intensity on T1-weighted images depending on the protein concentration and is typically hyperintense relative to muscle on T2-weighted images
  4. Fourth branchial cleft cysts
    1. Connected with the pyriform sinus
    2. Appearing similar to an external or mixed laryngocele
2. Ultrasonography
  1. A fluctuant, compressible, anechoic, or hypoechoic mass
  2. May have fine internal debris
3. Sinogram or fistulogram with radiopaque dye (Ramirez-Camacho et al. 2001)
  1. To help confirming the diagnosis
  2. To identify length and location of the fistulous tract
  3. To identify an associated cyst

Genetic Counseling

1. Recurrence risk
  1. Patient's sib

    1. Not increased in de novo case
    2. Fifty percent recurrence risk if a parent is affected with an autosomal dominant disorder
  2. Patient's offspring: 50% in autosomal dominant inheritance
2. Prenatal diagnosis by ultrasonography
  1. Demonstrate a cystic neck mass in the fetus with differential diagnosis including hemangioma, dermoid cyst, neuroblastoma, congenital cystic hygroma, teratoma, epignathus, esophageal duplication, goiter, and laryngocele
  2. Third branchial cleft anomaly detected in utero (Robichaud et al. 2000)
3. Management (Agaton-Bonilla and Gay-Escoda 1996)
  1. First branchial cleft cyst: complete surgical excision (only curative therapy) (Triglia et al. 1998)
  2. Second and third branchial cleft cysts: surgical excision recommended because of increased frequency of secondary infection
  3. Recurrence risk uncommon after surgical excision
  4. Antibiotics required for treating infections or abscess

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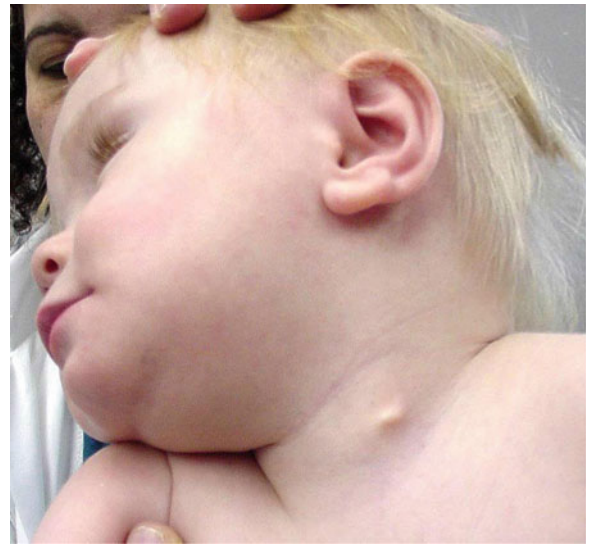

Fig. 1 A branchial cleft cyst in the *left* side of the neck

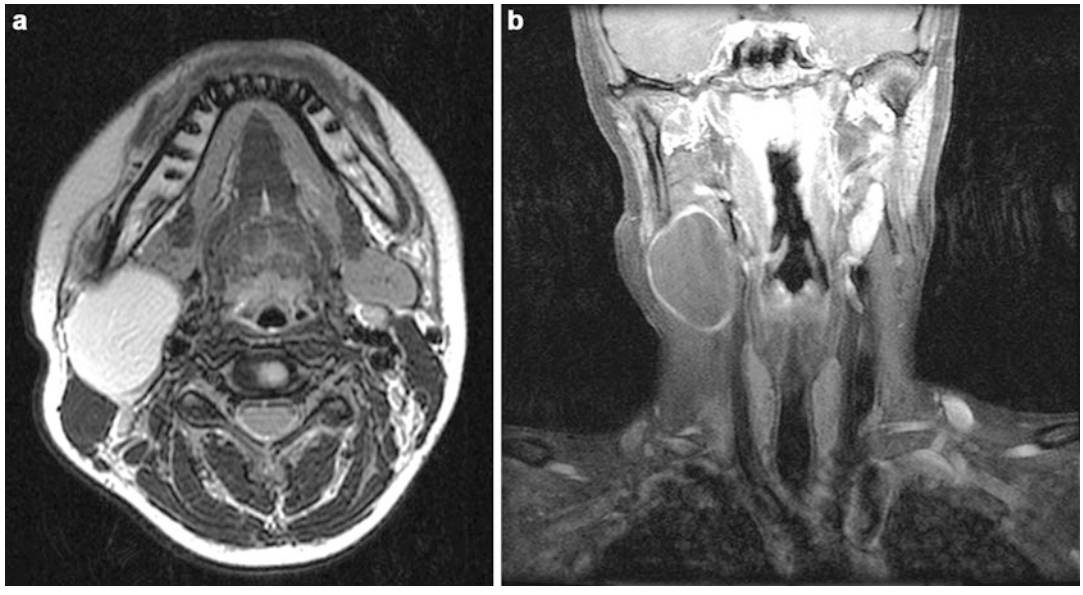

Fig. 2 (**a**, **b**) A 15-year-old female was evaluated for concerns of left neck swelling. Over the past 2 months, the swelling had decreased in size, but never returned to normal. The onset of the mass was gradual with complaints of left neck swelling with pain and upper respiratory tract infections. MRI Images (**a**, **b**) demonstrated a well-defined 4.4 cm lesion in the space posterior to the right angle of the mandible and anterior to the sternocleidomastoid muscle with mass effect on the surrounding structures. The axial image (**a**) showed the lesion with T2 hyperintensity. The coronal image (**b**) showed a mild thin peripheral enhancement. The findings are suggestive of a type II bronchial cleft cyst, which was confirmed with postsurgical pathology (Courtesy of Dr. Grace Guo)

Calcinosis Cutis

Contents

Calcinosis cutis is a group of disorders characterized by the deposition of crystals of calcium phosphate (hydroxyapatite) in the skin in various areas of the body (Ianello et al. 1998) and can be associated with both normal and elevated calcium levels. Classically, it is divided into dystrophic, metastatic, iatrogenic, and idiopathic types.

Synonyms and Related Disorders

Calcinosis cutis (dystrophic, metastatic, iatrogenic, or idiopathic types)

Genetics/Basic Defects

1. Dystrophic calcinosis cutis (Nunley and Jones 2009)
    1. A common form of calcinosis cutis
    2. Localized or generalized
3. Absence of calcium or phosphorus metabolic abnormalities
4. Depositions of calcium salts: secondary to local inflammation, tissue damage, and degeneration (Walsh and Fairley 1995)
5. Localized tissue damage
    1. Trauma
    2. Burn
    3. Inflammatory processes
        1. Acne
        2. Insect bites
    4. Varicose veins.
    5. Infections: Necrotic tissue produced by an infectious process may subsequently become calcified.
        1. Onchocerciasis
        2. Cysticercosis
        3. Histoplasmosis
        4. Cryptococcosis
        5. Intrauterine herpes simplex infection
    6. Tumors: Benign and malignant tumors may develop calcification.
        1. Pilomatrixoma
        2. Calcifying epithelioma of Malherbe
        3. Epithelial cysts
        4. Syringomas
        5. Basal cell carcinomas
        6. Rarely in melanocytic nevi, malignant melanoma, atypical fibroxanthoma, hemangioma, pyogenic granuloma, seborrheic keratoses, neurilemomas, and trichoepitheliomas

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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6. Generalized tissue damage (Reiter et al. 2011b)
    1. Connective tissue diseases (Balin et al. 2012)
        1. Dermatomyositis (Wu and Metz 2008)
        2. Scleroderma (Vereecken et al. 1998)
        3. Lupus erythematosus (Marzano et al. 1999)
        4. Lupus panniculitis
        5. Systemic sclerosis
        6. Mixed connective tissue disease
        7. Overlap connective tissue disease
        8. Mixed connective tissue disease
        9. Rheumatoid arthritis
        10. Calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias (CREST) syndrome
    2. Porphyria cutanea tarda
    3. Subcutaneous fat necrosis of the newborn
    4. Inherited disorders
        1. Ehlers-Danlos syndrome
        2. Werner syndrome
        3. Pseudoxanthoma elasticum
        4. Rothmund-Thomson syndrome
2. Metastatic calcinosis cutis
    1. Precipitation of calcium salts in normal tissue due to increased serum calcium and phosphate levels as a result of an underlying defect in calcium and/or phosphate metabolism.
    2. Generally indicates chronic renal failure.
    3. Calcification usually widespread and affects predominantly the blood vessels, kidneys, lungs, and gastric mucosa.
    4. Cutaneous and subcutaneous tissues may be involved: a rare complication.
    5. Some of the factors involved are:
        1. Factors involved in increased serum calcium levels:
            1. Primary or secondary hyperparathyroidism
            2. Paraneoplastic hypercalcemia
            3. Albright hereditary osteodystrophy
            4. Destructive bone disease (malignancies, Paget disease)
            5. Excessive vitamin D intake
            6. Milk-alkali syndrome
            7. Sarcoidosis
            8. Chronic renal failure (Tan et al. 2006)
            9. Calciphylaxis
        2. Factor involved in increased serum phosphate levels: chronic renal failure
3. Iatrogenic causes: secondary to a treatment or procedure
    1. Parenteral calcium (Kagen et al. 2000; Puvabanditsin et al. 2005): extravasation of intravenously administered calcium chloride or calcium gluconate
    2. Parental inorganic phosphate
    3. Tumor lysis syndrome (Rodriguez-Cano et al. 1996)
    4. Repeated heel sticks in the newborn
    5. Prolonged use of calcium-containing electrode paste
        1. Electromyography
        2. Electroencephalography
        3. Brain auditory evoked potential
4. Idiopathic calcinosis cutis (Ogretmen et al. 2002)
    1. Also known as calcinosis cutis universalis
    2. Sporadic occurrence
    3. Characterized by calcium deposits in the dermis, subcutis, and muscles without any metabolic disorder or tissue injury
    4. An uncommon type and may be solitary of multiple
    5. Causes
        1. Idiopathic calcinosis of scrotum/penis/vulva
        2. “Milia-like” idiopathic calcinosis cutis with or without Down syndrome (Bécuwe et al. 2004; Goirtz et al. 2006)
        3. Subepidermal calcified nodule
        4. Tumoral calcinosis
        5. Calcinosis cutis circumscripta
        6. Transplant-associated calcinosis

Clinical Features

1. Dystrophic calcinosis cutis (Nunley and Jones 2009)

1. Most common type of calcinosis cutis
2. Large and widespread deposits: termed calcinosis universalis
3. Dystrophic calcification occurring locally and consists of only a few deposits of calcium salts termed "calcinosis circumscripta"

2. Metastatic calcinosis
   1. First manifestations
      1. Bone demineralization
      2. Non-visceral and/or visceral calcification, mostly with mural deposits in arteries and arterioles
   2. Calcium deposition
      1. Frequently widespread
      2. Large deposits frequently found around large joints, such as the knees, elbows, and shoulders, in a symmetrical distribution
      3. Visceral organs: deposition of calcium in the lungs, kidneys, blood vessels, and stomach occurring more frequently than deposition within the skin or muscle
      4. Calciphylaxis: characterized by progressive vascular calcification, soft tissue necrosis, and ischemic necrosis of the skin
3. Iatrogenic calcinosis cutis
   1. Calcification generally localized at the site of an invasive procedure
   2. Diffuse deposition may occur
4. Idiopathic calcinosis cutis
   1. Uncommon
   2. Calcification deposit
      1. Most commonly localized to one general area
      2. Observed in the dermis, subcutis, and muscles without any metabolic disorder or tissue injury

Diagnostic Investigations

1. Laboratory studies (Nunley and Jones 2009)
   1. Serum calcium, inorganic phosphate, alkaline phosphatase, and albumin levels.
      1. Elevated serum calcium and alkaline phosphatase levels with a decrease in the inorganic phosphate level: suggestive of hyperparathyroidism
      2. An albumin value: needed to interpret the significance of hypocalcemia or hypercalcemia
      3. Serum blood urea nitrogen and creatinine concentrations: needed to measure renal function
   2. Abnormal complete blood cell count with differential: suggest an underlying malignancy or lupus erythematosus.
   3. Abnormal plasma bicarbonate or arterial pH value: indicates the presence of a metabolic alkalosis (milk-alkali syndrome).
   4. Parathyroid hormone concentration: direct measurement for hyperparathyroidism.
   5. Abnormal creatine kinase and aldolase value.
      1. Dermatomyositis
      2. Myositis
      3. Rhabdomyolysis
   6. Serum amylase or lipase levels: to assess pancreatic disease.
   7. Antinuclear antibody testing: helpful in screening for lupus erythematosus.
   8. Presence of SCL-70 (topoisomerase) antibody: portends a poor prognosis for scleroderma patient.
   9. Vitamin D levels: to evaluate for excess vitamin D. A test of the 24-h urinary excretion of calcium and/or inorganic phosphate may be useful.
2. Imaging studies
   1. Radiographic examination (Shahi et al 2014): effective in detecting cutis and to demonstrate the extent of tissue calcification
   2. Bone scintigraphy with radiolabeled phosphate compounds (technetium Tc 99 m methylene diphosphonate [MDP]): to evaluate non-visceral soft tissue calcification (Bhattacharya et al. 2005)
   3. CT for the identification of visceral and non-visceral calcification, particularly in assessing tumoral calcinosis
   4. MRI: to evaluate characteristic patterns of calcific deposits, particularly in evaluating granulomatous foreign-body reaction in tumoral calcinosis

3. Biopsy and histopathologic examination of a cutaneous lesion
    1. Observation of granules and deposits of calcium in the dermis, with or without a surrounding foreign-body giant cell reaction
    2. Massive calcium deposits: may be located in the subcutaneous tissue
    3. Calcium deposition: frequently found within the walls of small- and medium-sized blood vessels in areas of necrosis
    4. Calcium deposition: may be confirmed on Von Kossa and alizarin red stains
    5. Fine needle aspiration cytology: amorphous calcium salts in subcutaneous fibrofatty tissue (Aggawal and Shrestha 2013; Choudhury et al. 2015)

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib
        1. No increase in sporadic cases
        2. Autosomal recessive: a 25% recurrence risk (e.g., Rothmund-Thomson syndrome, Ehlers-Danlos syndrome types VI–VII, and familial hyperphosphatemic tumoral calcinosis)
        3. Autosomal dominant: not increased unless a parent is affected, in which case a 50% recurrence risk (e.g., pseudoxanthoma elasticum, Ehlers-Danlos syndrome types I–IV)
        4. X-linked recessive: 50% of male sibs affected if the mother is a carrier (e.g., Ehlers-Danlos syndrome type V)
    2. Patient's offspring:
        1. Autosomal recessive: not increased unless the spouse is also a carrier
        2. Autosomal dominant: a 50% risk
        3. X-linked recessive: all daughters of affected males will be carriers. All sons of an affected male will be normal.
2. Prenatal diagnosis: not reported
3. Management (Reiter et al. 2011a)
    1. Medical management: limited with variable benefit; should attempt to correct the underlying problems
        1. Intralesional corticosteroids: may be beneficial because of their anti-inflammatory and inhibitory effects on fibroblast activity.
        2. Probenecid and colchicines: beneficial in some individuals with extensive calcification related to juvenile dermatomyositis.
        3. Magnesium or aluminum antacids: may be effective phosphate binders in patients with hyperphosphatemia but the use of these agents in patients with renal insufficiency may result in magnesium or aluminum toxicity.
        4. Sodium etidronate and bisphosphonates: may reduce bone turnover and inhibit the growth of ectopic hydroxyapatite crystals. Paradoxical hyperphosphatemia may result from prolonged treatment. Improvement has been observed in extended soft tissue calcification in dermatomyositis.
        5. Minocycline: successfully treated calcinosis cutis in limited systemic sclerosis (reduction of size and decrease of inflammation/ulceration).
        6. Myoinositol hexaphosphate is a dietary substance shown to inhibit the crystallization of calcium salts in animal studies and potentially could be of benefit in humans.
        7. Diltiazem: successfully treated calcinosis cutis in dermatomyositis.
        8. Ceftriaxone: effectively treated morphea profunda with calcinosis cutis.
        9. Alminum hydroxide: size reduction and softening of subcutaneous calcification in a patient with systemic lupus erythematosus after oral aluminum hydroxide.
        10. Systemic warfarin: has shown benefit in small calcified deposits but no improvement in larger, longer-standing calcinosis cutis lesions.

11. The use of the calcium-channel blocker diltiazem over at least 5 years has variable benefits. The therapeutic effect is believed to be the antagonism of the calcium-sodium ion pump.
12. Response to intravenous immunoglobulin in some patients with dystrophic calcification (Schanz et al. 2008).

2. Carbon dioxide laser: effective in small, digital calcified deposits
3. Surgical removal (Hussman et al. 1995)
    1. Indications
        1. Pain
        2. Recurrent infection
        3. Ulceration
        4. Functional impairment
    2. Initial test removal of a test site before pursuing a large excision because the surgical trauma may stimulate calcification
    3. Recurrence common after excision
4. Electric shock wave lithotripsy
    1. Anecdotally successful in dermatomyositis-induced tissue calcification
    2. Complete relief of associated pain although reduction in the size of the calcification is minimal

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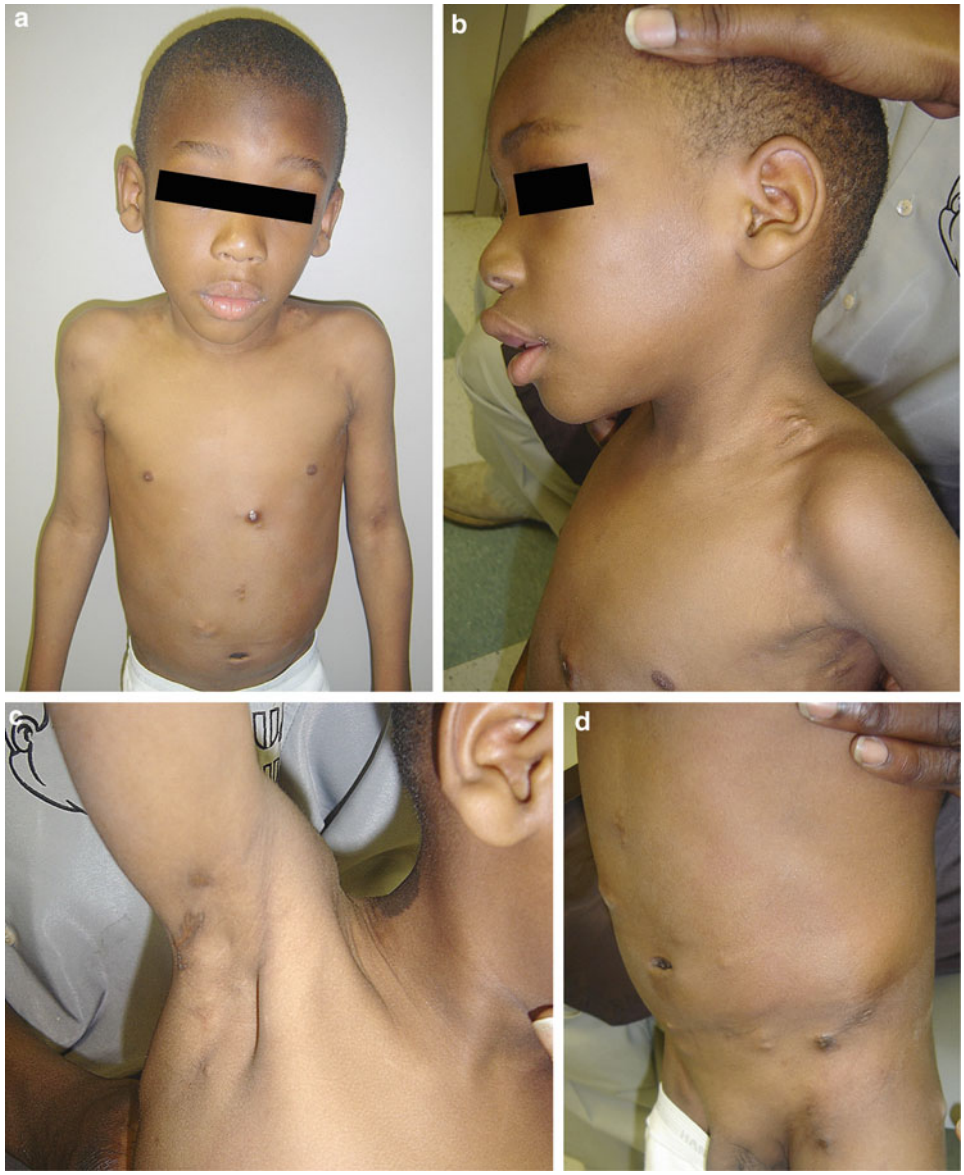

Fig. 1 (**a–d**) A 4-year-old boy has had numerous hard nodules in his neck, arms, legs, and trunk since early infancy. The subcutaneous hard nodules were tender and began to multiply and eventually became ulcerated. Recently he complained restricted arm and leg movement

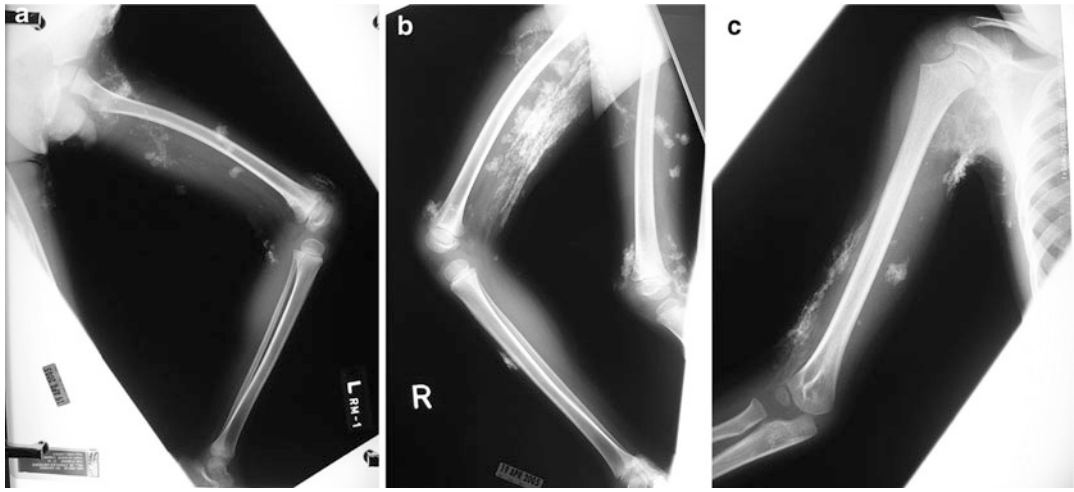

Fig. 2 (**a**–**c**) Radiologic studies revealed numerous subcutaneous calcifications throughout the body (only arm and legs are illustrated here). *GNAS1* gene mutation testing revealed no sequence variation

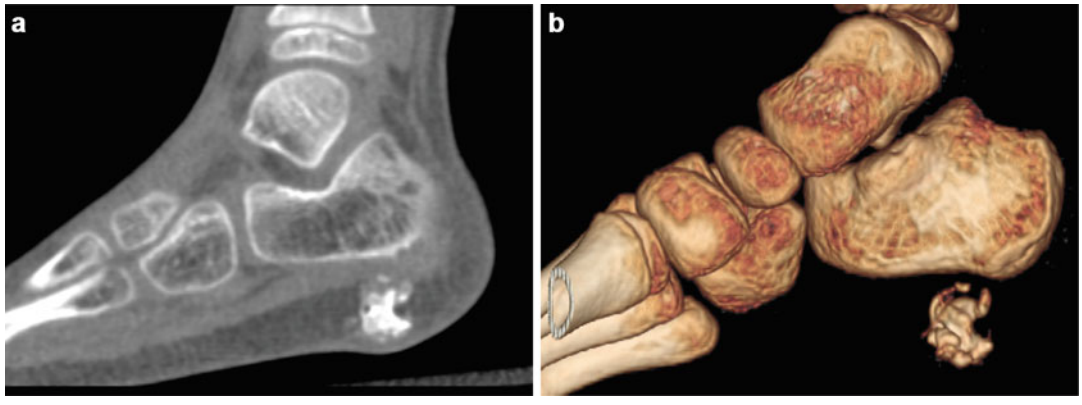

Fig. 3 (**a**, **b**) The patient was a healthy 3-year-old female with a history of a small mass on her right heel pad for over a year. Recently, she had intermittently complained of pain associated with slightly increased mass size. Plain CT (**a**) and 3D reconstruction CT (**b**) images of the right foot demonstrated an irregular calcification centered in the subcutaneous fat plantar and slightly medial to the posterior body of the calcaneus. There was an accompanying soft tissue component, with the mass being contiguous with and inseparable from the adjacent plantar musculature and overlying dermis. There was no evidence of periosteal reaction or cortical destruction of the adjacent calcaneus. The bones of the foot demonstrated normal osseous mineralization and no suspect sclerotic or lytic lesion was seen (Courtesy of Dr. Grace Guo)

Campomelic Dysplasia

Contents

Campomelic dysplasia is a rare, often lethal congenital osteochondrodysplasia associated with skeletal malformations and sex reversal. The term "campomelia" derives from Greek, meaning bent or curved limb. Since most patients die in the neonatal period due to respiratory distress, patients with campomelic dysplasia are most often sporadic but few familial cases have been reported. The incidence of campomelic dysplasia is reported to be 0.05–0.9 per 10,000 births (Iravani et al. 2000).

Synonyms and Related Disorders

Acampomelic campomelic dysplasia; Campomelic dysplasia with autosomal sex reversal; Camptomelic dysplasia

Genetics/Basic Defects

1. Inheritance
    1. Autosomal recessive (Hall and Spranger 1980)
    2. Autosomal dominant (Thurmon et al. 1973; Lynch et al. 1993) with variable expression (Savarirayan et al. 2003)
2. Etiology (Kwok et al. 1995): can be caused by heterozygous intragenic *SOX9* mutations or chromosomal aberrations (translocations, inversions, or deletions) affecting *SOX9* or the putative enhancer region (Wada et al. 2009)
    1. Assignment of a locus *CMPD1* to 17q24.3-q25.1 was based on characterization of three independent de novo chromosome 17 translocations in campomelic dysplasia patients (Tommerup et al. 1993).
    2. XY sex reversal of two of these translocation patients placed an autosomal sex-determining locus, *SRA1*, in the same region.
    3. *SOX9*, a gene related to the mammalian Y chromosome sex-determining gene SRY, was mapped to this region and found to be near the translocation breakpoint of a sex-reversed campomelic dysplasia patient.
    4. Subsequent identification of de novo mutations in sex-reversed campomelic patients

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demonstrated that SOX9 is the gene responsible for both campomelic dysplasia and autosomal sex reversal (Foster et al. 1994; Schafer 2001).

5. SOX9 mutations
    1. Disrupt skeletogenesis and chondrocytic differentiation
    2. Produce defective testicular development often resulting in sex reversal with female phenotype in chromosomal XY males
6. Proof of *SOX9* being responsible for both campomelic dysplasia and XY sex reversal: demonstration of de novo heterozygous loss-of-function mutations within the SOX9 coding region in non-translocation campomelic dysplasia patients (Iravani et al. 2000).
7. Isolation of the *SOX9* gene on chromosome 17q by positional cloning in combination with positional candidate information from the vicinity of breakpoints in campomelic dysplasia patients with reciprocal de novo translocations (Meyer et al. 1977).
8. Acampomelic campomelic dysplasia (ACD) (Gopakumar et al. 2014; Castori et al. 2016)
    1. Represents about 10% of individuals with *SOX9* coding region mutations: affected by an attenuated form of campomelic dysplasia without bent bones and can be associated with a longer survival (Mansour et al. 2002).
    2. A familial acampomelic dysplasia: caused by an inherited deletion mapping upstream of the *SOX9* gene (Lecointre et al. 2009).
    3. Can result from translocations and inversions involving the long arm of chromosome 17 that disrupt the coding region of *SOX9* (Leipoldt et al. 2007).
    4. Babies with acampomelic dysplasia frequently have missense mutations within the HMG domain, as in the present case, suggesting that the mutant SOX9 protein may retain some binding activity, in contrast to nonsense or frameshift mutations (Friedrich et al. 2000; Thong et al. 2000; Moog et al. 2001).

Clinical Features

1. Clinically a heterogeneous disorder (Khajavi et al. 1976; Houston et al. 1983; Iravani et al. 2000)
    1. Long-limbed variety
        1. Bent bones of normal thickness, may be slightly shortened
        2. Rarely involves the upper limbs
    2. Short-limbed variety
        1. Bent bones that are short and wide
        2. Two skull types
            1. Craniosynostotic type with cloverleaf skull
            2. Normocephalic type
    3. Acampomelic campomelic dysplasia
        1. The eponymous feature "campomelia" (the bending of the long bones): not an obligatory feature of the syndrome
        2. Absence of campomelia in about 10% of campomelic dysplasia cases
2. Prenatal history
    1. Polyhydramnios (30% of cases) in the third trimester common
    2. Growth retardation
3. Extreme hypotonia at birth
4. Characteristic craniofacial features
    1. Frequent macro-dolichocephaly
    2. Cloverleaf skull
    3. Wide fontanel
    4. Short, narrow, and upslanted palpebral fissures
    5. Ocular hypertelorism
    6. Flat nasal bridge
    7. Long philtrum
    8. Micrognathia (Pierre Robin sequence)
    9. Cleft palate in two thirds of the cases
    10. Low-set and posteriorly rotated ears
    11. Prominent nuchal folds
    12. Hearing loss (deaf) in survivors
5. Prominent and characteristic musculoskeletal features

1. Congenital bowed lower limbs (anterior bowing of the tibiae) with pretibial skin dimples. Pretibial dimples that appear to result from the loss of subcutaneous tissue secondary to marked stretching of the skin overlying the apexes of the bony curvatures during fetal life
2. Short limbs
3. Short neck
4. Pterygium colli
5. Narrow thorax
6. Kyphoscoliosis
7. Talipes equinovarus
8. Hand anomalies
    1. Brachydactyly
    2. Clinodactyly
    3. Camptodactyly
9. Congenital dislocation of the hips
10. Winging of the scapula
11. Fewer ribs

6. Genitalia
    1. Genotypic XY males (three fourths of karyotypic males with sex reversal) (Mansour et al. 1995)
        1. External genitalia: range from an unambiguous female external genitalia to hypospadias with a bifid scrotum and an enlarged clitoris
        2. Internal genitalia: various combinations of internal Müllerian and Wolffian duct structures
    2. Genotypic XX females: remain phenotypic female
7. CNS
    1. Mental retardation in survivors
    2. Large brain
    3. Hydrocephalus (25%)
    4. Polygyria
    5. Absent olfactory bulbs and/or tracts
    6. Dysgenesis of the corpus callosum
    7. Gross cellular disorganization, especially of the cerebral peduncle, thalamus, and caudate nucleus
8. Respiratory insufficiency secondary to:
    1. Robin sequence
    2. Narrow airways due to laryngotracheobronchomalacia (the most characteristic finding)
    3. Hypoplastic lungs
    4. A small bell-shaped thorax
9. Occasional abnormalities
    1. Congenital heart diseases
        1. Patent ductus arteriosus
        2. Ventricular septal defects
        3. Coarctation of the aorta
        4. Tetralogy of Fallot
    2. Renal anomalies
        1. Hydronephrosis
        2. Hydroureter
        3. Renal hypoplasia
        4. Renal cortical and medullary cysts
    3. Ear anomalies
        1. Hypoplastic cochlea and semicircular canals
        2. Anomalies in incus and stapes
10. Diagnostic criteria (Mansour et al. 1995)
    1. Clinical
        1. Seven or more of the following: macrocephaly, micrognathia, cleft palate, flat nasal bridge, low-set ears, talipes equinovarus, congenital dislocation of hips, bowed femora, bowed tibiae, pretibial skin dimples, and respiratory distress
        2. Sex reversal and bowed lower limbs
    2. Radiological
        1. Hypoplastic scapulae
        2. Bowed femora (marked or mild)
        3. Bowed tibiae (marked or mild)
        4. Vertically narrow iliac wings
        5. Non-mineralized thoracic pedicles
11. Cause of death
    1. Usually due to respiratory insufficiency
        1. Primarily owing to airway and pulmonary defects, lack of laryngotracheobronchial cartilages and hypotonia
        2. Resulting in apneic spells, atelectasis, aspiration, and pneumonia
    2. A high rate of neonatal death
        1. Most deaths occurring neonatally (77%)
        2. 90% of deaths before 2 years
12. Life expectancy that varies depending on the severity of the phenotype
    1. Young infants who survive
        1. Feeding difficulties

2. Stridor
3. Retractions
4. Frequent otitis media
5. Bronchitis
6. Poor growth

2. Infants who survive several years
   1. May be mentally retarded
   2. May show variable breakpoints within the vicinity of chromosome 17 (q21-q25)
   3. Oldest reported survivor: 17 years of age with an IQ of 45
3. Complications of survivors of campomelic dysplasia (Mansour et al. 2002)
   1. Recurrent apnea
   2. Upper respiratory infections
   3. Progressive kyphoscoliosis
   4. Mild to moderate learning difficulties
   5. Short stature
   6. Dislocation of the hips
4. Possible explanations for the survival of patients with campomelic dysplasia
   1. Mosaicism of the *SOX9* mutations
   2. Chromosomal rearrangements involving chromosome 17q (q23.3-q25.1) shown to cause campomelic dysplasia without disrupting the *SOX9* gene, resulting in a milder phenotype (Staffler et al. 2010)

Diagnostic Investigations

1. Radiography (skeletal survey)
   1. Affected infants (Khoshhal and Letts 2002)
      1. Tubular bones
         1. Bowed femora and tibiae
         2. Short fibulae
         3. Radioulnar dislocation
      2. Thorax
         1. Severe hypoplastic, bladeless scapulae
         2. Thin short clavicles
         3. Non-mineralized sternum
         4. Small thoracic cage with slender and/or decreased number of ribs (usually 11 pairs)
      3. Spine
         1. Abnormal cervical vertebrae
         2. Kyphoscoliosis
         3. Non-mineralized thoracic pedicles
      4. Pelvis
         1. Dislocation of the hips
         2. Narrow iliac wings
         3. Poorly developed ischiopubic rami
         4. Coxa vara
      5. Hands and feet
         1. Short first metacarpal bone
         2. Talipes equinovarus
      6. Skeletal maturation
         1. Delayed bone age
         2. Delayed ossification of proximal tibial and distal femoral epiphysis and talus
   2. Survivors
      1. Hypoplastic scapulae
      2. Defective ischiopubic ossification
      3. Absent or hypoplastic patellae
      4. Spinal dysraphism
   3. Considerable radiographic overlap with ischiopubic-patella syndrome
2. Hearing screening
3. Gonadal histology (Cameron et al. 1996)
   1. Similar to XY gonadal dysgenesis
   2. Ranging from dysplastic testicular tissue to poorly differentiated ovarian tissue with a few primordial follicles
4. Histology of growth plate: unremarkable epiphyseal resting cartilage
5. Cytogenetic analysis
   1. Abnormal in about 5% of patients (Unger et al. 2013)
      1. A de novo reciprocal translocation with one breakpoint in chromosome region 17q24.3-q25.1 where SOX9 is located: rarely the translocation may be familial, thus parental karyotypes should be obtained.
      2. A de novo interstitial deletion of 17q.

2. Identification of the sex reversal (fetal karyotype does not match fetal phenotype) (Gentilin et al. 2010)

6. Molecular analysis of *SOX9* mutation (Unger et al. 2013; Carvajal et al. 2016)
    1. Molecular testing is important as affected individuals with aberration of the regulatory domain of SOX9 and chromosome rearrangement tend to have better clinical outcomes.
    2. Sequence screening of the three *SOX9* exons: to detect coding regions and splice mutations (positive in about 90%).
    3. Deletion analysis: to detect partial or whole-gene deletions by quantitative PCR, MLPA, or array CGH and by cytogenetic analyses to detect translocations or larger inversions (positive in about 5%) (Scherer et al. 2013).

Genetic Counseling

1. Recurrence risk (Unger et al. 2013)
    1. Patient's parents: risk of recurrence considered to be as low as 1% for parents in whom a negative molecular test result is obtained (Gentilin et al. 2010)
    2. Patient's sib
        1. An affected parent (non-mosaic): a 50% risk
        2. Not increased unless somatic or gonadal mosaicism or *SOX9* deletion is present in one of the parent
            1. Unaffected mother with somatic mosaicism for the *SOX9* mutation has been reported (Wagner et al. 1994).
            2. An unaffected father of three affected children was reported to have germline, but not somatic, mosaicism (Cameron et al. 1996).
            3. A *SOX9* deletion in a mildly/minimally affected father of two affected children has been reported (Smyk et al. 2007).
            4. There is an estimated recurrence risk of 5% due to the possibility of germline mosaicism in either of the parents (Cameron et al. 1996).
        3. Proband with an unbalanced chromosome constitution
            1. If neither parent has the chromosome rearrangement: a negligible risk
            2. If a parent has a balanced chromosome rearrangement: an increased risk, dependent on the specific chromosome rearrangement and the possibility of other variables
    3. Patient's offspring: provided the patient survives to the reproductive age
        1. A 50% risk to offspring when the proband has a non-mosaic *SOX9* mutation.
        2. Risk to offspring depends on the proband's cytogenetic abnormality involving *SOX9*.
2. Prenatal diagnosis (Unger et al. 2013)
    1. Possible by ultrasonography as early as 18 weeks of gestation
        1. Ultrasonographic findings (Cordone et al. 1989; Tongsong et al. 2000)
            1. Symmetrical anterior bowing of femurs and tibiae
            2. Hypoplastic or absent scapulae
            3. Small thorax compared to the abdomen
            4. Bilateral talipes equinovarus
            5. External genitalia not compatible with 46,XY karyotype
            6. Polyhydramnios
            7. Fetal growth retardation
            8. Large head with internal hydrocephalus
            9. Sagittal scan of the face showing a flat nasal bridge, elongated philtrum, and micrognathia
        2. 3D ultrasound allowing better capture of facial dysmorphic features (Promsonthi and Wattanasirichaigoon 2006)
            1. Telecanthus
            2. Depress nasal bridge
            3. Bowing of forearm
            4. Skin dimpling over the anterior surface of the bowed legs
            5. Fanlike position of the toes

3. Ultrasound findings of acampomelic campomelic dysplasia
    1. Bowing of long bones: evident until the 18th week of gestation (Preiksaitiene et al. 2015)
    2. Some fetuses may manifest with straight bones (acampomelic campomelic dysplasia) (Barone et al. 2014)
4. Major differential diagnosis of ultrasonographic features
    1. Osteogenesis imperfecta
    2. Hypophosphatasia
    3. Unclassifiable varieties of congenital bowing of the long bones
2. Amniocentesis result of 46,XY with ultrasonographic finding of female external genitalia
3. Identification of *SOX9* mutation in the fetus (Barone et al. 2014) by sequence analysis or deletion/duplication analysis: Prenatal diagnosis for pregnancies at risk as a result of a mildly affected parent or potential somatic or germline mosaicism that requires prior identification of the disease-causing mutation in a previously affected child or the mildly affected parent
4. Preimplantation genetic diagnosis for pregnancies at risk as a result of a result of a mildly affected parent or potential somatic or germline mosaicism that requires prior identification of the disease-causing mutation in a previously affected child or the mildly affected parent

3. Management
    1. Supportive medical care.
    2. Orthopedic treatment of the musculoskeletal malformations to prevent additional morbidity.
        1. Hip dislocation
        2. Bracing or spinal fusion for spinal deformity
        3. Serial casting or surgical correction for foot deformity
    3. Gonadodectomy advocated in surviving phenotypic females with Y chromosome fragments owing to the increased risk of gonadoblastoma.
    4. In mothers with severe kyphoscoliosis and preexisting ventilatory failure, nocturnal noninvasive ventilation can assist in maintaining respiratory stability during pregnancy with close observation for consideration of early delivery to avoid overt ventilatory failure (Khor et al. 2014).

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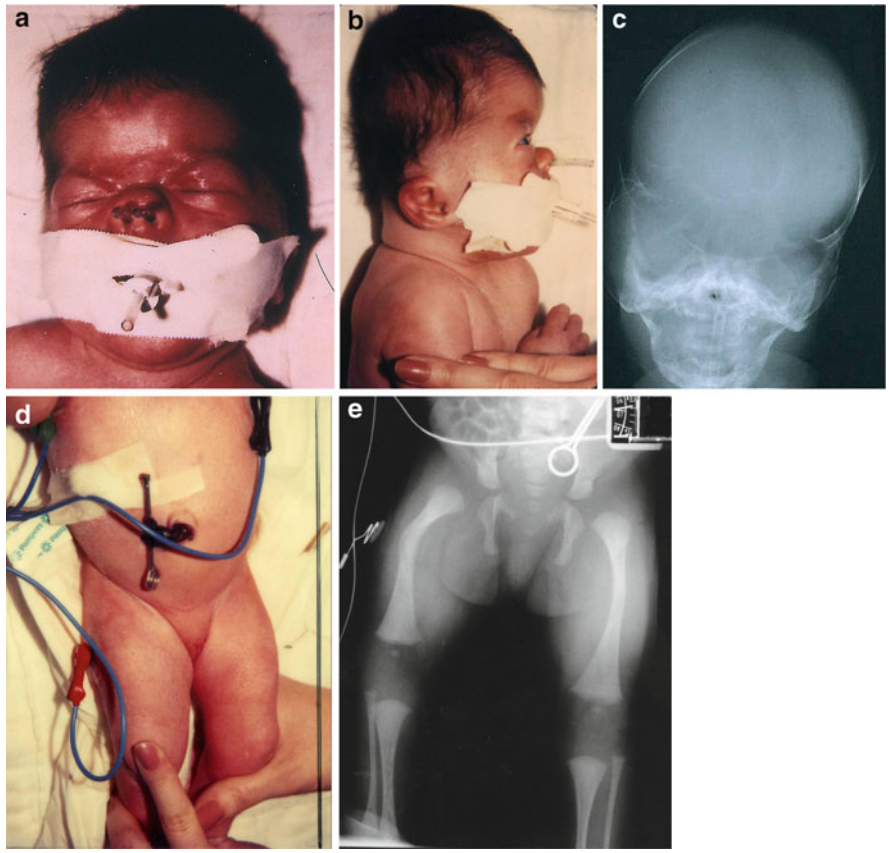

Fig. 1 (**a**–**e**) A neonate with campomelic dysplasia showing cloverleaf skull and bowed femurs, illustrated by radiographs

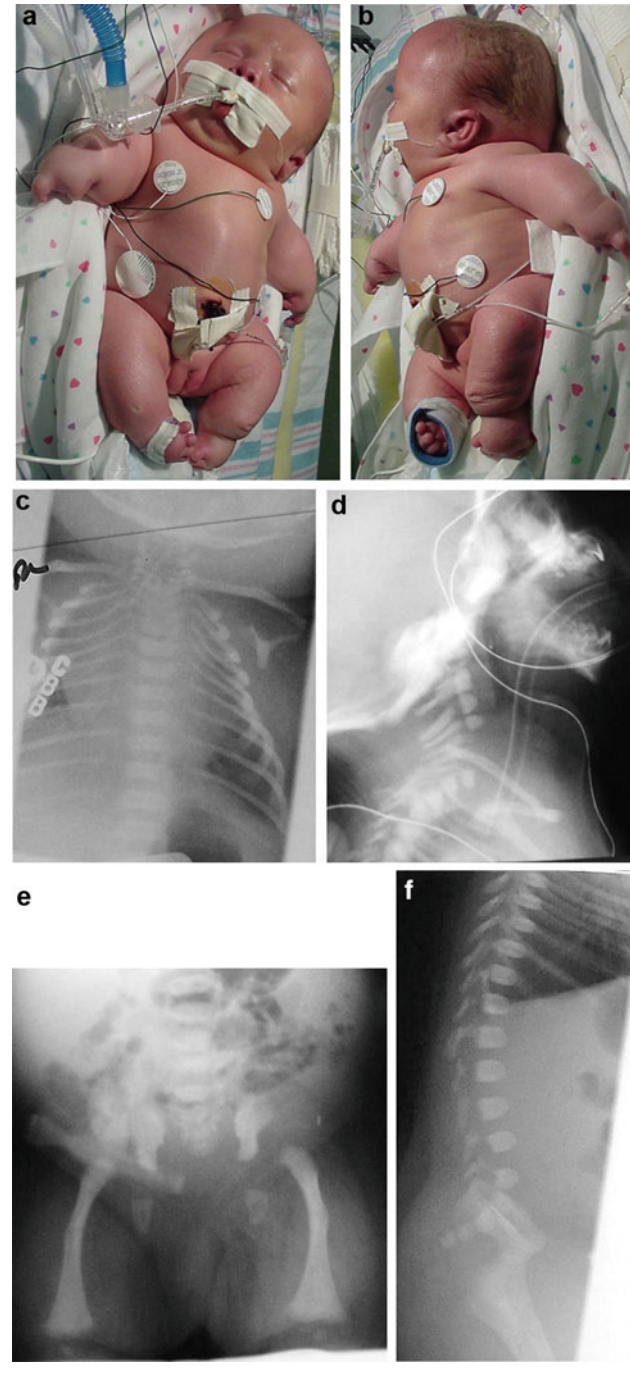

Fig. 2 (**a**–**f**) An infant with campomelic dysplasia showing bowing of the limbs with pretibial skin dimples, hypoplasia of cervical vertebra and scapula, 11 pairs of ribs, non-mineralized pedicles, *vertical*/*narrow* iliac wings, and bowing of femurs

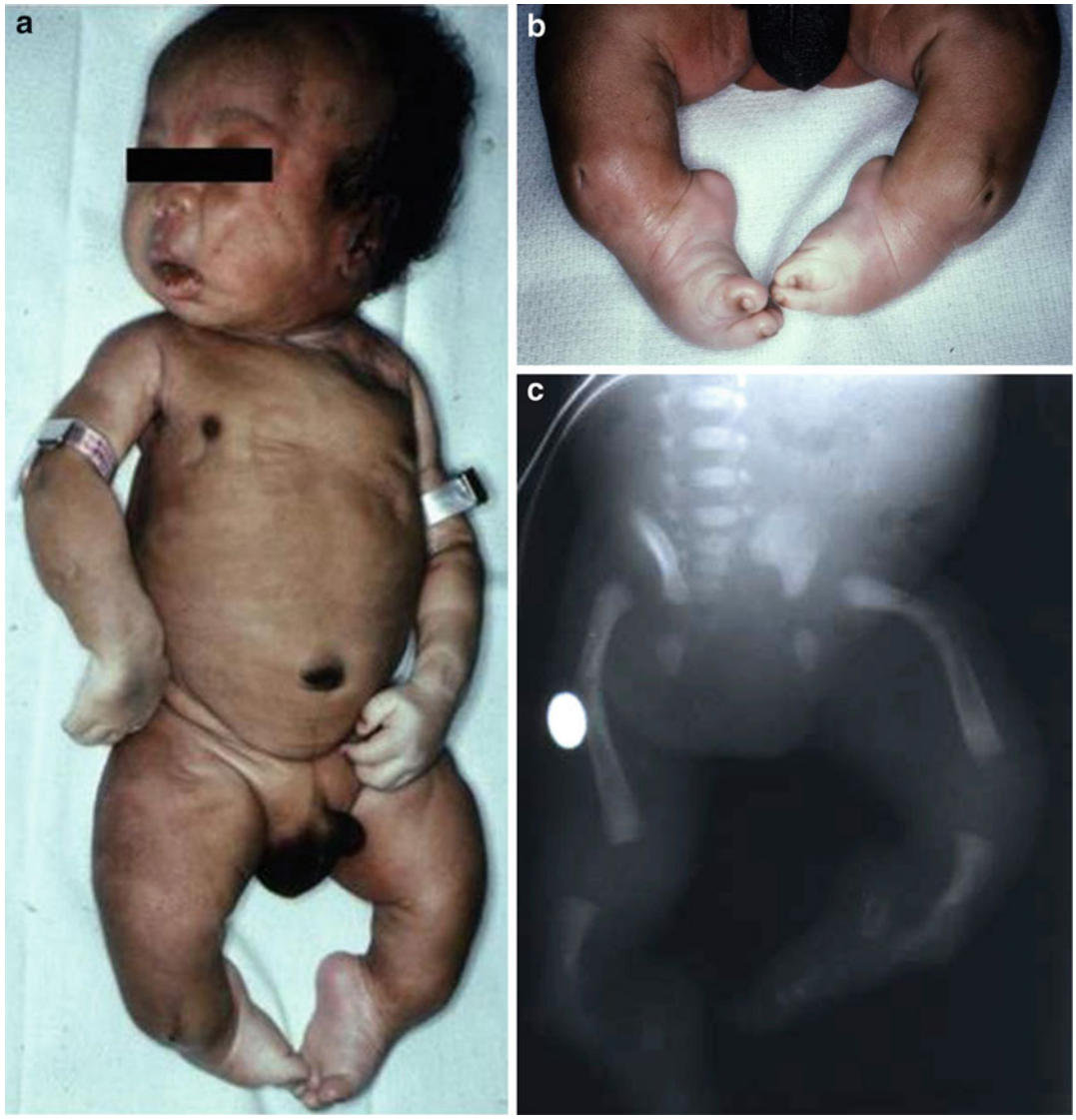

Fig. 3 (**a**–**c**) A neonate with campomelic dysplasia showing large head, flat face, flat nasal bridge, low-set ears, micrognathia, and bowed lower legs with pretibial dimples. The radiograph showed bowing of the femora, tibia, and fibulae

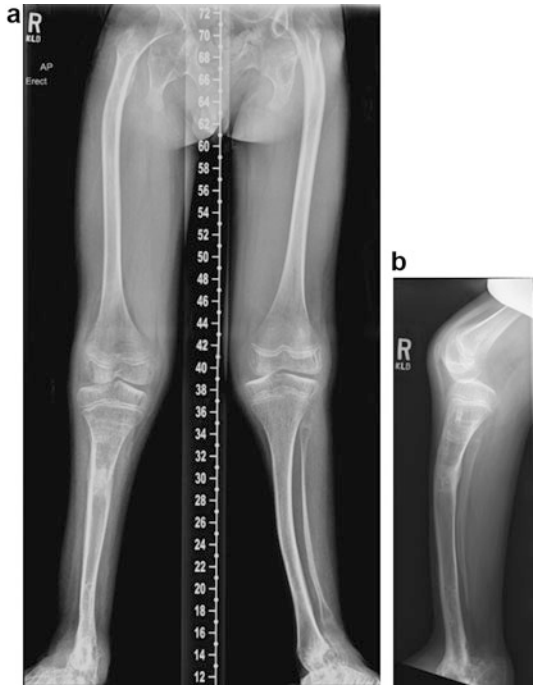

Fig. 4 A 13-year-old male was diagnosed to have camptomelic dysplasia shortly after birth. According to the mother, the diagnosis was confirmed by the genetic testing. The radiography of bilateral lower extremities demonstrated bilateral hip dislocation. There was generalized osteopenia. The femurs were mildly bowed laterally, but appeared normal. The tibiae were shortened and thin bilaterally with medial bowing on the left (**a**). Lateral view of the right tibia (**b**) showed mild anterior bowing of the tibia and partial deficiency of the distal right fibula. There was fusion of the ankle joints bilaterally. Sclerotic focus identified in the proximal third of the right tibial diaphysis corresponds to a healing lengthening osteotomy. Diffuse muscular atrophy was present (Courtesy of Dr. Grace Guo)

Carpenter Syndrome

Contents

Carpenter in 1901 (Carpenter 1901) described two living siblings and one stillborn sibling with peculiar facies, acrocephaly, brachydactyly, syndactyly of the hands, and preaxial polydactyly and syndactyly of the toes. Temtamy in 1966 (Temtamy 1966) documented 12 additional cases (ten of which were familial) and proposed the eponymous designation "Carpenter syndrome."

Synonyms and Related Disorders

Acrocephalopolysyndactyly type II; Goodman syndrome; Summit syndrome

Genetics/Basic Defects

1. An autosomal recessive inheritance: unlike other acrocephalosyndactyly syndromes or acrocephalopolysyndactyly syndrome
2. Caused by mutations in ras-like rat brain 23 (*RAB23*), a negative regulator of hedgehog signaling involved in cranial suture development (Jenkins et al. 2007; Cohen 2009)
3. Caused by mutations in the multiple epidermal growth factor-like-domains 8 (*MEGF8*) in some cases (Jenkins et al. 2007; Cohen 2009; Twigg et al. 2012)

Clinical Features

1. Marked intrafamilial variability (Cohen et al. 1987; Gershoni-Baruch 1990)
2. Marked phenotypic variability within this disorder (Perlyn and Marsh 2008)
3. Craniofacial anomalies (Perlyn and Marsh 2008)
    1. Craniosynostosis (abnormal fusion of the cranial sutures) (Cohen 2009): the basic abnormality of the craniofacial skeleton in Carpenter syndrome
        1. Premature closure of the sagittal, metopic, and lambdoid sutures, with coronal suture often remaining patent until the remaining sutures became synostotic (Marsh and Vannier 1995)
        2. Pattern of craniosynostosis at birth may vary among affected siblings.
    2. Cranial configuration (Marsh and Vannier 1995)
        1. Acrocephalic
        2. Often asymmetric

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Marked absence or underdevelopment of the anterior cranial fossa and bulging of the middle cranial fossa
4. Maxillofacial manifestations (Carpenter 1901; Temtamy 1966; Der Kaloustian et al. 1972; Eaton et al. 1974; Poole 1993; Puri et al. 1980)
    1. Brachycephaly
    2. Flat facies with midface hypoplasia
    3. Eyes
        1. Hyper/hypotelorism
        2. Shallow orbits
        3. Epicanthal folds
        4. Corneal opacity
        5. Microcornea
        6. Optic atrophy
    4. Fat nasal bridge
    5. High-arched palate
    6. Teeth
        1. Missing teeth
        2. Delayed loss of deciduous teeth
    7. Ears
        1. Low-set/malformed ears
        2. Preauricular pits
        3. Conductive hearing loss
        4. Sensorineural hearing loss
    8. Short muscular neck
4. Acral anomalies
    1. Preaxial polydactyly of the feet: allowing differentiation from other autosomal-recessive acrocephalopolysyndactyly syndromes (Robinson et al. 1985)
    2. Clinodactyly of the fingers
    3. Brachydactyly of the hands and feet
    4. Syndactyly of the hands and feet
5. Neurologic findings: presence of phenotypic variability
    1. Dilatation of ventricles
    2. Discernible brain abnormalities
6. Growth
    1. Short stature
    2. Obesity
7. Other features
    1. Cardiovascular defects
        1. Atrial septal defect
        2. Ventricular septal defect
        3. Pulmonic stenosis
        4. Tetralogy of Fallot
        5. Transposition of the great vessels
        6. Patent ductus arteriosus
    2. Abdomen
        1. Umbilical hernia
        2. Omphalocele
    3. Genitourinary tract anomalies
        1. Cryptorchidism
        2. Hydronephrosis
        3. Hydroureter
    4. Other skeletal anomalies
        1. Spine
            1. Pilonidal dimple
            2. Absent coccyx
            3. Spina bifida occulta
            4. Scoliosis
        2. Pelvis
            1. Coxa valga
            2. Decreased hip joint mobility
            3. Flared ilia
        3. Limbs
            1. Genu valgum
            2. Lateral displacement of patellae
    5. Endocrine features
        1. Hypogenitalism
        2. Precocious puberty
    6. Learning disability
8. Cohen syndrome, Goodman syndrome, and Summit syndrome: fall within the clinical spectrum of the same disorder (Cohen et al. 1987; Gershoni-Baruch 1990)

Diagnostic Investigations

1. Radiography/CT scan of the skull
    1. Craniosynostosis
        1. Sagittal suture
        2. Metopic suture
        3. Lambdoidal suture
        4. Coronal suture
    2. Cranial configuration: acrocephalic and often asymmetric
2. Radiography of the hands and feet
    1. Polysyndactyly
    2. Brachydactyly
    3. Clinodactyly
3. Molecular genetic testing of *RAB23* and *MEGF8* mutations: not available clinically at present

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25%
    2. Patient's offspring: not increased unless the spouse is also a carrier, in which case there is a 50% risk of having an affected offspring
2. Prenatal diagnosis (Haye et al. 2014)
    1. Ultrasonography: abnormal craniofacial shape with polysyndactyly of the hands and feet
    2. Fetal CT scan: preaxial hexadactyly of the feet and bowed femora
    3. Fetal bone CT scan: abnormal shape of the skull with partial synostosis of the sagittal and left lambdoid sutures
    4. Molecular genetic diagnosis: A novel *RAB23* mutation in a fetus with Carpenter syndrome (Haye et al. 2014)
3. Management
    1. Correction of skull malformations within the first year of infancy
    2. Reconstructive management for cranial abnormalities, hypotelorism and hypertelorism, ear abnormalities, and maxillary and mandibular hypoplasia (Kadakia et al. 2014)
    3. Correction of other anomalies
        1. Congenital heart defects
        2. Polysyndactyly
    4. Care for eyes, vision, and hearing impairments
    5. Intervention programs
        1. Speech therapy
        2. Occupational therapy
    6. Dietary control for obesity

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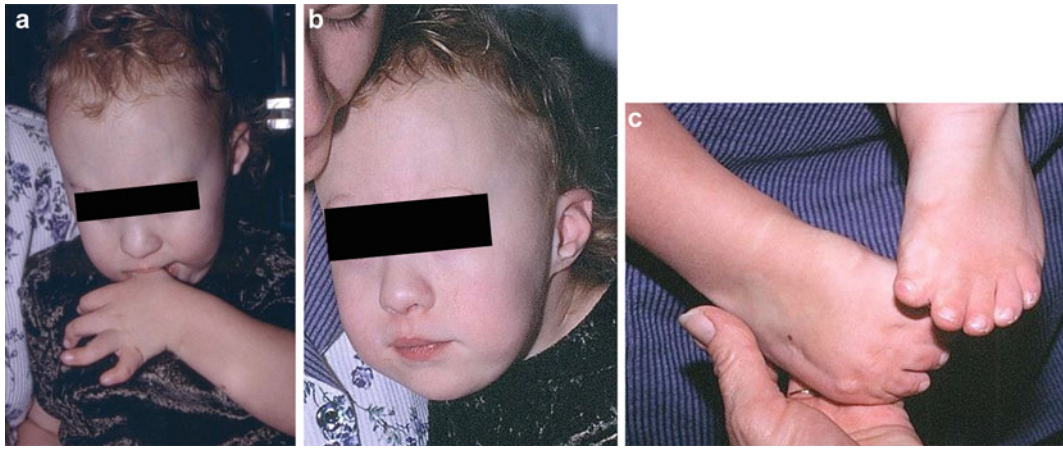

Fig. 1 (**a**–**c**) A two-and-a-half-year-old girl had a cone-shaped head, clinodactyly of the 5th fingers, and extra big toes of both feet (surgically excised at 1 month of age). The patient also had no opening of the anterior fontanel which was surgically repaired. She was noted to have brachycephaly, shallow orbits, high forehead, scanty eyebrows, lateral displacement of inner canthi, operation scars on the coronal sutures and sagittal suture, low-set malformed ears, small chin, high-arched palate, and operation scar for the umbilical hernia. Fingers and toes were abnormal with brachydactyly, clinodactyly, syndactyly, and polydactyly (surgically excised)

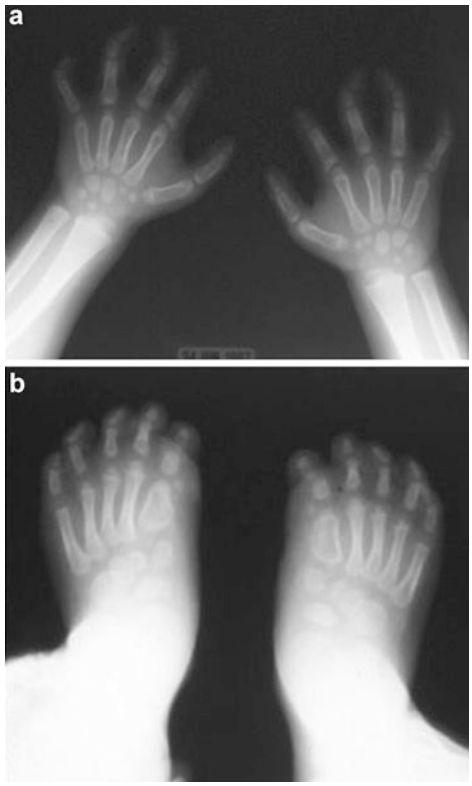

Fig. 2 (**a**, **b**) X-ray of hands and feet

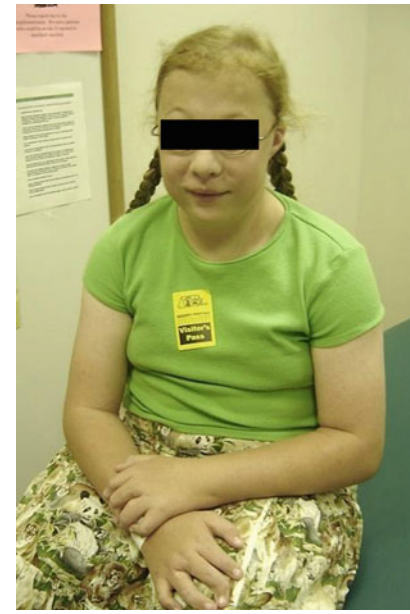

Fig. 3 Patient at 10 years of age

Cat Eye Syndrome

Contents

Cat eye syndrome is a clinically recognizable congenital malformation syndrome consisting primarily of colobomas, anal anomalies, preauricular anomalies, cardiac and renal defects, and mild to moderate mental retardation. The name "cat eye" was introduced because of iris colobomas resembling the pupils of the cat.

Synonyms and Related Disorders

Chromosome 22 partial tetrasomy inv dup(22)(q11); Schmid-Fraccaro syndrome

Genetics/Basic Defects

1. Historic background
   1. In 1965, an extra bisatellited marker chromosome was described in patients with cat eye syndrome phenotype (Schachenmann et al. 1965).
   2. Later in 1981, the marker was determined to be an inverted dicentric duplication of a part of chromosome 22 [inv dup(22)(pter → q11::q11 → pter)].
2. Molecular and cytogenetic bases
   1. Associated with the presence of three copies (partial trisomy) or four copies (partial tetrasomy) (Schinzel et al. 1981; Wilson et al. 1984; McDermid et al. 1986; Liehr et al. 1992) of a segment of chromosome 22q11.2, usually in the form of a bisatellited, isodicentric supernumerary chromosome (Footz et al. 2001).
   2. Formation of transient or unstable dic r (22) during early fetal development, which subsequently are lost from most cells, resulting in cat eye syndrome features.
   3. The minimal common duplication required to produce features of cat eye syndrome (the cat eye syndrome critical region) (Mears et al. 1995): defined by the dic r(22) patient, breakpoints between proximal locus ATP6E and distal locus D22S57, and covering approximately 2 Mb of 22q11.2.
   4. Maternal origin of the supernumerary chromosome in cases studied (Magenis et al. 1988).
   5. Direct correlations between the extent of duplicated chromosome 22 materials and the severity of the cat eye syndrome remain difficult (McTaggart et al. 1998).
   6. Human homolog of insect-derived growth factor, *CECR1*: a candidate gene for

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_33

features of cat eye syndrome (Riazi et al. 2000).
7. Occurrence of direct transmission of supernumerary marker chromosome (Kvarnung et al. 2012):
    1. Presence of a direct correlation between the degree of mosaicism and the symptoms, varying from no obvious symptoms to classical cat eye syndrome
    2. Examination of parental epithelial cells: preferred to blood cells in order to exclude a recurrence risk in parents of a child with cat eye syndrome
    3. Interphase FISH analysis of spermatozoa: the most sensitive method to exclude paternal germ line mosaicism
3. 22q11.2 region (Jezela-Stanek et al. 2009)
    1. Highly susceptible to chromosomal rearrangement: mediated by low-copy repeats causing nonallelic homologous recombination (Stankiewicz and Leepski 2002).
    2. A variety of clinical disorders are associated with either increased or decreased gene dosage (McDermid and Morrow 2002).
        1. Most common: DiGeorge/velocardiofacial syndrome caused by microdeletion of 22q11.2
        2. Other well characterized but less frequently recognized disorders:
            1. Cat eye syndrome (CES) because of 22pter-q11 trisomy/tetrasomy
            2. Emanuel syndrome – the result of unbalanced 11, 22 chromosomal translocation, resulting in der (22) (22pter-22q11: 11q23-11qter) (Zackai and Emanuel 1980)
        3. Other 22q11.2 rearrangements have been recognized recently.
            1. Microduplication 22q11.2 (Yobb et al. 2005; Kriek et al. 2006; Courtens et al. 2008)
            2. Triplication 22q11.2 (Yobb et al. 2005)
            3. Deletion of CES critical region (Kriek et al. 2006)
            4. 22q11.2 distal deletion (Ben-Shachar et al. 2008)
            5. Aberrations resulting in CES phenotype: proximal 22q duplication (Lindsay et al. 1995; Feenstra et al. 2006) or interstitial duplication 22q11 (Ensenauer et al. 2003)

Clinical Features

1. Marked phenotypic variability (Guanti 1981; Berends et al. 2001; Rosias et al. 2001)
2. Major features
    1. Preauricular skin tags and/or pits: most consistent features
    2. Ocular coloboma
    3. Congenital heart defect (Freedom and Gerald 1973)
        1. Ventricular septal defect
        2. Total anomalous pulmonary venous connection
        3. Atrial septal defect
        4. Patent ductus arteriosus
        5. Pulmonary stenosis
        6. Aortic malformation
        7. Tricuspid atresia
        8. Hypoplastic left heart syndrome
    4. Anorectal malformations
        1. Anal atresia or imperforate anus
        2. Anal stenosis
        3. Anorectal atresia
        4. Ectopic anus
        5. Associated rectal fistulas
    5. Urogenital malformations
        1. Male external genital malformation
        2. Renal agenesis/hypoplasia
        3. Hydro(uretero)nephrosis
        4. Vesicoureteral reflux
        5. Female genital malformation
        6. Renal dysplasia or polycystic kidney
        7. Bladder defects
        8. Renal cystic malformation
        9. Ectopic/horseshoe kidney
3. Minor features
    1. Craniofacial abnormalities
        1. Microcephaly
        2. Ocular abnormalities
            1. Downslanting palpebral fissures

2. Hypertelorism
3. Ocular motility defect
4. Epicanthal folds
5. Microphthalmia

3. Oral abnormalities
1. Micrognathia
2. Cleft palate or absent uvula

4. Low-set or dysplastic ears

2. Skeletal abnormalities
1. Arm or hand deformity
2. Leg or foot deformity
3. Scoliosis or chest deformity
4. Vertebral anomaly
5. Congenital dislocation of the hip
6. Rib or sternal anomaly

3. Abdominal abnormalities
1. Umbilical hernia
2. Malrotation of the gut
3. Hirschsprung or megacolon
4. Biliary atresia or choledochal cyst
5. Volvulus
6. Meckel diverticulum

4. Neurodevelopmental outcome
1. Growth and development
1. Short stature
2. Mental development: markedly variable
1. Normal-borderline normal
2. Mild-moderate retardation
3. Severe mental retardation

2. Neurological abnormalities
1. Dysregulation of muscle tone
2. Visual defect
3. Hearing impairment
4. Ventricular dilatation
5. Abnormal slow EEG
6. Seizures
7. Spasticity
8. Cerebral or cerebellar atrophy
9. Hyperactive behavior
10. Ataxia
11. Facial nerve palsy

Diagnostic Investigations

1. Chromosome analysis from blood and other tissues (Crolla et al. 1997)
1. Conventional cytogenetic study
2. Molecular (array comparative genomic hybridization) (Córdova-Fletes et al. 2012; Haltlrich et al. 2014) and FISH studies to determine small supernumerary marker (22) chromosomes

2. Radiography for limb defect
3. Echocardiography for congenital heart defects
4. Renal ultrasonography for renal anomalies
5. Developmental evaluation

Genetic Counseling

1. Recurrence risk
1. Patient's sib: a small recurrence risk because of possible presence of germ line mosaicism
2. Patient's offspring
1. Patients with an inv dup(22): 50%
2. Patients with mosaic form of an inv dup (22): lower than 50%, depends on the percentage of the marker chromosomes
3. A review of sporadic and familial cases illustrate the heterogeneity of the syndrome and the challenge to genetic counseling (Bofinger and Soukup 1977)

2. 2D/3D ultrasonography; may show severe prenatal presentation of cat eye syndrome such as microretrognathia and low-set ears (Jedraszak et al. 2013)
3. Prenatal diagnosis by amniocentesis or CVS
1. Presence of a bisatellited, dicentric supernumerary chromosome
2. FISH with a chromosome 22-specific cosmid probe to identify chromosome 22 (Beeser et al. 1994)
3. Molecular characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 22 associated with cat eye syndrome (Chen et al. 2013)

4. Management
1. Supportive
2. Surgery
1. Congenital heart defect
2. Anorectal anomalies
3. Urogenital anomalies

4. Gastrointestinal anomalies
5. Skeletal anomalies

3. Potential anesthetic risks (Devavaram et al. 2001)
   1. Potential difficult airway management
   2. Congenital heart disease
   3. Renal and hepatic dysfunction

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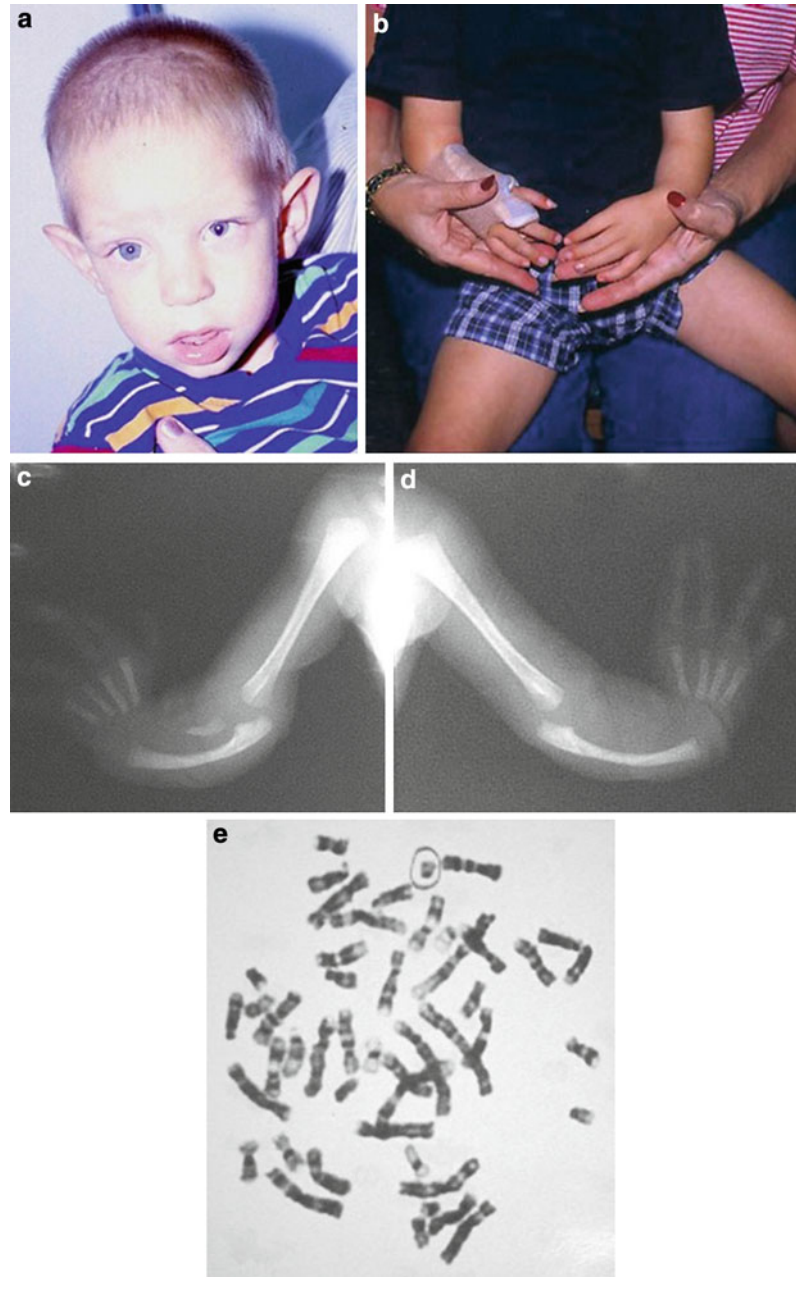

Fig. 1 (**a**–**e**) A boy with cat eye syndrome showing ocular coloboma (**a**) and bilateral club hands with missing thumbs (**b**). The radiographs (**c**, **d**) show bilateral radial aplasia/hypoplasia with missing thumbs. The patient has a supernumerary marker chromosome 22 (*circled*), illustrated by the chromosome spread (**e**)

Celiac Disease

Contents

Celiac disease is a gastrointestinal disorder characterized by chronic inflammation of the small intestine that can develop in genetically susceptible individuals ingesting proteins in wheat (gliadin), rye (secalin), and barley (hordein), collectively called gluten. The prevalence of celiac disease in the United States and Canada is as high as 0.5–1%, similar to earlier estimates outside North America (Hill et al. 2000).

Synonyms and Related Disorders

Celiac sprue; Gluten-sensitive enteropathy

Genetics/Basic Defects

1. Pathogenesis
    1. Celiac disease occurs in genetically susceptible individuals who ingest gluten, a protein found in certain grains.
    2. Caused by a combination of adaptive and innate immune responses that both are triggered by gluten (Koning 2005).
    3. Gluten causes an abnormal T-cell-mediated immune response and inflammatory injury to the mucosa of the small intestine, resulting in malabsorption of nutrients in these individuals.
    4. Gliadin fraction of gluten is mainly responsible for this intestinal damage.
    5. Approximately 97% of individuals with celiac disease have genetic markers on chromosome 6 called human leukocyte antigen (HLA) DQ2 and HLA DQ8, compared with 40% of the general population.
    6. T-cell and B-cell immunity in celiac disease (du Pré and Sollid 2015).
        1. T cells and B cells
            1. Heavily involved in the pathogenesis of celiac disease.
            2. Their cooperation may be crucial for the generation of antibodies as well as the amplification of the gluten-reactive T-cell response.
        2. T-cell epitopes: generated as a result of resistance to proteolytic digestion, substrate affinity to the deamidating enzyme TG2, and their binding to HLA-DQ2.5, HLA-DQ2.2, and HLA-DQ8 molecules
        3. Presence of limited number of mutations in TG2 (transglutaminase 2)- and gluten-reactive IgA plasma cells

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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7. An individual's intolerance to gluten is lifelong and self-perpetuating because of this genetic predisposition.

2. A multifactorial disorder with complex genetics (Sollid 2002; Sollid and Lie 2005)
    1. Interplay between genetic and environmental factors
        1. Gluten (consisting of the gliadin and glutenin subcomponents): a critical environmental component
        2. Both HLA and non-HLA genes: considered to be predisposing genetic factors
        3. HLA as a necessary but not sufficient genetic factor for celiac disease development
            1. HLA-DQ as the chief locus mediating the HLA-linked effect in celiac disease.
            2. The great majority of the patients carry a variant of DQ2 (*DQA1*05/DQB1*02*).
            3. A minority of the patients carry DQ8 (*DQA1*03/DQB1*0302*).
    2. HLA molecules
        1. The role of the molecules: to bind and present peptide fragments to T cells.
        2. Different HLA molecules thus present different sets of peptides.
        3. Gluten-reactive T cells of the celiac intestinal mucosa uniquely recognize gluten peptides in the context of DQ2 and DQ8, suggesting that these HLA molecules predispose to celiac disease by preferentially presenting gluten peptides to CD4 T cells (Lundin et al. 1994).
    3. Genetic variants associated with disease risk (Dieli-Crimi et al. 2015)
        1. Six MHC (major histocompatibility complex) and 39 non-MHC loci plus additional regions: recently implicated in the disease.
        2. The firmly described genetic variants: account for roughly 31% of celiac disease heritability, being 25% explained by the MHC influence.
        3. Forty-one different loci have been identified, explaining 47% of the genetic variation (Ricaño-Ponce et al. 2015).
3. Metabolomics investigation of celiac disease: accounts for following three different but complementary components (Calabrò et al. 2014)
    1. Malabsorption
    2. Energy metabolism
    3. Alterations in gut microflora and/or intestinal permeability
4. Prevalence of the disease (Fersano et al. 2003)
    1. 4.54% among first-degree relatives of patients with celiac disease
    2. 0.75% in the not-at-risk subjects

Clinical Features

1. Variable clinical presentations may lead to difficulty in diagnosis (Poon and Nixon 2001; Farrell and Kelly 2002; Westerberg et al. 2006; Fasano and Catassi 2012; Ediger and Hill 2014; Guandalini and Assiri 2014).
    1. Signs and symptoms of celiac disease in children
        1. Onset: classically between the ages of 4 and 24 months
        2. Abdominal distention/bloating
        3. Chronic or recurrent diarrhea (more typical)
        4. Constipation
        5. Vomiting
        6. Pallor and edema
        7. Iron deficiency (alopecia, pruritus, aphthous ulceration, angular stomatitis, glossitis, and koilonychia)
        8. Zinc deficiency (alopecia)
        9. Vitamin B_{12} (folic acid) deficiency (angular stomatitis, glossitis, aphthous ulcers, pigmentation)
        10. Rickets
        11. Delayed puberty
        12. Growth failure (failure to thrive)
        13. Behavioral disturbances (depression, irritability, may perform poorly in school)

2. Signs and symptoms of celiac disease in adults (Cranney et al. 2007)
    1. Abdominal pain (83%)
    2. Chronic diarrhea (76%)
    3. Infertility or recurrent spontaneous abortion
    4. Iron deficiency anemia
    5. Irritable bowel syndrome (29%) (Verdu et al. 2009)
    6. Peripheral neuropathy
    7. Persistent fatigue/malaise
    8. Weight loss (69%)
3. Nongastrointestinal manifestations of celiac disease
    1. Anemia or iron deficiency
    2. Aphthous stomatitis
    3. Ataxia
    4. Behavioral problems
    5. Dental enamel defects
    6. Depression
    7. Dermatitis herpetiformis
    8. Epilepsy with intracranial calcifications
    9. Headaches
    10. Hypotonia
    11. Infertility
    12. Neuropathy
    13. Osteopenia
    14. Osteoporosis
    15. Pubertal delay
    16. Short stature
    17. Transaminase elevation
4. Associated conditions
    1. Alopecia areata
    2. Autoimmune disorders
    3. Chronic alopecia
    4. Cutaneous vasculitis
    5. Diabetes mellitus (type I) (3–12%)
    6. Dermatitis herpetiformis
    7. Down syndrome
    8. Epilepsy
    9. Erythema elevatum diutinum
    10. Idiopathic dilated cardiomyopathy
    11. Immunoglobulin A deficiency (2–8%)
    12. Immunoglobulin A nephropathy
    13. Microscopic colitis
    14. Osteoporosis or other bone diseases
    15. Rheumatoid arthritis
    16. Sjögren syndrome
    17. Systemic lupus erythematosus
    18. Thyroiditis
    19. Turner syndrome
    20. Williams syndrome
    21. Turner syndrome
    22. Type I diabetes mellitus
2. Causes of persistent symptoms in celiac disease (Mooney et al. 2014)
    1. Continued exposure to gluten
    2. Bacterial overgrowth of the small bowel
    3. Exocrine pancreatic insufficiency
    4. Microscopic colitis
    5. Irritable bowel syndrome
    6. Lactose intolerance
    7. Refractory celiac disease
    8. Cancer (small bowel lymphoma or adenocarcinoma)
3. Complications (Farrell and Kelly 2002)
    1. Refractory sprue
    2. Enteropathy-associated T-cell lymphoma
    3. Carcinoma of the oropharynx, esophagus, and small bowel
    4. Ulcerative jejunoileitis
    5. Collagenous sprue
4. Differentiation from non-celiac gluten sensitivity (Rubio-Tapia et al. 2013)
    1. Symptoms or symptom response to a gluten-free diet alone should not be used to diagnose celiac disease, as these do not differentiate celiac disease from non-celiac gluten sensitivity.
    2. A diagnosis of non-celiac gluten sensitivity should be considered only after celiac disease has been excluded with appropriate testing.
5. Changing celiac disease pattern
    1. Less frequent so-called classic/typical celiac disease with a malabsorption syndrome in childhood. The symptomatic cases (about 10%) are considered to be the tip of the iceberg (Kaukinen et al. 2002).
    2. Increasingly common to diagnose children who have subtle or no gastrointestinal or nongastrointestinal symptoms (Ravikumara et al. 2006).

Diagnostic Investigations

1. Initial serology tests before eliminating gluten from diet (Hill et al. 2005; Rostom et al. 2006; Westerberg et al. 2006).
    1. IgA-tissue transglutaminase (tTG) antibody and endomysial antibody (EMA) (performed to identify candidates for duodenal biopsy)
    2. Total serum IgA (performed to identify individuals with IgA deficiency)
2. Serologic tests are helpful in screening at-risk populations for celiac disease (Rashid et al. 2009).
    1. Helpful in screening at-risk populations for celiac disease, such as:
        1. First- and second-degree relatives of patients with celiac disease (Gudjónsdóttir et al. 2004)
        2. Individuals with type 1 diabetes mellitus and other autoimmune endocrinopathies
        3. Individuals with atypical symptoms
    2. Serum antigliadin antibody (AGA) assay (IgG and IgA) for the general population screening feasible (Catassi et al. 1994).
    3. Anti-deamidated gliadin-related peptide (a-DGP) antibodies IgA and IgG: detect antibodies binding synthetic deamidated gliadin-related peptides (DGPs) (Liu et al. 2007; Niveloni et al. 2007).
    4. An over-the-counter home self-testing kit for celiac disease has recently been marketed in Canada. Using a tiny blood sample obtained by a pinprick of the fingertip, the home blood test identifies the tTG antibodies present in the blood of those with celiac disease. This test is for screening only and should not replace a medical diagnosis.
    5. Serum tests for the diagnosis of celiac disease (Fasano and Catassi 2012).
        1. IgA anti-tTG (tissue transglutaminase) antibodies
        2. IgG anti-tTG antibodies
        3. IgA antiendomysial antibodies
        4. IgG DGP (deamidated gliadin peptides)
        5. *HLA-DQ2* or *HLA-DQ8*
3. The diagnosis of celiac disease still requires upper gastrointestinal endoscopy (Balaban et al. 2015) and the biopsy findings of typical histologic alterations of the small intestinal mucosa of patients eating gluten (Rodrigues and Jenkins 2008).
4. Histopathology of celiac mucosa (Sollid 2002):
    1. Villus atrophy
    2. Enlarged hyperplastic crypts
    3. Increased infiltration of lymphoid cells in the lamina propria and epithelium
5. A clinical response on a gluten exclusion diet: considered to be important in diagnosis.
6. Recent recommendations also include HLA genotyping as a diagnostic adjunct (Hill et al. 2005).
    1. DQ2 heterodimer (encoded by specific *HLA-DQA1**05 alleles and specific *HLA-DQB1**02 alleles)
    2. DQ8 heterodimer (encoded by specific *HLA-DQA1**03 and *HLA-DQB1**0302 alleles)
    3. Clinical molecular testing by targeted mutation analysis to determine *HLA-DQA1* and *HLA-DQB1* genotypes to detect the presence or absence of the celiac disease-associated alleles, *HLA-DQA1**0501, *HLA-DQA1**0505, *HLA-DQB1**0201, *HLA-DQB1**0202, and *HLA-DQB1**0302 (Taylor et al. 2015)
7. Diagnosis of celiac disease: "four out of five rule" (Catassi and Fasano 2010; Sapone et al. 2012)
    1. Typical symptoms of celiac disease
    2. High-titer elevated celiac disease antibodies
    3. A compatible HLA haplotype (DQ2 or DQ8)
    4. Enteropathy found on small bowel biopsy
    5. Response to a gluten-free diet
8. Informing an individual that she or he is the carrier of predisposing genes has an ethical aspect, and the possibility of a psychological impact of an HLA test in relation to celiac disease must be considered (Sollid and Lie 2005). The presence of celiac disease predisposing HLA alleles means little, whereas

the absence of the same HLA alleles makes celiac disease an improbable disorder for that patient.

Genetic Counseling

1. Recurrence risk (Taylor et al. 2015)
    1. Patient's sib
        1. The overall empiric risk for celiac disease in sibs of a proband is 7–20% if the HLA haplotype is not known (Treem 2004).
        2. If the HLA haplotype of the parents is known, the risk to the sibs can be refined.
        3. Sibs who share the same celiac disease-susceptibility HLA haplotype with the proband have a risk of developing celiac disease that approaches 40% (Treem 2004).
        4. The risk to a sib of having celiac disease is estimated at 23.6% when multiple family members are affected (Gudjónsdóttir et al. 2004).
        5. If a parent of the proband has the DQ2 celiac disease-susceptibility haplotype in *cis* configuration or the DQ8 celiac disease-susceptibility HLA haplotype, the risk to each sib of inheriting the celiac disease-susceptibility HLA haplotype is 50%.
        6. If one parent of the proband has half of the DQ2 heterodimer (*HLA-DQA1**0501 or *0505) and the other parent has half of the DQ2 heterodimer (*HLA-DQB1**0201 or *0202), the risks to sibs are as follows:
            1. Risk of inheriting both HLA haplotypes and having the full DQ2 heterodimer encoded in *trans* configuration: 25%
            2. Risk of inheriting half of the DQ2 heterodimer (*HLA-DQA1**0501 or *0505) or (*HLA-DQB1**0201 or *0202): 50%
            3. Risk of inheriting neither the *HLA-DQA1**0501 or *0505 nor the *HLA-DQB1**0201 or *0202 celiac disease-susceptibility haplotype: 25%
    2. Patient's offspring
        1. The overall risk for celiac disease in offspring of a proband is 5–10% if the celiac disease-susceptibility HLA haplotype is not known.
        2. The risk increases when the offspring has the DQ2 celiac disease-susceptibility HLA haplotype and/or the DQ8 celiac disease-susceptibility HLA haplotype (Treem 2004).
        3. The risk is lower when only half of the DQ2 heterodimer (i.e., the *DQA1* sequence variant **or** the *DQB1* sequence variant, but not both) is present (Qiao et al. 2005).
        4. Each child of an individual with the DQ2 celiac disease-susceptibility HLA haplotype or the DQ8 celiac disease-susceptibility HLA haplotype has a 50% chance of inheriting the celiac disease-susceptibility HLA haplotype.
        5. The child of a proband who has the DQ2 celiac disease-susceptibility HLA haplotype in the *trans* configuration will inherit one of the celiac disease-susceptibility HLA haplotypes from the affected parent.
        6. Because the DQ2 or DQ8 heterodimer is found in 30–40% of the general population, testing the proband's reproductive partner is appropriate.
2. Prenatal diagnosis: While technically possible, prenatal testing of celiac disease-susceptibility HLA haplotypes does not seem relevant in this complex disorder (Taylor et al. 2015)
    1. The genetic change is common in the general population.
    2. The genetic change is predisposing to, but not predictive of, celiac disease.
    3. A highly effective treatment is available.
3. Management
    1. Gluten-free diet (Ediger and Hill 2014).
        1. All those with a confirmed diagnosis of celiac disease should follow a strict gluten-free diet for life.

2. A gluten-free diet involves complete elimination of all foods that contain gluten, including, but not limited to, wheat, barley, and rye ingredients.
3. Oats should not be ingested unless they are guaranteed pure and free of contamination with wheat flour.
4. Gluten-free grains and starches:
    1. Amaranth
    2. Arrowroot
    3. Buckwheat
    4. Corn
    5. Flax
    6. Nuts, bean, and seed flour
    7. Millet
    8. Potato starch, potato flour
    9. Quinoa
    10. Rice, rice bran
    11. Sago
    12. Sorghum
    13. Soybean
    14. Tapioca flour
    15. Teff
5. Avoid all beers, lagers, ales, and stouts.
6. Wine, liqueurs, most ciders, and other spirits, including whiskey and brandy, are allowed.
7. Give essential medications parenterally initially if malabsorption is severe.
8. All patients with celiac disease should be referred to a nutritionist with specialized knowledge of celiac disease and the gluten-free diet.
9. Many patients cope easily.
10. Some patients may find that the dietary restrictions are laborious, negatively influencing their quality of life.
11. Requires strict adherence to a gluten-free diet for life for symptomatic and asymptomatic children with characteristic histological findings on small bowel biopsy.
12. Compliance with the gluten-free diet is often incomplete among celiac disease patients.
13. When maintained on a long-term gluten-free diet (including wheat starch-based gluten-free flours), there is probably no increase in mortality, morbidity, or malignancies (Holmes et al. 1989) in patients with celiac disease over the population in general, although there are conflicting reports whether gluten-free food completely eliminates all risks (Green et al. 2003).
2. Treat nutritional deficiencies and osteoporosis.
3. Future therapeutic options (Sollid and Khosla 2005):
    1. Oral enzyme supplementation is designed to accelerate gastrointestinal degradation of proline-rich gluten, especially its proteolytically stable antigenic peptides.
    2. Complementary strategies aiming to interfere with activation of gluten-reactive T cells include the inhibition of intestinal tissue transglutaminase activity to prevent selective deamidation of gluten peptides and blocking the binding of gluten peptides to the HLA-DQ2 or HLA-DQ8 molecules.
    3. Other possible treatments include cytokine therapy and selective adhesion molecule inhibitors that interfere with inflammatory reactions, some of which are already showing promise in the clinic for other gastrointestinal diseases.

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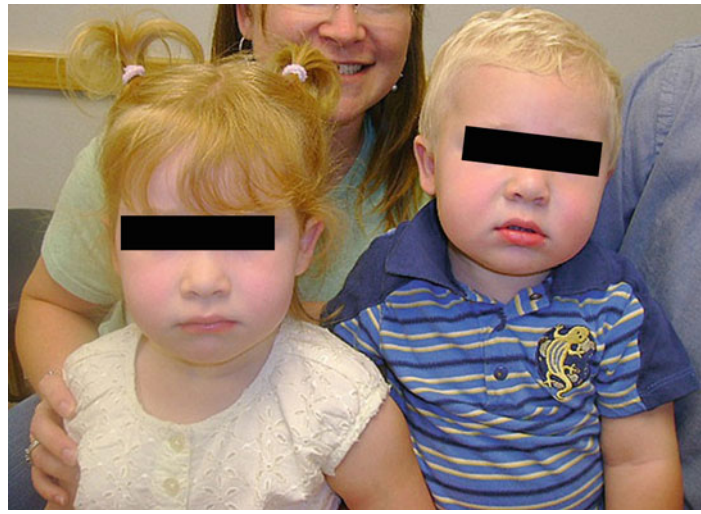

Fig. 1 A 3-year-old girl was healthy until 1 year of age when she developed severe watery diarrhea and abdominal distention for approximately a year and 9 months. She was diagnosed to have gluten-induced gastroenteropathy. The diarrhea stopped immediately upon withdrawal of gluten. She has been healthy since then. Her 18-month-old brother was admitted to a local hospital at 11 days of age for 6 days including 3 days of intensive care stay for a respiratory syncytial virus bronchiolitis. He again developed RSV infection at 2 months of age. In addition, he developed severe watery diarrhea with abdominal distention which improved upon discontinuation of gluten from his diet. He has since been healthy. HLA allelic variants associated with celiac disease were detected in both siblings: DQ2 heterodimer (HLA DQA1*05/DQB1*02). These alleles are present in 96–99% of confirmed celiac disease

Cerebral Palsy

Contents

Cerebral palsy (CP) is currently considered as a clinically defined symptom complex applied to individuals with a static, nonprogressive motor impairment of early onset that is cerebral in origin. It describes a group of motor impairment syndromes secondary to genetic and acquired disorders of the developing brain. Therefore, it is not a single entity with respect to pathogenesis but rather an etiologically heterogeneous entity with multiple possible causes that result in an aberration or injury to the maturing central nervous system. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior and/or by a seizure disorder. The prevalence is estimated between 1.5 and 2.5 per 1,000 live births (Ferriero 1999).

Synonyms and Related Disorders

Ataxic–hypotonic CP; Dyskinetic CP; Mixed CP; Monoplegic/hemiplegic CP; Spastic diplegic CP; Spastic quadriplegic CP; Spastic triplegic CP

Genetics/Basic Defects

1. Components of CP classification (Bax et al. 2005)
    1. Motor abnormalities
        1. Nature and typology of the motor disorder
            1. Tonal abnormalities assessed on examination (e.g., hypertonia or hypotonia)
            2. Diagnosed movement disorders (e.g., spasticity, ataxia, dystonia, or athetosis)
        2. Functional motor abilities: motor function in all body areas, including oromotor and speech function
    2. Associated impairments
        1. Presence or absence of associated non-motor neurodevelopmental or sensory problems
            1. Seizures
            2. Hearing or vision impairments
            3. Attentional, behavioral, communicative, and/or cognitive deficits

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2. The extent to which impairments interact in individuals with cerebral palsy
3. Anatomic and radiological findings
    1. Anatomic distribution (the parts of the body affected by motor impairments or limitations), e.g.:
        1. Limbs
        2. Trunk
        3. Bulbar region
    2. Radiological findings: the neuroanatomic findings on computed tomography or magnetic resonance imaging, e.g.:
        1. Ventricular enlargement
        2. White matter loss
        3. Brain anomaly
4. Causation and timing
    1. Clearly identified cause
        1. Usually postnatal CP (e.g., meningitis or head injury)
        2. Brain malformations (Garne et al. 2008; Krägeloh-Mann and Cans 2009)
    2. Presumed time frame during which the injury occurred, if known

2. Common etiologies of cerebral palsy (Paneth 1986; Kuban and Leviton 1994; Shevell et al. 2003; Russman and Ashwal 2004; Dodge 2008)
    1. Before pregnancy
        1. History of fetal wastage
        2. Long menstrual cycles
    2. Prenatal onset
        1. Low social class
        2. Brain malformations
        3. Intrauterine infection such as cytomegalovirus infection
        4. In utero stroke
        5. Toxemia
        6. Placental abruption
        7. Low birth weight
        8. Fetal growth retardation
        9. Twin gestation
        10. Abnormal fetal presentation
    3. Perinatal onset
        1. Hypoxic-ischemic encephalopathy (birth asphyxia)
        2. Viral encephalitis
        3. Meningitis
        4. Kernicterus
        5. Trauma
    4. Postnatal onset
        1. Newborn encephalopathy
        2. Infection
        3. Accidental head trauma
        4. Anoxic insult
        5. Child abuse
        6. Progressive hydrocephalus
3. Occurrence of CP phenotype has been seen in a variety of recognizable genetic syndromes including (Fisher and Russman 1974)
    1. Coffin–Lowry syndrome
    2. Cerebro-oculo-facio-skeletal syndrome
    3. Rett syndrome
    4. Angelman syndrome
    5. Hereditary spastic paraplegia
    6. Pelizaeus–Merzbacher spectrum
    7. West syndrome (infantile spasm and status dystonicus)
4. Recently described metabolic conditions associated with cerebral palsy phenotype (Schaefer 2008)
    1. Glucose transport disorders
    2. Molybdenum cofactor deficiency (sulfite oxidase deficiency)
    3. Serine biosynthesis disorder
    4. Glycine cleavage encephalopathy
    5. Creatine biosynthesis disorder
    6. Neurotransmitter disorders
    7. Nonlactic acidemia Leigh syndrome
    8. Adenylosuccinate lyase deficiency
    9. Congenital disorders of glycosylation
    10. Glutamate transporter EAAT1
    11. 2-methylbutyryl-CoA dehydrogenase deficiency
    12. Mitochondrial disorders (Fryer et al. 1994)
        1. Report of a family, affected with Leigh's encephalopathy and the mitochondrial DNA (mtDNA) mutation 8993, presented with nonspecific delayed development or cerebral palsy.
        2. There was some correlation in this family between the disease severity and the proportion of mutant mtDNA in the blood.

3. This mutation appears to segregate to high levels of mutant mtDNA rapidly within pedigrees.
4. The mother of a severely affected child has a high risk of having further children with a high proportion of mutant mtDNA and a severe phenotype.

5. Physiological classification of cerebral palsy (Agarwal and Verma 2012)
   1. Spastic (80%)
      1. Velocity-dependent increase in muscle tone with passive stretch
      2. Joint contractures: common
   2. Athetoid
      1. Dyskinetic, purposeless movements
      2. Joint contractures: common
   3. Choreiform: continual purposeless movements
   4. Rigid: hypertonicity occurring in the absence of hyperreflexia, spasticity, and clonus
   5. Ataxic
      1. Disturbance of coordinated movement, most commonly walking
      2. Normal head/neck control
   6. Hypotonic
      1. Low muscle tone
      2. Normal deep tendon reflexes
   7. Mixed
      1. Features of more than one type
      2. No head/neck control
6. Geographical classification of cerebral palsy (Agarwal and Verma 2012)
   1. Monoplegia: one extremity involved, usually lower
   2. Hemiplegia (30%)
      1. Both extremities on same side involved
      2. Usually upper extremity involved more than lower extremity
   3. Paraplegia: both lower extremities equally involved
   4. Diplegia (50%)
      1. Lower extremities more involved than upper extremities
      2. Fine motor/sensory abnormalities in upper extremity
   5. Quadriplegia
      1. All extremities involved equally
      2. Normal head/neck control
   6. Double hemiplegia: all extremities involved, upper more than lower
   7. Total body
      1. All extremities severely involved
      2. No head/neck control

Clinical Features

1. Prenatal and perinatal history (Green et al. 2003)
   1. Prenatal history: potential pregnancy complications
      1. Maternal illnesses during pregnancy
      2. Exposure to toxins (e.g., alcohol or drugs)
      3. Prenatal care
      4. Fetal movements
      5. History of trauma
   2. Perinatal history
      1. Gestational age at delivery
      2. Delivery type and presentation
      3. Length of labor
      4. Birth weight
      5. Apgar scores
      6. Cord gas pH
      7. Presence of intraventricular hemorrhage
      8. Procedures done during hospitalization
      9. Ability to feed
      10. Degree of tone
2. Developmental history
   1. Age of attainment of developmental milestones
   2. Age-appropriate developmental function
   3. Assessment of gross motor function
      1. Head control
      2. Trunk control
      3. Rolling
      4. Sitting
      5. Crawling
      6. Standing
      7. Cruising
      8. Walking

4. Assessment of fine motor function
    1. Handedness
    2. Hand-to-mouth movements
    3. Bimanual activities
    4. Grasping
    5. Writing
    6. Feeding
5. Assessment of language ability
    1. Babbling
    2. Size of vocabulary
    3. Ability to string words together
    4. Counting
    5. Naming of body parts, colors, alphabet, and comprehension
6. Current social and personal skills

3. Other histories
    1. Nutritional status, including feeding style, ability, and content
    2. Medications and allergies
    3. Past surgeries
    4. Presence of seizures
    5. Tone and body movement patterns
    6. Bowel and bladder concerns
    7. Visual and hearing concerns
    8. General health
    9. Immunization history
    10. Positioning devices
    11. Bathing equipment
    12. Wheelchair and seating equipment
    13. Adaptive devices
    14. Communication devices
    15. Computers
    16. Environmental control units
    17. Transportation systems
    18. Educational information
        1. Early intervention programs
        2. School environment
        3. Special services
        4. Individualized education plan
        5. Adaptive physical education and recreation
        6. Vocational and vocational activities in adults

4. Criteria for diagnosis (Paneth 2008): presence of one or more of the following four types of neurologic impairment of the motor system (in order of frequency)
    1. Spasticity
        1. Commonest neurologic abnormality
        2. Characterized by increased muscle tone manifesting as increased resistance to stretch that is velocity dependent
        3. Generally accompanied by hyperreflexia, which may include prolonged or sustained clonus, as well as pathologic reflexes such as an abnormal Babinski response (Sanger et al. 2003)
        4. When spasticity affects the lower limbs:
            1. Internal rotation and adduction of the hips is often seen, leading to the typical flexed posture and pigeon-toed gait of CP.
            2. Spasticity of the gastrocnemius muscle in the calf leads to another characteristic finding of toe walking due to plantar flexion.
    2. Dyskinesia
        1. Stereotyped, involuntary movements accentuated with effort
        2. Presence of two forms of dyskinesia
            1. Dystonia in which abnormal postures due to sustained muscle contractions are the essential feature.
            2. Choreoathetosis, in which abnormal movements predominate, consists of two related motor disorders: choreiform movements are rapid and jerky, whereas athetoid movements have a writhing quality. Athetoid CP is characteristic of children who suffered kernicterus in the neonatal period. With control of rhesus hemolytic disease, and better management of all forms of neonatal hyperbilirubinemia, this form of cerebral palsy has become very rare. Patients with the dystonic form of cerebral palsy generally have spasticity as well, whereas patients with choreoathetoid cerebral palsy often have varying tone, with hypertonia and hypotonia both found.
    3. Hypotonia
        1. More often in combination with spasticity than alone.

2. Truncal hypotonia with spasticity of the extremities is not unusual.
4. Ataxia
   1. Usually the presence of both truncal and gait ataxia, which can both be observed (e.g., wide-based gait) and elicited by examination (e.g., inability to accurately place finger on nose).
   2. Intention tremor commonly seen.
   3. Fine motor skills are particularly limited.
   4. Tone is usually hypotonic in this form of cerebral palsy.

5. Musculoskeletal features
   1. Hip assessment should include evaluation for contractures involving flexion, internal and external rotation, adduction, and leg length discrepancies.
   2. The knee should be tested for hamstring contracture.
   3. The foot and ankle should be tested for contractures and tibial torsion.
   4. The back should be examined for posture, spinal curves, or asymmetries.
   5. The upper extremities should be assessed for resting posture and spontaneous movement.
   6. An occupational therapy evaluation of grip and fine motor coordination often is beneficial.
6. Neurologic features
   1. CP is a disorder of movement resulting in a delay in the development of gross motor skills.
   2. Focus on tone.
      1. If movement has a velocity-dependent component, it is spastic.
      2. Deep tendon reflexes: often increased in spastic CP.
      3. Babinski, or plantar, response: often upgoing.
7. Spastic cerebral palsy
   1. Spasticity.
      1. Definitions
         1. An increase in the physiologic resistance of muscle to passive motion
         2. Hypertonicity that increases with increased velocity of movement (or having an increased stretch reflex)
      2. Most common of cerebral palsy (70–80% of children who have cerebral palsy are spastic) (Panteliadis 2004)
      3. A part of the upper motor neuron syndrome characterized by:
         1. Hyperreflexia
         2. Clonus
         3. Extensor plantar responses
         4. Persistent primitive reflexes
   2. Cause: damage to the pyramidal parts of the brain.
   3. Subdivision of spastic cerebral palsy: according to the area of the body involved.
      1. Diplegia
         1. Fifty percent of children with spastic cerebral palsy have diplegia (Berker and Yalçin 2008).
         2. The most common type seen in premature infants (Schaefer 2008).
         3. Greater involvement of legs than arms.
         4. Children with spastic diplegia are late in attaining all gross motor skills, but the delay in standing and walking is most notable. Generally, there is only mild functional impairment of the upper extremity. In a prospective study, being able to sit independently at 2 years was a good predictive sign of future ambulation. Children who could not sit by age 4 did not ambulate.
      2. Quadriplegia
         1. Thirty percent of children with spastic cerebral palsy have quadriplegia (Berker and Yalçin 2008).
         2. The only type associated with asphyxia in term infants (Schaefer 2008).
         3. All four extremities, the trunk, and muscles that control the mouth, tongue, and pharynx get affected.
         4. Children with spastic quadriplegia present a much broader spectrum of disability.

5. The severity of motor involvement affects the delay in developmental milestones.
6. About one-fourth of children with spastic quadriplegia have only mild involvement, with minimal functional limitation with regard to mobility or self-care.
7. About one-half are moderately impaired.
8. These patients are unable to achieve complete independence but are able to function reasonably well.
9. About one-quarter of patients are severely involved, require total care, and are unable to ambulate.
10. Independent sitting at 2 years and suppression of obligatory reflexes are good prognostic signs for eventual ambulation.

3. Hemiplegic/monoplegia
   1. Most likely causes (focal traumatic, vascular, or infectious lesion).
   2. Not typically associated birth asphyxia (Schaefer 2008).
   3. Twenty percent of children with cerebral palsy have hemiplegia (Berker and Yalçin 2008).
   4. One-sided (unilateral) involvement: a unilateral brain infarct with posthemorrhagic porencephaly apparent on MRI.
   5. Upper extremity generally more affected than the lower.
   6. Exhibit definite hand preference before 1 year of age, compared with most children who display handedness at about age 2.
   7. Display either an asymmetric crawl or no crawl at all.
   8. Almost all children with spastic hemiplegia do ambulate. Most become independent with activities of daily living, using some aids.
   9. Seizures, mild mental retardation, learning difficulties, and behavioral disturbances may complicate the management and integration into society.
   4. Double hemiplegic: both sides, arms > legs
4. Children with spastic syndromes, in general, often show white matter injury on imaging.
5. Most closely linked to periventricular leukomalacia but may also be secondary to congenital human immunodeficiency virus, dopa-responsive dystonia, hereditary spastic paraplegia, or spinal pathology, arginase deficiency, and Sjögren–Larsson syndrome, with characteristic appearances on imaging.

8. Dyskinetic cerebral palsy
   1. Dyskinetic cerebral palsy accounts for approximately 10–15% of all cases of cerebral palsy (Berker and Yalçin 2008).
   2. The most probable etiology: hyperbilirubinemia or severe anoxia that causes basal ganglia dysfunction.
   3. Choreoathetoid (hyperkinetic) and chorea: the main movement disorders seen in dyskinetic children.
   4. Dysarthria, dysphagia, and drooling accompany the movement problems.
   5. Children with dyskinetic cerebral palsy typically suffer from severe neuromuscular dysfunction. The abnormal movements are first noticed in the hands and fingers, but abnormal movements are usually noted in all extremities by 18 months of age. The writhing, involuntary movements give way to dystonia. As a result, all of their gross motor milestones are significantly delayed. Only about one-half of these children are able to walk, and they normally do not walk until after 3 years of age. Children who are able to walk usually develop the coordination necessary to perform their activities of daily living. Those who do not walk typically require almost total care.
   6. Abnormal movements that are most obvious when a patient initiates a movement. These abnormal movements are caused by

inadequate regulation of muscle tone and coordination.
7. When the patient is relaxed, there is usually full range of motion with decreased tone.
8. The patient often has a "cogwheel"-type resistance, without changes in the deep tendon reflexes. Tone decreases when the patient is supine, and tone may "shake loose."
9. There are two main types of dyskinetic movement.
    1. The first is dystonia, in which abnormal shifts of general muscle tone are induced by movement. These patients tend to retain abnormal posture in the same stereotyped patterns.
    2. The second main type of dyskinetic movement is choreoathetoid, in which the initiation of movement in one extremity leads to movement of other muscle groups. These patients exhibit slowly writhing involuntary movements in combination with abrupt, irregular, jerky movements.

9. Ataxic cerebral palsy
    1. Ataxic CP is the disturbance in the coordination of voluntary movements caused by muscle dyssynergia.
    2. Usually caused by cerebellar dysfunction.
    3. Ataxia becomes apparent toward the age of 2–3 years.
    4. Generally seen in association with spastic diplegic cerebral palsy.
    5. Now often categorized in the group of dyskinetic CP.
10. Mixed cerebral palsy
    1. Ataxia and dystonia occurring together with spasticity.
    2. The damage, usually, is more global, and the patients are quadriplegic.
11. Extrapyramidal cerebral palsy syndromes
    1. Characterized by rigidity, elicited clinically by passive stretch independent of velocity or dystonia, which is often action-induced twisting or fixed postures.
    2. Arm use is typically more affected than leg function.
    3. Children with extrapyramidal syndromes, in general, frequently have basal ganglia abnormalities on imaging.
    4. May result from genetic metabolic disorders such as glutaric aciduria type 1 (caudate/putamen), mitochondrial disorders such as Leigh syndrome (globus pallidus/caudate/putamen), kernicterus (globus pallidus), or hypoxic-ischemic encephalopathy (putamen/thalamus).
12. Associated conditions in children with cerebral palsy (Ashwal et al. 2004)
    1. Mental retardation (52%)
        1. Cognitive and neuropsychological function in children with CP are commonly impaired.
        2. In general, no absolute relation between the type of CP and severity of cognitive impairment. However, the following correlations are noted:
            1. Greater degree of mental impairment in spastic quadriplegia than in spastic hemiplegia.
            2. Severity of cognitive deficits appears to correlate with motor deficits associated with spastic cerebral palsy in contrast to dyskinetic cerebral palsy where this relation is lacking.
            3. Greater intellectual impairment in cerebral palsy in the presence of epilepsy, abnormal EEG, or abnormal neuroimagings.
    2. Speech and language disorders (38%)
        1. Anarthric or dysarthric speech and other impairments related to oral motor dysfunction are common due to bilateral corticobulbar dysfunction (i.e., articulation disorders and impaired speech intelligibility present in 38%).
        2. Inability to develop the linguistic skills necessary to develop more complex speech patterns due to impaired mobility which causes

limited interaction with individuals in the environment.
3. Language (as opposed to speech) deficits in CP closely related to verbal intellectual limitations associated with mental retardation.
4. Oral motor problems may lead to potential serious impacts on nutrition and growth, oral health, respiration, and self-esteem.
1. Feeding difficulties
2. Swallowing dysfunction
3. Drooling

3. Ophthalmologic defects (28%)
1. Visual impairments and disorders of ocular motility are common.
1. Strabismus
2. Amblyopia
3. Nystagmus
4. Optic atrophy
5. Refractive errors
2. Visual perceptual problems more likely in those due to periventricular leukomalacia.

4. Hearing impairment (12%)
1. More commonly in children with following etiologies:
1. Low birth weight
2. Kernicterus
3. Neonatal meningitis
4. Severe hypoxic-ischemic insults
2. Greater risk in children with CP who have mental retardation or abnormal neuroimaging studies

5. Epilepsy (43%)

13. Clues to the so-called cerebral palsy of unknown etiology (Dodge 2008)
1. Family history (familial spastic paraplegia)
2. Normal deep tendon reflexes (transient toe walking)
3. Calf hypertrophy with positive Gower sign (muscular dystrophy)
4. Regression, lethargy, and unusual vomiting
1. Ichthyosis (Sjögren–Larsson syndrome)
2. Severe self-mutation (Lesch–Nyhan syndrome)
5. Recurrent stroke, cardiomyopathy, and hypoglycemia (mitochondrial disorders)
6. Multiple anomalies
7. Lissencephaly (Miller–Dieker syndrome)
8. Acquired microcephaly, hand wringing (Rett syndrome)

14. Medical complications associated with cerebral palsy (Dougherty 2009)
1. Spasticity
2. Joint contractures, misalignment secondary to muscle spasticity
3. Hip dislocation
4. Osteoporosis
5. Intellectual disability (seen in 30–50% of individuals)
6. Seizures
7. Gastroesophageal reflux
8. Dysphagia or aphagia
9. Failure to thrive/malnutrition
10. Hearing loss

15. Possible source of pain (Dodge 2008)
1. Cranial
1. Increased intracranial pressure
2. Migraines and other headaches
2. Ophthalmologic
1. Corneal abrasion
2. Glaucoma
3. Dental
1. Abscesses
2. Temporomandibular joint pain
4. Gastrointestinal
1. Gastroesophageal reflux
2. Constipation
5. Musculoskeletal
1. Hip dislocation
2. Scoliosis
6. Neuromuscular (muscle spasms)
7. Urologic
1. Urolithiasis
2. Bladder spasms
8. Other (decubitus ulcers)

16. Proposed diagnostic criteria of cerebral palsy (Kavčič and Vodušek 2005)
1. Possible CP
1. Mandatory inclusion criteria
1. Disorder of movement and posture manifesting as spastic diplegia, spastic hemiplegia, spastic

tetraplegia, ataxia, dystonia, choreoathetosis – alone or in any combination
2. Onset early in life
3. No evidence of progression
2. Mandatory exclusion criteria
1. Active disease that could explain the foregoing features
2. Chromosomal disorders
3. Supportive features
1. Other signs of brain dysfunction that could be caused by the same pathological process as the foregoing disorders of movement and posture (epilepsy, learning disorders, disorders of speech, vision, or hearing)
2. Born after multiple pregnancy
3. Vanishing twin syndrome
4. Intrauterine growth retardation
5. Major antenatal placental abruption
6. Preterm birth
7. Acute intrapartum hypoxia
8. Reduced fetal heart rate variability from the onset of labor
9. Extensive chorioamnionitis
10. Congenital coagulation disorders
11. Autoimmune disease of the mother
12. No child with the same/similar clinical picture in a family
2. Probable CP: Mandatory inclusion criteria:
1. Disorder of movement and posture as in possible CP
2. Onset early in life
3. No evidence of progression or other disease that could explain the foregoing features at school age
3. Definite CP: Mandatory inclusion criteria:
1. Disorder of movement and posture as in probable CP
2. Plus still no evidence of progression unrelated to aging or other disease that could explain the foregoing features at age 18 or older

17. Prognosis (Blair et al. 2001)
1. Most severely affected persons with cerebral palsy (spastic quadriplegia, dyskinetic, and "mixed" cerebral palsy) survive to adulthood (Evans et al. 1990).
2. Survival strongly associated with degree of intellectual deficit.
3. Mortality declines with age during childhood.
4. Cause of death usually due to respiratory problems such as aspiration pneumonia.

Diagnostic Investigations

1. EEG
1. For features suggesting the presence of epilepsy or epileptic syndrome
2. Probably not very helpful in determining the etiology of cerebral palsy
2. Neonatal audiometric screening
3. Neuroimaging (Shimony et al. 2008)
1. Cranial ultrasound
1. Performed through open fontanelle (its use is restricted to the first 6 months of life)
2. Sensitive to detect the following:
1. Blood products
2. Ventricular size
3. Gross brain malformations
4. Cystic changes in the brain parenchyma
2. Computed axial tomography (CT) with the following advantages:
1. Acute blood products
2. Bone abnormalities
3. Short examination time
4. Wide availability
3. MRI (preferred to CT scanning) (Russman and Ashwal 2004)
1. Higher yield of suggesting an etiology and timing of insult leading to CP
2. Acquired lesions
1. Periventricular leukomalacia with other areas of injury
2. Diffuse encephalopathy (cortical/subcortical atrophy/ventriculomegaly)
3. Focal ischemic/hemorrhagic (e.g., infarct porencephaly)
4. Multicystic encephalomalacia

5. Trauma (at birth or later)
6. Infection

3. Malformations
   1. Cortical dysplasia/polymicrogyria
   2. Schizencephaly
   3. Pachygyria/lissencephaly
   4. Complex brain malformation
   5. Agenesis/hypoplasia of the corpus callosum
   6. Arachnoid cyst
   7. Vermian/cerebellar hypoplasia
   8. Hydrocephalus/holoprosencephaly/hydranencephaly
4. Miscellaneous or unknown
   1. Miscellaneous etiologies
   2. Delayed/abnormal myelination
5. Normal

4. Metabolic and genetic testing (Russman and Ashwal 2004; Schaefer 2008)
   1. Features of family history that might prompt a genetics/metabolic workup.
      1. Thromboses/vascular accidents
      2. Mental retardation/developmental disabilities
      3. Seizures
      4. Cerebral palsy
      5. Neuromotor disorders
      6. Tumors
      7. Neurobehavioral disorders
      8. Joint contractures/stiffness
      9. Congenital anomalies
      10. Infertility
      11. Recurrent miscarriages/stillborns
      12. Adult-onset neurodegenerative conditions
   2. Features on medical history and physical examination prompting a genetics/metabolic workup (Schaefer 2008).
      1. Neuroregression
      2. Seizures/change in seizure type
      3. Late onset/acquired microcephaly
      4. Macrocephaly
      5. Pigmentary changes
      6. Major and minor dysmorphic features
      7. Congenital anomalies
   3. Metabolic or genetic causes for CP to occur infrequently (0–4%; true incidence unknown).
   4. Neuroimaging studies showing 7–11% of children with cerebral palsy have a brain malformation suggest the presence of additional risk for genetic and possibly a metabolic etiology.
   5. Metabolic studies.
   6. High-resolution chromosome analysis.
   7. Chromosome microarray analysis.
5. Recognizable genetic syndromes known to be associated with a cerebral palsy phenotype
   1. MECP2 mutation study for Rett syndrome
   2. Chromosome 15 anomaly and UBE3A mutation studies for Angelman syndrome
   3. L1CAM mutation study for hereditary spastic paraplegia (Finckh et al. 2000)
   4. PLP1 mutation study for Pelizaeus–Merzbacher spectrum
   5. ARX (X-linked aristaless-related homeobox gene) mutation study for West syndrome (triad of infantile spasms, hypsarrhythmia, and mental retardation) (Guerrini et al. 2007)

Genetic Counseling

1. Recurrence risk: depends on the underlying genetic disorders (rare) of cerebral palsy
   1. Patient's sib
      1. Recurrence risk is low in most cases caused by hypoxic or ischemic injury to the brain.
      2. Autosomal recessive: 25%.
      3. Autosomal dominant: not increased unless a parent is affected or having gonadal mosaicism.
      4. X-linked recessive disorder: 50% of male sibs affected if the mother is a carrier.

5. Mitochondrial: all sibs are at risk of being affected if the mother has the mitochondrial DNA mutation.

2. Patient's offspring
   1. Autosomal recessive: not increased.
   2. Autosomal dominant: 50%.
   3. X-linked recessive: all daughters of affected males will be carriers. All sons of an affected male will be normal.
   4. Mitochondrial:
      1. Offspring of males with a mtDNA mutation are not at risk.
      2. All offspring of females with a mtDNA mutation are at risk of inheriting the mutation.
      3. A female harboring a heteroplasmic mtDNA point mutation may transmit a variable amount of mutant mtDNA to her offspring, resulting in considerable clinical variability among sibs within the same nuclear family (Poulton and Turnbull 2000; Chinnery 2014).

2. Prenatal diagnosis: not reported to date
3. Management
   1. Management strategy and rehabilitation of the child with cerebral palsy (Berker and Yalçin 2008)
      1. Support growth and nutrition
      2. Therapy for vision
         1. Rehabilitation
         2. Glasses
         3. Surgery
      3. Dental hygiene
      4. Gastrointestinal problems
         1. Medications for reflux
         2. Gastrostomy
         3. Antireflux surgery
      5. Therapy for motor function
         1. Physical therapy
         2. Occupational therapy
         3. Adaptive seating
         4. Bracing
         5. Wheeled motility
         6. Orthopedic surgery
         7. Sports–recreation
      6. Oromotor therapy
         1. Chewing
         2. Swallowing
         3. Speech
      7. Seizure prevention
      8. Spasticity and dyskinesia
         1. Medical treatment
         2. Botulinum toxin
   2. Timing of rehabilitative measures
      1. Infancy
         1. Goal: supportive measures for prolonging and optimizing physical status and life
         2. Methods: nutritional support and infant stimulation and positioning
      2. Childhood
         1. Goal: strategies to obtain maximum independent mobility
         2. Methods: medication to minimize spasticity, exercise, botulinum toxin, bracing
      3. Preschool
         1. Goal: maximum independent mobility
         2. Methods: minimize deformity, medication, exercise, botulinum toxin, bracing, orthopedic surgery
      4. Adolescence
         1. Goal: education, vocation, and integration into the community
         2. Methods: schooling, sports, psychosocial support
   3. Effects of physiotherapy (Berker and Yalçin 2008)
      1. Physiotherapy to improve:
         1. Postural control: decreasing spasticity and contracture
         2. Muscle strength: increasing muscle elasticity and joint laxity
      2. Range of motion
         1. Joint alignment: increasing coordination/agility
         2. Motor control: balance
         3. Muscular/cardiovascular endurance and mobility skills: transitions, use of assistive devices

4. Oral sensorimotor therapy
    1. May be effective in promoting oral motor function
    2. Not shown to be effective in promoting oral feeding efficiency, caloric intake, weight gain, or pharyngeal motility and airway protection during feedings
5. Gastrostomy tube feeding (Rogers 2004)
    1. An important alternative nutritional source for children with cerebral palsy
    2. Relative indications
        1. Dysphagia resulting in undernutrition
        2. Aspiration with associated respiratory disease
        3. Insufficient fluid intake and/or refusal of oral medications
        4. Excessive effort or stress during oral feedings.
6. Early intervention programs
    1. Work to optimize development.
    2. Goals: improve function and encourage independence.
    3. Improve family interaction.
    4. Provide family support.
    5. Provide education in how to promote development.
    6. The Individuals with Disabilities Education Act mandates early intervention for all children 0–3 years old who demonstrate developmental delay.
        1. These programs are typically multidisciplinary and may take place in centers or in the family's home.
        2. The therapists directly provide hands-on therapy to the child or educate the family on how to provide the interventions themselves.
7. Orthopedic treatment of cerebral palsy (Aversano et al. 2015)
    1. Lower extremity muscle imbalance leading to gait abnormalities in spastic cerebral palsy
        1. Ankle equinus: gastrocnemius recession procedure.
        2. Stiff knee gait: rectus femoris (RF) lengthening provides a viable alternative to RF tendon transfer.
        2. Knee flexion contracture: distal femoral osteotomies
        3. Single-event multilevel surgery of the lower extremity
        4. Foot and ankle deformity
            1. Calcaneal lengthening for correction of pes planovalgus deformities in children with cerebral palsy
            2. Additional medial stabilization procedures (posterior tibialis reefing or talonavicular arthrodesis)
            3. Intra-articular subtalar fusion technique for surgical correction of pes planovalgus
        5. Acetabular dysplasia and hip displacement
            1. Early detection and management of hip subluxation and dislocation
            2. Osteotomies
            3. Salvage hip procedures
8. Management of spasticity
    1. The management of spasticity is a large part of the treatment of children with cerebral palsy.
    2. Daily range of motion shown to decrease muscle tone for several hours after it is done and may delay or prevent contractures.
    3. The use of heat or cold can modify tone in the short term, but either modality is impractical for long-term use.
    4. Casting and splinting often used as adjuncts to regular range of motion: Casting for 2–3 weeks can decrease tone and improve range of motion for several months.
    5. Cyclical use of electrical stimulation has been found to decrease upper extremity contractures and improve agonist/antagonist balance, but these affects last only for hours.
    6. Medications.
9. Management of seizures
10. Complemental and alternative therapies (Liptak 2005)
    1. Hyperbaric oxygen (delivery of 100% oxygen)

    1. Theory/benefits: awakens dormant brain tissue surrounding the original injury.
    2. Adverse effects: ear trauma, pneumothorax, fire, and explosions.
    3. Evidence: improvements in the treated children in uncontrolled studies, improvement in treated, and controls in controlled study.
    4. Comments: more evidence is required.
2. Adeli suit (originally developed for Russian cosmonauts to counteract the adverse effects of zero gravity, including muscle atrophy and osteopenia)
    1. Theory/benefits: resistance across muscles improves strength, posture, and coordination
    2. Adverse effects: discomfort from suit, expense for intensive therapy, and travel to centers that prescribe the suit
    3. Evidence: no conclusive evidence
3. Patterning (passively putting children through certain repeated normal motions)
    1. Theory/benefits: passively repeating steps in normal development overcome brain injuries.
    2. Adverse effects: time, energy, and expenses required.
    3. Evidence: results of uncontrolled studies are inconsistent; controlled trials show no benefits.
    4. Comments: not recommended.
4. Electrical stimulation (elicits muscle contraction): more evidence required
5. Threshold electrical stimulation
    1. Theory/benefits: increased blood flow from electrical current leads to stronger muscles.
    2. Adverse effects: expense for units, generally safe.
    3. Evidence: subjective improvements in some uncontrolled trials and inconclusive in controlled trials.
6. Functional neuromuscular stimulation
    1. Theory/benefits: increased muscle contraction improves strength and function.
    2. Adverse effects: expense, infection from needles, and discomfort.
    3. Evidence: somewhat more positive than for threshold stimulation but still inconclusive.
7. Conductive education (interventions including promoting independent functioning using repetition and verbalization by the child)
    1. Theory/benefits: problems with motor skills are due to problems of learning. New abilities are created out of teaching.
    2. Adverse effects: not known.
    3. Evidence: benefit shown in uncontrolled trials and mixed results in controlled trials.
    4. Comments: conductive education implemented in many different ways making generalizations from a single program difficult.
8. Hippotherapy (equine-assisted therapy)
    1. Theory/benefits: riding a horse improves muscle tone, head and trunk control, mobility in the pelvis, and equilibrium.
    2. Adverse effects: trauma from a fall and allergies.
    3. Evidence: beneficial effects on body structures and functioning shown by uncontrolled and controlled trials.
    4. Comments: increases social participation.
9. Craniosacral therapy (a cranial rhythm linked with movements in the sacrum transmitted through the dura of the spinal cord by light corrective pressure applied to various points along the craniosacral axis)
    1. Theory/benefits: used to remove impediments to the flow of cerebrospinal fluid within the cranium and spinal cord.

2. Adverse effects: none known.
3. Evidence: no studies showing efficacy; some question the basis of the intervention.

10. Feldenkrais intervention method
    1. Theory/benefits: gentle change of position and directed attention to relax muscles and improve movement, posture, and functioning
    2. Adverse effects: none known
    3. Evidence: no studies showing efficacy
11. Acupuncture
    1. Theory/benefits: help to restore the normal flow of Qi (energy)
    2. Adverse effects: forgotten needles, pain, bruising, and infection
    3. Evidence: improvements in several areas shown by uncontrolled and some controlled studies
    4. Comments: appears promising, but more studies needed
12. Potential future nanotherapeutic approaches in cerebral palsy (Balakrishnan et al. 2013)
    1. Dendrimer-based drug delivery to pregnant mothers with infection/inflammation may reduce inflammatory response in the mother and the fetus.
    2. Prenatal therapies may involve systemic treatment of the mother to modulate the maternal immune response and/or treatment of the fetus by intra-amniotic administration of the nanodevices.
    3. Postnatal therapies would involve treatment of ongoing injury after birth.
    4. Therapies may potentially involve the use of stem cells in combination with drugs or after modification by nanoparticles to promote differentiation, delivery of trophic and growth factors, or delivery of combination therapies using nanoparticles.

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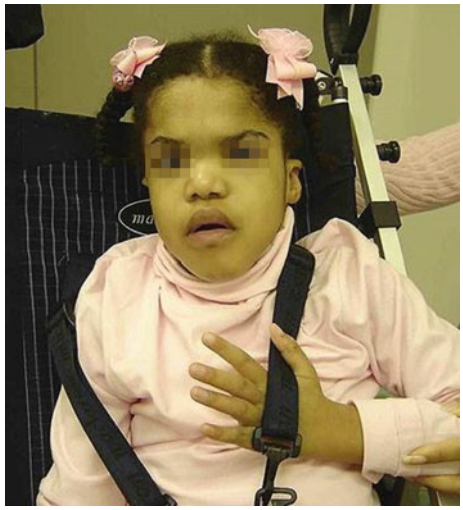

Fig. 1 A 10-year-old girl with cerebral palsy secondary to anoxic encephalopathy

Fig. 2 The patient, a 14-year-old boy, was diagnosed with diplegia cerebral palsy. He was born 27 weeks gestation by C-section and was one of the fraternal twins. He had a grade IV intraventricular bleed. Birth weight was 2 lbs. 1 oz. He was in NICU for 2 months

Fig. 3 The patient, a 14-year-old boy, was diagnosed with triplegia cerebral palsy. He was born 32 weeks gestation and on the ventilator for several weeks

Cerebrocostomandibular Syndrome

Contents

Cerebrocostomandibular syndrome (CCMS), a rare congenital syndrome, consists of severe micrognathia, often with the Pierre Robin anomaly, posterior rib-gap defects, and developmental delay (Smith et al. 1966). It is also known as "rib-gap syndrome," "rib-gap defect with micrognathia syndrome," and "Smith-Theiler-Schachenmann syndrome."

Synonyms and Related Disorders

Rib-gap defects with micrognathia; Rib-gap syndrome; Smith-Theiler-Schachenmann syndrome

Genetics/Pathogenesis

1. Caused by heterozygous mutation in the SNRPB gene on chromosome 20p13 (Lynch et al. 2014; Bacrot et al. 2015; Tay 2015)
2. Inheritance
    1. Sporadic in majority of cases
    2. Familial occurrence in a few instances
        1. Autosomal recessive pattern (Clarke and Nguyen 1985; Hennekam et al. 1985; Trautman et al. 1985; McNicholl et al. 1970; Drossou-Agakidou et al. 1991)
        2. Autosomal dominant pattern (Leroy et al. 1981; Merlob et al. 1987; Flodmark and Wattsgård 2001; Morin et al. 2001)
3. Pathogenesis of the rib gaps (Megier et al. 1998)
    1. Not well understood.
    2. Rib abnormality results from a lack of fusion between two mesenchymal tissues derived from the somatic mesoderm (posteriorly) and the lateral plate mesoderm (anteriorly).
    3. Defective organization of the somite results in discontinuities of the ribs.

Clinical Features

1. Variable inter- and intrafamilial expression (Plötz et al. 1996)
2. Cardinal signs
    1. Rib abnormalities
        1. Posterior rib gaps
            1. Present in almost all affected newborn infants
            2. Showing great variability in severity

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_36

   3. Disappear in time
   4. Sometimes replaced by callus or pseudo-arthroses
2. Segmentation defects and rudimentary rib development, fusion of most ribs to the vertebrae, and absence of any normal costovertebral articulations
3. Thin ribs
4. Agenetic ribs (Hennekam and Goldschmeding 1998)

2. Micrognathia/Pierre Robin anomaly (Miller et al. 1972)
3. Cerebral abnormalities
   1. Microcephaly
   2. Agenesis of the corpus callosum
   3. Dilated lateral ventricles
   4. Porencephalic cyst
   5. Variable degree of mental retardation probably secondary to hypoxia following respiratory distress

3. Other skeletal anomalies
   1. Vertebral anomalies including hemivertebrae
   2. Hip dislocation
   3. Subluxation of the elbows
   4. Pectus carinatum
   5. Hypoplasia of the sternum, clavicles, and pubic rami
   6. Epiphyseal stippling
   7. Abnormal phalanges and toes
   8. Clubfoot
4. Intrauterine growth retardation
5. Postnatal growth deficiency
6. Respiratory distress
7. Feeding difficulties
8. Language delay
9. Conductive deafness
10. Palatal defect
    1. Short soft palate
    2. Cleft palate
11. Dental defects
12. Laryngeal and tracheal abnormalities
13. Pterygium coli
14. Renal anomalies
    1. Renal cysts
    2. Ectopia
15. Congenital heart defects (Kuhn et al. 1975)
16. Prognosis (Ramaswamy et al. 2016)
    1. Mental retardation: often among the late survivors
    2. High mortality (40% in the first year of life, 50% in the first month of life) mostly due to respiratory insufficiency secondary to rib abnormalities and flail chest
    3. General development progresses well once the initial respiratory problems are survived.

Diagnostic Investigations

1. Radiography
   1. Rib malformations
      1. Multiple gaps consisting of fibrous or cartilaginous tissue
      2. Thin ribs
      3. Agenetic ribs
   2. Vertebral anomalies
   3. Other associated skeletal anomalies
   4. Micrognathia
2. Serial radiographs: demonstrate a progressive diminution of the characteristic posterior rib-gap defects (Williams and Sane 1976)
3. Thoracic CT studies
   1. Three-dimensional CT of costothoracic skeleton: demonstration of variable gaps in the posterior ribs and absence of ribs (Su et al. 2010)
   2. Multidetector thoracic CT: rib gaps and failure of costovertebral separation (Watson et al. 2014)
4. Cranial ultrasonography for cerebral abnormalities
5. Exome sequencing and Sanger sequencing: detection of heterozygous variants in the small nuclear ribonucleoprotein polypeptides B and B1 (*SNRPB*) gene (Bacrot et al. 2015)
6. Histology of rib gaps: fibrovascular tissue (Kang et al. 1992) and muscles, instead of cartilage and bone

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Not increased in sporadic cases and in a fresh mutation case of an autosomal dominant disorder
      2. 25% in an autosomal recessive disorder
   2. Patient's offspring: not increased unless the patient survives and is affected with an autosomal dominant disorder in which case there is a 50% risk of having an affected child
2. Prenatal diagnosis by ultrasonography (Ibba et al. 1997; Morin et al. 2001)
   1. Increased fetal nuchal translucency thickness detectable at 11 weeks
   2. Micrognathia at 12 weeks
   3. A narrow and short (bell-shaped) chest and defective ribs (with lack of rib display) at 18 weeks
   4. Growth retardation
   5. Vertebral anomalies
   6. Limb anomalies
   7. Cystic hygroma
   8. Polyhydramnios
3. Management (Hosalkar 2000)
   1. Ex utero intrapartum treatment (EXIT) at 36 weeks 6 days of gestation for prenatally diagnosed CCMS (Ogasawara et al. 2014)
   2. Treatment of respiratory distress
   3. Nasogastric tube feeding
   4. Tracheostomy may be required
   5. Management of recurrent infections
   6. Surgery for cleft palate
   7. Early intervention and multidisciplinary team approach.
   8. Orthopedic care for skeletal anomalies.

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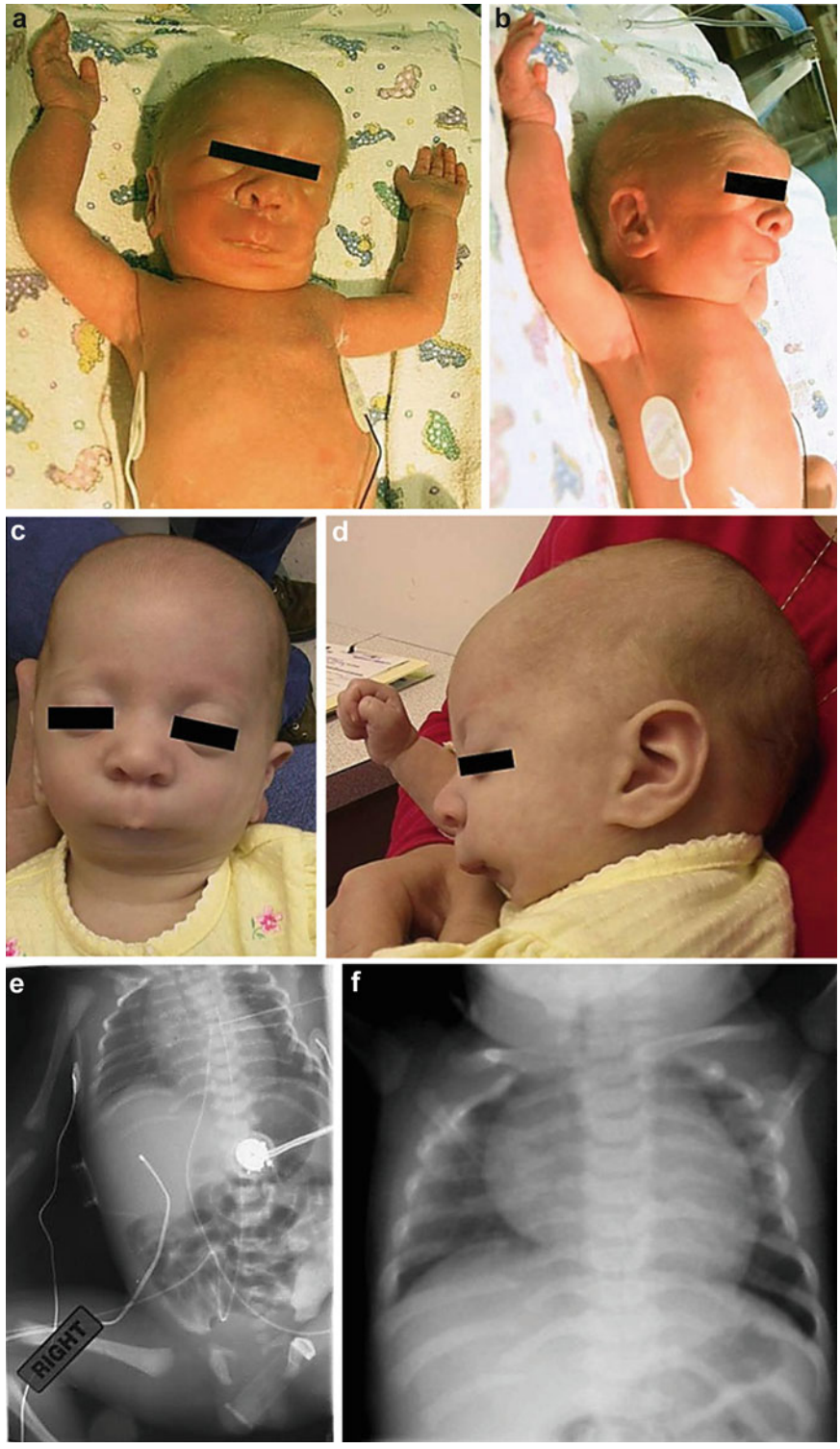

Fig. 1 (**a**–**f**) An infant with cerebrocostomandibular syndrome (at birth and 12 weeks of age) showing severe micro/retrognathia and malformations of the ribs with multiple gaps and segmentation defects

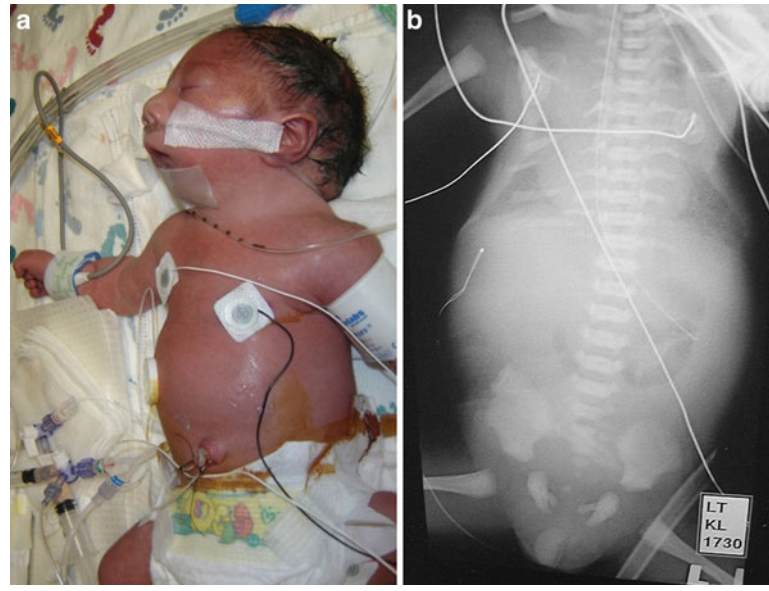

Fig. 2 (**a**, **b**) Another infant with cerebrocostomandibular syndrome showing severe micro/retrognathia, a narrow chest, and rib malformations with multiple gaps

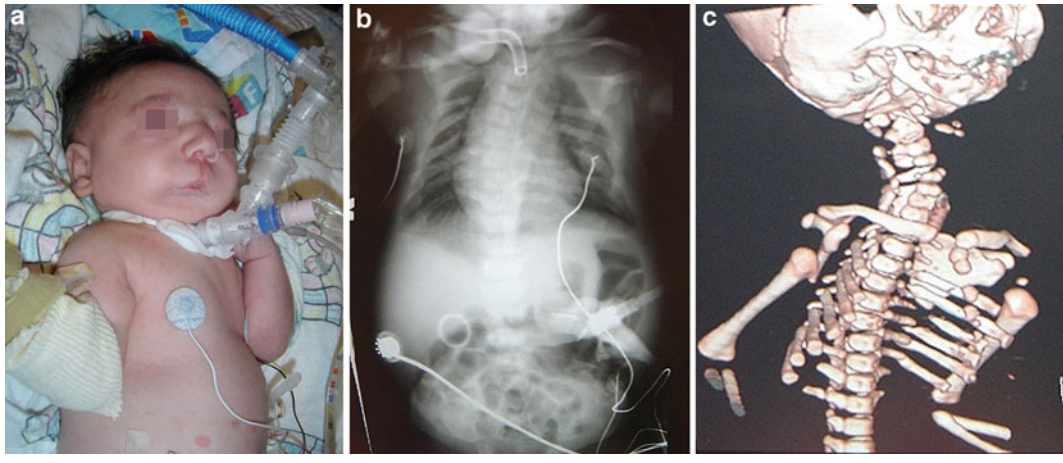

Fig. 3 (**a**–**c**) A neonate presented with severe respiratory distress, requiring tracheostomy. He has severe retromicrognathia and a small chest. Radiographs showed malformations of the ribs with multiple gaps and segmentation defects. A 3-D CT showed variable gaps in the posterior ribs and absence of several ribs

Charcot-Marie-Tooth Disease

Contents

Charcot-Marie-Tooth (CMT) disease is the most common inherited peripheral neuropathy. It is a pathologically heterogeneous group of hereditary motor and sensory neuropathies (HMSN), characterized by slowly progressive weakness and atrophy, primarily in the distal leg muscles. The incidence is estimated to be approximately 1 in 2,500.

Synonyms and Related Disorders

Hereditary motor and sensory neuropathy

Genetics/Basic Defects

1. Charcot-Marie-Tooth disease type 1 (CMT1) (Berger et al. 2002; Barisic et al. 2008; Banchs et al. 2009; Pareyson and Marchesi 2009; Szigeti and Lupski 2009; Harel and Lupski 2014; Rossor et al. 2013; Bird 2015b, d)
   1. Also called hereditary motor and sensory neuropathy type I (HMSN I)
   2. The most common subtype (accounting for about 50% of CMT)
   3. A demyelinating neuropathy
   4. Autosomal dominant demyelinating form of CMT1
      1. CMT1A (90% of CMT1 patients): caused by *PMP22* duplication or point mutations (17p11.2-12)
      2. CMT1B (5–10%): caused by mutations of the myelin protein zero (*MPZ/PO*) gene (1q22)
      3. CMT1C: caused by mutations of *SIMPLE/LITAF* gene (16p13.1-p12.3)
      4. CMT1D: caused by mutations of early growth response gene 2 (*EGR2*) gene (10q21.1-q22.1)
      5. CMT1E: *PMP22* (17p11.2)
      6. CMT1F: *NEFL* gene (8p21)
      7. CMT1 plus: FBLN5
2. Charcot-Marie-Tooth disease type 2 (CMT2) (Vance 2000; Rossor et al. 2013; El-Abassi et al. 2014; Harel and Lupski 2014; Saporta 2014; Bird 2015c, d)
   1. Also called hereditary motor and sensory neuropathy type II (HMSN II)
   2. An axonal neuropathy
   3. Accounting for 20–40% of CMT
   4. Autosomal dominant axonal form of CMT2: disease gene loci

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. CMT2A1: *KIF1B* (1p36.2)
2. CMT2A2: *MFN2* (1p33-p36)
3. CMT2B: RAB7 (3q21)
4. CMT2C: unknown (12q23-q24)
5. CMT2D: *GARS* (7p15)
6. CMT2E: *NEFL* (8p21)
7. CMT2F: *HSPB1* (*HSP27*) (7q11-q21)
8. CMT2G: unknown (12q12-q13.3)
9. CMT2H/K: *GDAP1* (8q13-q21.1)
10. CMT2I/J: *MPZ* (1q22-q23)
11. CMT2L: *HSPB8*/*HSP22* (12q24.3)
12. CMTM: *DNM2*
13. CMT2N: *AARS*
14. CMT2O: *DYNC1H1*
15. CMT2P: *LRSAM1*
16. CMP2Q: *DHTKD1*
17. CMT2S: *IGHMBP2*
18. CMT2T: *DNAJB2*
19. CMT2U: *MARS*
20. Hereditary motor and sensory neuropathy with proximal dominance: *TFG*
21. Hereditary spastic paraplegia type 10: *KIF5A*

5. Autosomal recessive axonal form CMT2 (Tazir et al. 2013)
   1. CMT2B1: *LMNA* (1q21.2)
   2. CMT2B2: *Med25* (19q13.3)
   3. CMT2H/2 K: *GDAP1* (8q13-q21.1)
   4. CMT2R: *TRIM2*
   5. Neuromyotonia and axonal neuropathy: *HINT1*

3. Intermediate form of autosomal dominant CMT (rare) (Rossor et al. 2013; El-Abassi et al. 2014; Harel and Lupski 2014; Bird 2015d)
   1. DI-CMTA: unknown (10q24.1-q25.1)
   2. DI-CMTB: *DNM2* (19p12-p13.2)
   3. DI-CMTC: *YARS* (1p34-p35)
   4. DI-CMTD: *MPZ* (1q22)
   5. DI-CMTE: *IFN2*
   6. DI-CMTF: *GNB4*
4. Recessive form of autosomal recessive CMT (Rossor et al. 2013; Harel and Lupski 2014; El-Abassi et al. 2014)
   1. RI-CMTA: *GDAP1*
   2. RI-CMYB: *KARS*
   3. RI-CMT: *PLEKHG5*
5. Autosomal recessive demyelinating form of CMT4 (Tazir et al. 2013; Harel and Lupski 2014; Bird 2015d, e)
   1. CMT4A: the first locus identified: 8q13-q21.1 (corresponding gene, *GDAP1*)
   2. CMT4B1: *MTMR2* (11q22)
   3. CMT4B2: *MTMR13*/*SBF2* (11p15)
   4. CMT4C: *KIAA1985*/*SH3TC2* (5q32)
   5. CMT4D (HSMN-Lom): *NDRG1* (8q24.3)
   6. CMT4E: *EGR2* (10q21.1-q22, 17p)
   7. CMT4F: *PRX* (19q13.1-q13.2)
   8. CMT4G: unknown (10q23.2)
   9. CMT4H: *FGD4* (12p11.21-q13.11)
   10. CMT4J: *FIG4* (6q21)
6. Autosomal recessive axonal form of CMT4
   1. CMT4C1 (AR CMT2B1): lamin A/C (1q21.2-q21.3)
   2. CMT4C2 (AR-CMT2C or AR-CMT2H): unknown (8q21.3)
   3. CMT4C3 (AR-CMT2B2): *ARC92*/*ACID1* (MED25) (19q13.3)
   4. CMT4C4 (AR-CMT2K): *GDAP1* (8q13-q21.1)
7. X-linked dominant form of CMT (CMTX1) (Harel and Lupski 2014; Bird 2015a, d; Wang and Yin 2015): accounting for 10–20% of CMT (the second most common form of inherited demyelinating neuropathy, next to CMT1A)
   1. CMTX1: caused by mutations in the gene for the gap junction protein 1 (*GJB1*) or connexin 32 (*Cx32*) on Xq13.1
   2. CMT3A(Dejerine-Sottas syndrome): PMP32 (17p11.2-12)
      1. Also called hereditary motor and sensory neuropathy type III (HMSN III).
      2. A severe demyelinating neuropathy.
      3. Autosomal dominant new mutations (*PMP22* mutations).
      4. Clinical symptoms overlapping with CMT1: these two disorders may represent a spectrum of related clinical phenotypes that can arise from allelic missense point mutations in the *PMP22* gene.
      5. Allelic mutations in the *MPZ* gene similarly identified in sporadic patients

with DSS, also implying that CMT type 1 and DSS constitute a spectrum of peripheral neuropathy phenotypes with common genetic bases.
3. CMT3B: *MPZ* (1q22-q23)
4. CMT3C: unknown (8q23-q24)
5. DSS-EGR: *EGR2* (10q21-q22)
6. CMT3D or CMT4F: *periaxin* (19q13.1-q13.2)
7. CMTX6: *PDK3* (Xp22.11)

8. X-linked recessive form of CMT (Bird 2015a, d; Wang and Yin 2015)
   1. CMTX2: unknown (Xp22.2)
   2. CMTX3: unknown (Xq26.3-q27.1)
   3. CMTX4 (Cowchock syndrome): *AIFM1* (Xq24-q26.1)
   4. CMTX5: *PRPS1* (Xq22.3) (Kim and Kim 2013)
9. Autosomal dominant distal hereditary motor neuropathy (HMN) form of CMT
   1. Distal HMN I: unknown (7q34-q36)
   2. Distal HMN II: *HSP22*, *HSP27* (12q24.3, 7q11-q21)
   3. Distal HMN V (HMN 5A): *GARS* (7p15)
   4. Distal HMN V (Silver syndrome, HMN 5B): *BSCL2* (11q12-q14)
   5. Distal HMN VII A: unknown (2q14)
   6. Distal HMN VII B: *DCTN1* (2p13)
   7. Distal HMN ALS4: *SETX* (9q34)
10. Autosomal recessive distal HMN form of CMT
    1. Distal HMN III: unknown (11q13)
    2. Distal HMN IV: unknown (11q13)
    3. Distal HMN VI: *IGHMBP2* (11q13.2-q13.4)
    4. Distal HMN-Jerash: unknown (9p21.1-p12)
11. Autosomal dominant hereditary sensory and autonomic neuropathy (HSAN)
    1. HSAN I: *SPTLC1* (9q22.1-q22.3)
    2. HSAN 1B associated with cough and gastroesophageal reflux: unknown (3p22-p24)
12. Autosomal recessive HSAN form
    1. HSAN II: *HSN2* (12p13.33)
    2. HSAN III (Riley-Day syndrome): *IKBKAP* (9q31)
    3. HSAN IV: *TRKA*/*NGF* (1q21-q22)
    4. HSAN V: *TRKA*/*NGF* (1q21-q22), *NGFβ* (1p13.2-p11.2)
    5. HSAN with deafness and global delay: unknown
    6. HSAN with spastic paraplegia: unknown (5q15.31-q14.1)
    7. X-linked HSAN associated with deafness: unknown (Xq23-q27.3)
13. Problems in classification of inherited neuropathies
    1. *PMP22* deletion causes HNPP.
    2. PMP22 duplication causes CMT1A.
    3. Deletion and duplication of *PMP22* causes HNPP and CMT1A, respectively, establishing a singular genetic mechanism as the cause of the two most common inherited neuropathies.
    4. *PMP22* mutations cause DSS, CMT1A, and HNPP.
    5. *MPZ* mutations cause DSS, CMT1B, and a CMT2-like phenotype.
    6. *GJB1* mutations cause CMT1X.
    7. *EGR2* mutations cause CMT1 and DSS.

Clinical Features

1. Family history (Jani-Acsadi et al. 2008)
   1. Autosomal dominant
      1. Multiple generations affected
      2. Male-to-male transmission
      3. Females and males affected
   2. Sporadic: only one member in the family affected
   3. Autosomal recessive
      1. Consanguinity
      2. Multiple children affected
      3. Parents unaffected
   4. X-linked
      1. No male-to-male transmission.
      2. Males may be more severely affected than females.
2. Clinical phenotype of all forms of CMT
   1. Generally similar
   2. Clinical presentation with distal leg weakness and atrophy

3. Followed by hand involvement
3. Presence of a wide range of variation and severity of symptoms in the affected areas and in the rate of progression of symptoms
4. CMT1A (Garcia 1999; Bird 2015b)
    1. Accounting for 90% of CMT1 patients
    2. A wide range of variation in clinical presentation and severity among affected members of large families with CMT1A
    3. CMT1A *PMP22* duplication
        1. Asymptomatic patients
            1. Observed in some family members in large pedigrees
            2. No symptoms
            3. Normal neurologic examination including ability to walk on their heels and normal stretch reflexes
            4. Slow MNCV
            5. Duplication of *PMP22* confirming the diagnosis of CMT1A
        2. Symptomatic patients
            1. Onset: first decade or early in the second decade
            2. Presenting symptoms in infants and children: walking on their toes and have severe tightness of the heel cord
            3. Occasional patients born with foot deformities including clubfeet
            4. Other symptoms: abnormal gait, foot deformities, or loss of balance
            5. Muscle weakness starting in the feet and legs
            6. Frequently trip over objects on the floor and sprain ankles as a result of weakness of the dorsiflexor muscles of the feet, innervated by the peroneal nerves
            7. Difficulty or inability to walk on heels
            8. Tight heel cords
            9. Foot drops with each step, forcing the patient to flex the hip, giving the steppage or equine gait
            10. Pes cavus deformity developing with age
            11. Atrophy of the legs, due to wasting of the peroneal muscles giving the stork legs or "inverted champagne bottle" appearance
            12. Weakness of the intrinsic hand muscles usually occurring late in the course of the disease
            13. Claw hands
            14. Mild sensory loss to pricking pain in the legs in some patients
            15. Frequently decreased vibratory sense
        3. Associated symptoms
            1. Enlarged (auricular, ulnar, and peroneal) nerves in 20–25% of the patients, not related to the age of the patient or the severity of the disease.
            2. Tremor in 40% of the patients.
            3. Hip dysplasia with hip pain and a limp.
            4. Restrictive lung disease usually not a major problem in patients with CMT1.
            5. Other associated features: spastic paraparesis, deafness, optic atrophy, Marfan-like appearance, and absence of eyebrows.
            6. Exacerbation of the weakness in 50% of the patients with early-onset disease during pregnancy and delivery.
            7. Certain medication and neurotoxic substances may aggravate the neuropathy in patients with CMT.
    4. CMT1A point mutations in *PMP22*
        1. Show severe disease in childhood.
        2. Found in patients that have been diagnosed with the Dejerine-Sottas syndrome.
5. CMT1B (Bird 2015b)
    1. Accounting for less than 10% of CMT1 patients
    2. *MPZ* mutations identified in CMT1B, DDS, or congenital hypomyelination phenotype
    3. Differentiating from CMT1A
        1. An earlier onset of the symptoms manifested by delayed ability to walk
        2. Proximal leg weakness without decreasing ambulation

3. Slower motor NCVs

6. Pregnancy and delivery in CMT1 (Rudnik-Schöneborn et al. 1993)
   1. Rate of obstetric complications: same as in the normal population
   2. No deleterious effect on fetal outcome
7. CMT2 (Bird 2015c)
   1. Neuronal type (a progressive peripheral motor and sensory neuropathy)
   2. Clinical phenotype similar to the type 1 CMT
      1. Symptoms
         1. Tingling
         2. Numb feeling
         3. Pain
         4. Muscle cramp
         5. Slow deterioration of muscle strength (distal weakness with feet involvement first) and increase in disability (Teunissen et al. 2003)
         6. Walking instability
         7. Increased loss of strength
         8. Increased sensory loss
      2. Signs
         1. Atrophied hands
         2. Atrophied legs
         3. Postural tremors
         4. Fasciculations
         5. Pes cavus
         6. Claw toes
         7. Steppage gait
         8. Leg atrophy
         9. Short calf muscles
         10. Abnormal Romberg sign
         11. Absent biceps, triceps, knee, and ankle jerks
   3. Other characteristics
      1. Generally a later onset of the symptoms than seen in type 1
      2. Pes cavus and short calf muscles: predominantly present in patients with early-onset disease
      3. Less involvement of the hand muscles
      4. No clinical evidence of palpable enlarged nerves
      5. No sensory deterioration
      6. Normal or slightly diminished motor nerve conduction velocities
8. Autosomal recessive CMT (CMT4) (Bird 2015e)
   1. Progressive motor and sensory neuropathy
   2. Rare heterogeneous forms with a broad spectrum of clinical severity
   3. Presentation of symptoms in infancy by delay in walking
   4. Early and rapidly progressive deformities of the feet and spine
   5. A high incidence of associated features such as sensorineural hearing loss
   6. Weakness beginning in the feet but affecting both distal and proximal muscles
   7. No enlargement of superficial nerves
   8. Presence of three pathologic forms
9. X-linked CMT (CMTX) (Bird 2015a)
   1. The second most frequent form of CMT (Dubourg et al. 2001)
   2. Inheritance
      1. Dominant form in 90% of cases
      2. Recessive form in 10% of cases
   3. A disease-causing mutation and a family pedigree consistent with X-linked dominant inheritance
      1. Presence of a disease-causing mutation in the *GJB1* (*Cx32*) gene
      2. Lack male-to-male transmission
   4. Males and females with peripheral motor and sensory neuropathy
      1. Affected males
         1. More severe phenotype than the affected females
         2. More severe progressive peripheral motor and sensory neuropathy than that seen in CMT1A
         3. Moderately slow median nerve MNCV: 34.5 ± 6.2 m/s
         4. Reduced motor and sensory nerve amplitudes (median nerve CMAP): 3.7 ± 3.7 mV
      2. Affected females
         1. Normal or mild to moderate signs and symptoms
         2. Moderately slow MNCV: 45.8 ± 7.3 m/s
         3. Reduced motor and sensory nerve amplitudes (median nerve CMAP): 7.8 ± 3.4 mV

5. Signs and symptoms
    1. Typical presenting symptom: weakness of the feet and ankles
    2. Initial physical findings: depressed or absent tendon reflexes with weakness of foot dorsiflexion at the ankle
    3. Typical adult patients
        1. Bilateral foot drop
        2. Symmetrical atrophy of muscles below the knee with stork leg appearance
        3. Pes cavus
        4. Atrophy of intrinsic hand muscles especially the thenar muscles of the thumb
        5. Absent tendon reflexes in both upper and lower extremities
        6. Proximal muscles usually remaining strong
        7. Mild to moderate sensory loss (deficits of position, vibration, and pain/temperature) commonly occurring in the feet
6. Other characteristics
    1. Symptoms typically develop between ages 5 and 25 years.
    2. Onset commonly within the first decade in males.
    3. Earlier onset with delayed walking in infancy as well as later onset beyond the fourth decades possible.
    4. Mild symptoms may be overlooked by patient and physician.
    5. Severe motor slowing in most families, consistent with a demyelinating form of the disease.
    6. A predominant axonal type has also been described.
10. Dejerine-Sottas syndrome (DSS) (Pareyson 1999)
    1. The syndrome still used to define the rare cases of severe hypo-demyelinating neuropathy of early onset.
    2. Criteria for diagnosis:
        1. Early onset of the disease by age 2 years with delayed motor milestones.
        2. Severe motor, sensory, and skeletal muscle deficits, frequently extending to proximal muscles. Sensory ataxia and scoliosis also present.
        3. Very low conduction velocities, usually <12 m/s.
        4. Nerve biopsy reveals severe hypomyelination and basal lamina reduplication, with multiple onion bulb formation.
        5. Presence of the enlarged nerves.
    3. De novo point mutations in either *MPZ* or *PMP22* found in most DSS cases.
    4. May be a variant of CMT1A or CMT1B.
11. Congenital hypomyelination (CH) (Pareyson 1999)
    1. An ill-defined and extremely rare disease merging into Dejerine-Sottas disease.
    2. A clinical syndrome characterized by infantile hypotonia due to distal muscle weakness and very slow NCVs. Severe weakness may lead to early death.
    3. Severe contractures of joints or arthrogryposis multiplex congenita in severe cases.
    4. Mutation analysis showing *MPZ* mutations, suggesting some of the DSS and CH are part of a spectrum of the demyelinating form of CMT1B.
12. Hereditary neuropathy with liability to pressure palsies (HNPP) (Pareyson 1999)
    1. Also called familial recurrent polyneuropathy or tomaculous neuropathy
    2. Clinical manifestations
        1. Periodic/transient/recurrent episodes of numbness, muscular weakness, and atrophy
        2. Palsies after relatively minor compression or trauma of the peripheral nerves (the axillary, median, radial, ulnar, and peroneal nerves)
    3. Nerve conduction abnormalities mainly localized at common entrapment sites
    4. Nerve biopsy: occurrence of focal myelin thickenings (tomacula) in several fibers
    5. Commonly associated with deletion of *PMP22* gene (De Jonghe et al. 1997)
13. Genotype-phenotype classification of CMT disorders
    1. CMT demyelinating types

1. CMT1A PMP22 duplication
    1. Roussy-Levy syndrome: a phenotypic variant of the CMT1A (pes cavus, distal limb weakness, areflexia, tremor in the upper limbs, gait ataxia, and distal sensory loss)
    2. Dejerine-Sottas syndrome or HMSN III: an interstitial hypertrophic neuropathy of infancy, characterized by early onset, severe clinical features, and the presence of the enlarged nerves
    3. CMT1A with calf hypertrophy
    4. Scapuloperoneal form of muscular atrophy, associated with pes cavus, areflexia and distal sensory loss (Davidenkow syndrome)
2. CMT1A PMP22 point mutations: Dejerine-Sottas syndrome
3. CMT1B
    1. Dejerine-Sottas syndrome
    2. Congenital hypomyelination: characterized by infantile hypotonia due to distal muscle weakness, areflexia, very slow NCVs, and hypomyelination (few thin myelin lamella)
4. CMT1C
5. Autosomal recessive demyelinating CMT
6. Hereditary neuropathy with liability to pressure palsies (HNPP)
7. CMTX: Cx32 mutations

2. CMT type 2 neuronal types
    1. CMT2A (1p36)
    2. CMT2B (ulcerations and limb amputations, linkage on chromosome 3)
    3. CMT2C (diaphragm weakness and vocal cord paralysis)
    4. CMT2D (a locus on chromosome 1)

14. Genotype/phenotype correlation in X-linked dominant CMT disease (Hahn et al. 1999)
    1. Cx32 missense mutations located within the second transmembrane domain and/or cytoplasmic loop might be associated with milder clinical phenotype.
    2. Missense, chain-terminating, or deletion mutations in all other locations of the connexin 32 protein caused severe forms of CMTX and disease onset in the first decade.

Diagnostic Investigations

1. Two types of CMT, currently distinguishable by the value of motor nerve conduction velocity (MNCV) of median nerve on electrophysiologic examination and nerve biopsy findings
    1. Demyelinating form (CMT1)
        1. Slowing of MNCV (15–30 m/s)
        2. Hypertrophy of peripheral nerves with onion bulb formation and segmental demyelination
    2. Axonal form (CMT2)
        1. Normal or mildly slow MNCV (>40 m/s)
        2. Normal size nerves
        3. No evidence of segmental demyelinations
2. Motor nerve conduction velocity of the median nerve (MNCV) of inherited demyelinating neuropathies (Lewis et al. 2000)
    1. Uniform conduction slowing
        1. CMT1A
        2. CMT1B
        3. CMT4
        4. Dejerine-Sottas syndrome
        5. Metachromatic leukodystrophy
        6. Cockayne disease
        7. Krabbe disease
    2. Multifocal conduction slowing
        1. CMTX
        2. Hereditary neuropathy with liability to pressure palsies (HNPP)
        3. Adrenomyeloneuropathy
        4. Pelizeus-Merzbacher disease with proteolipid protein null mutation
        5. Refsum disease (retinitis pigmentosa, deafness, ataxia, and ichthyosis)
    3. Incompletely characterized electrophysiology
        1. *PMP22* point mutations
        2. *MPZ* point mutation
        3. *EGR2* mutations

4. *P0* point mutations
5. Adult-onset leukodystrophies
6. Merosin deficiency

4. Usually normal in CMT2

3. EMG testing: evidence of an axonal neuropathy in CMT2
   1. Positive waves
   2. Polyphasic potentials
   3. Fibrillations
   4. Reduced amplitudes of evoked motor and sensory responses
4. Compound motor action potentials (CMAP): greatly reduced in CMT2
5. Muscle biopsy (Ericson et al. 1998)
   1. CMT1 (demyelinating form): angular atrophic fibers that were scattered or in small groups, findings commonly described as neuropathic
   2. CMT2 (with normal or near-normal MNCV)
      1. Atrophic fibers that were rounded or elongated in groups and hypertrophic fibers with central nuclei and fiber splitting
      2. Increased amounts of connective tissue, "whorled fibers," degeneration, and signs of regeneration, findings commonly regarded as myopathic.
6. Nerve biopsy (Bassam 2014)
   1. CMT1A
      1. Regression of onion bulb
      2. Significantly increased ratio of axon diameter/total fiber diameter, indicating arrested remyelination
   2. CMT1B
      1. Demyelinating process with onion bulb formation (sural nerve biopsy).
      2. Ultrastructural finding of uncompacted myelin is consistent with the accepted function P0 as a homophilic adhesion molecule.
   3. CMT2
      1. No histological evidence of well-formed onion bulbs on the nerve biopsies
      2. Loss of myelinated fibers with signs of regeneration, axonal sprouting, and atrophic axons with neurofilaments
   4. Autosomal recessive demyelinating CMT with three pathologic forms
      1. Classical onion bulbs
      2. Basal laminar onion bulbs
      3. Focally folded myelin sheaths
   5. CMTX
      1. Nerve hypertrophy or onion bulb formation: rare
      2. A primary axonal neuropathy with axonal sprouting in most affected individuals
      3. Prominent demyelination consistent with a CMT1 phenotype in some cases
   6. Congenital hypomyelination: hypomyelination (few thin myelin lamella) without active myelin breakdown products and early onion bulb formations
   7. Hereditary neuropathy with liability to pressure palsies (HNPP): demyelination and remyelination with tomacula or sausage-like thickening on the myelin sheath
7. Molecular genetic testing
   1. CMT1
      1. CMT1A
         1. Sequence analysis for point mutations in the *PMP22* gene
         2. Mutation scanning for point mutations in the *PMP22* gene
      2. CMT1B
         1. Sequence analysis for point mutations in the *MPZ* gene
         2. Mutation scanning for point mutations in the *MPZ* gene
      3. CMT1C: direct DNA/linkage analysis for point mutation in *LITAF*
      4. CMT1D
         1. Sequence analysis for point mutations in the *EGR2* gene
         2. Mutation scanning for point mutations in the *EGR2* gene
   2. CMT2E: sequence analysis for mutations in *NEFL*
   3. CMT4
      1. CMT4E: molecular genetic testing for *EGR2*
      2. CMT4F: molecular genetic testing for *PRX*

4. CMTX: sequence analysis to detect mutations in the *GJB1* coding region (accounting for about 90% of mutations in patients with CMTX)
5. Molecular genetic testing approach
    1. In cases of HNPP
        1. Test for the *PMP22* deletion (since this is by far the major cause).
        2. If negative, then sequence *PMP22*.
    2. In CMT patients with uniform slowing of motor NCVs between 10 and 35 ms
        1. Test for the *PMP22* duplication (since this is the major cause of CMT1).
        2. If negative, sequence *PMP22*, *MPZ*, *GJB1*, and *EGR2*.
    3. In DSS with appropriately slowed NCVs
        1. Test for the duplication: usually negative.
        2. Sequence *PMP22*, *MPZ*, *GJB1*, *EGR2*, and *PRX* genes.
    4. In cases where CMT1X is the most likely diagnosis (based on intermediate slowing of NCVs, no male-to-male transmission)
        1. Sequence *GJB1* alone: the appropriate initial test.
        2. If negative, sequence *MPZ* and *NEFL*.
    5. In cases of suspected CMT2
        1. Probably premature to test for *MPZ* and *NFEL* mutations alone (the only commercially available tests).
        2. Await a comprehensive battery in the future.
8. Targeted testing strategies (Hoyle et al. 2015)
    1. Conduction velocity less than 15 m/s and severe phenotype: *PMP22* duplication most common, but *MPZ* with a sizable minority
    2. Conduction velocity 15–35 m/s and classic phenotype: *PMP22* duplication testing (as high as 89% sensitivity in this category)
    3. Conduction velocity 35–45 m/s and classic phenotype: *GJB1* with high sensitivity with no male-to-male transmission. *MPZ* next most frequent
    4. Conduction velocity greater than 45 m/s or responses unobtainable: *MPZ* approximately 20% of cases (highest sensitivity with severe phenotype or unobtainable responses)
9. Next-generation sequencing: boosted the identification of CMT associated genes (Timmerman et al. 2014)
    1. Targeted next-generation sequencing and its limitation in CMT gene finding
    2. Whole-exome sequencing as a successful approach in CMT gene finding
    3. First whole-genome sequencing of a CMT patient (Lupski et al. 2010)
    4. Future perspectives and the need to share large datasets and genetic variants
10. Presymptomatic diagnosis from newborn cord blood for those couples who decide not to test prenatally (Lebo 1998)

Genetic Counseling

1. Recurrence risk (Bird 2015a, b, c, d)
    1. Patient's sib
        1. Autosomal dominant CMT
            1. Majority of CMT1 patients carry the *PMP22* duplication and represent de novo mutation cases (De Jonghe et al. 1999): recurrence risk to sib not increased unless a parent is affected, in which case the recurrence risk is 50%.
            2. Patients with de novo *MPZ* mutation: recurrence risk to sibs not increased unless a parent is affected, in which case the recurrence risk is 50%.
        2. Autosomal recessive CMT: 25%
        3. X-linked dominant CMT (patients with Cx32 mutation)
            1. A carrier mother has a 50% risk of transmitting the disease-causing mutation with each pregnancy. Sons who inherit the mutation will be affected. Daughters who inherit the

mutation will be carriers and may or may not be affected.
2. A noncarrier mother: recurrence risk to sibs low but not zero since the risk of germ line mosaicism in mothers is not known.

2. Patient's offspring
1. Autosomal dominant CMT: patients with *PMP22* duplication, *PMP22* deletion, or *MPZ* mutation will have a 50% risk of transmitting the disease to the offspring.
2. Autosomal recessive CMT: not increased unless the spouse is a carrier or affected.
3. X-linked dominant CMT (patients with *Cx32* mutation):
1. All the daughters of an affected male inherit the mutation but may or may not have symptoms.
2. None of his sons will be affected.

2. Prenatal diagnosis: available to pregnancies at risk for CMT1A, CMT1B, CMT2E, CMT4E, CMT4F, and CMTX
1. Identify the disease-causing allele of an affected family member before prenatal diagnosis.
2. Mutation analysis of fetal DNA obtained from amniocentesis or CVS.
3. CMT1
1. Prenatal diagnosis of CMT1A by FISH (Lebo et al. 1993; Kashork et al. 1999a, b)
1. Parental blood samples confirmed to be duplicated for *PMP22* by FISH.
2. Interphase FISH assay performed on amniotic fluid specimens and chorionic villus samples to detect a submicroscopic 17p12 duplication in the fetus with CMT1A.
2. Preimplantation diagnosis for CMT1A (De Vos et al. 1998, 2003): selection of healthy embryos is made based on the presence of the nonduplicated haplotype and heterozygosity of a marker (Löfgren et al. 1999)
4. CMT2E: molecular genetic testing of DNA extracted from fetal cells obtained from amniocentesis or CVS for testing of *NEFL* mutation when both disease-causing alleles of an affected family member are identified
5. CMT4E and CMT4F: molecular genetic testing of DNA extracted from fetal cells obtained by amniocentesis or CVS for testing of *EGR2* and *PRX* mutations, respectively, when both disease-causing alleles of an affected family member are identified
6. CMTX
1. Prenatal diagnosis: available to pregnancies of women who are heterozygotes for a disease-causing *GJB1* mutation that has been identified in an affected family member.
2. Amniocentesis or CVS:
1. Determination of the fetal sex
2. DNA extracted from cells from male fetuses tested to determine if a disease-causing mutation is present

3. Preimplantation genetic diagnosis (Sharapova et al. 2004; Lee et al. 2013; Bird 2015d) may be available for some families in which the pathogenic variant(s) have been reported.
4. Management:
1. No specific treatment to reverse or slow the natural disease process
2. Supportive care (Jani-Acsadi et al. 2008)
1. Musculoskeletal dysfunctions: scoliosis, foot deformities, and hand atrophy
1. Evaluation by physiatry
2. Physical therapy
3. Occupational therapy
4. Orthotics and assistive devices
5. Corrective surgery
2. Respiratory dysfunction
1. Pulmonary evaluation
2. Continuous positive airway pressure (CPAP)
3. Bi-level positive airway pressure (BiPAP)
4. Scoliosis correction
3. Sensory dysfunction
1. Pain control
2. Topical medications (lidocaine patch)
3. Antidepressants: tricyclics (amitriptyline, nortriptyline, desipramine)

4. Anticonvulsants: gabapentin, pregabalin
5. Lamotrigine, carbamazepine

4. Iatrogenic neurology
   1. Avoid medications that are known to cause nerve damage: chemotherapeutic drugs (vincristine, cis-platinum, mivacurium), Taxol, cisplatin, isoniazid, and nitrofurantoin.
   2. Refer to CMTA Web site regarding updated lists of medication (www.charcot-marie-tooth.org).

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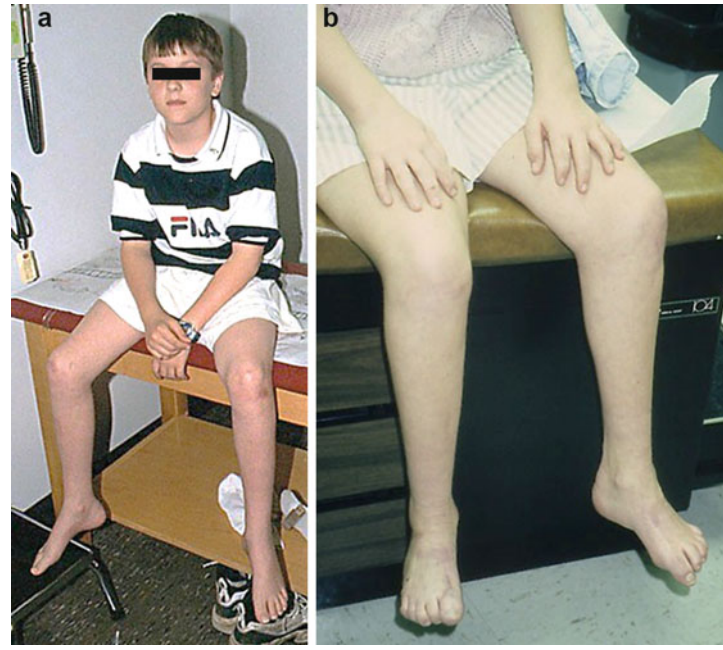

Fig. 1 (**a**, **b**) Two patients with Charcot-Marie-Tooth disease showing stork-like legs and pes cavus deformities

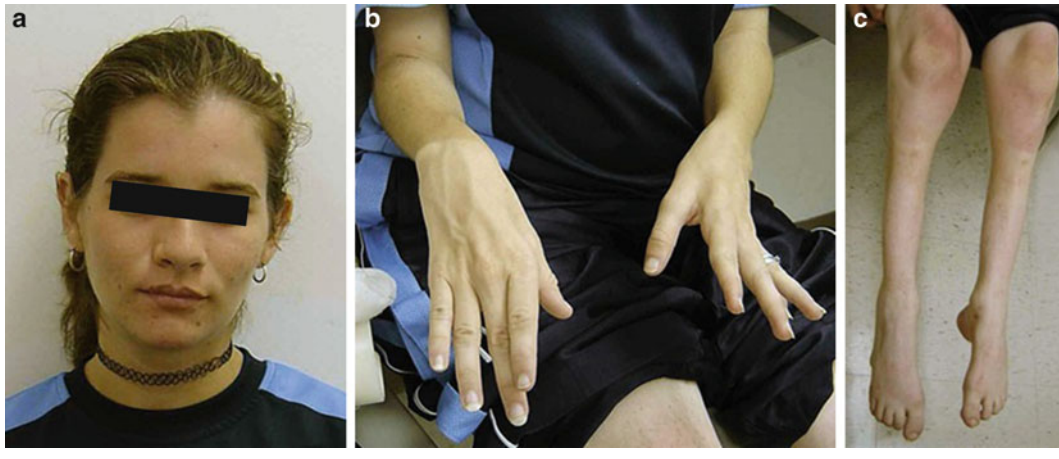

Fig. 2 (**a**–**c**) A 23-year-old female with Charcot-Marie-Tooth disease showing stork legs with muscle wasting, pes cavus deformities, and foot drop. She has absent deep tendon reflexes. Her onset of disease began in the third grade with a history of tripping, falling, and clumsiness. Family history revealed affected individuals in three generation

Fig. 3 An 11-year-old girl was evaluated for "stork-like legs." She was noted to have loss of balance, tip-toe walking, and muscle weakness, particularly in her lower extremities. On examination, she was noted to have claw hands (finger contractures at PIP), "stork-like" legs, muscle weakness in the lower extremities, tight heel cord, pes cavus, and absent deep tendon reflexes. The motor nerve and sensory nerve conduction tests showed severe prolonged latency and severe reduced amplitude. The left median, radial, tibial, and peroneal motors and median, ulnar, radial, and sural sensories were absent. The study showed electrophysiologic evidence of a severe sensorimotor polyneuropathy. A complete CMT molecular evaluation showed her to possess one known recessively inherited mutation in the *GDAP1* gene and one or more DNA variants of unknown significance

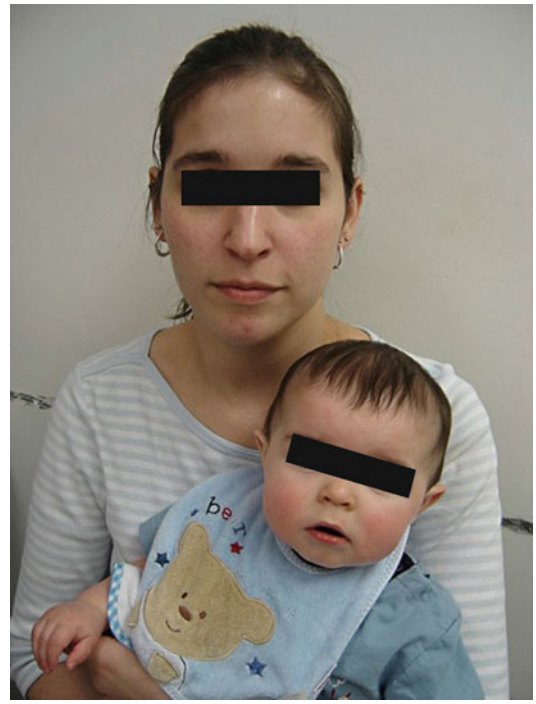

Fig. 4 A 26-year-old mother was diagnosed to have Charcot-Marie-Tooth disease type 1A at 15 years of age with complaints of weakness and pain in the arms, shoulders, hips, and neck and had a slight decrease in the pulmonary function test. Her DNA testing showed duplication of peripheral myelin protein (*PMP22*) gene, inherited from her father. The 5-month-old daughter is asymptomatic and carries no *PMP22* gene mutation

Fig. 5 A 31-year-old man with Charcot-Marie-Tooth disease type 1A, confirmed molecularly to have *PMP22* gene mutation associated with 17p12 microduplication. A son died at 3 month of age of ACTA1-related nemaline myopathy. The baby's chromosome microarray analysis showed 17p12 and 16q23.1 microduplications. Duplication of *PMP22* gene on 17p12 is associated with Charcot-Marie-Tooth disease type 1A. The clinical significance of 16q23.1 is unclear

CHARGE Syndrome

Contents

CHARGE syndrome is a genetic disorder characterized by a specific and a recognizable pattern of anomalies, namely, *c*oloboma, *h*eart defects, *a*tresia of choana, *r*etardation of growth and/or development, *g*enitourinary defects, and *e*ar anomalies and/or deafness. The pattern of anomalies associated with CHARGE syndrome was described independently by Hall and Hittner et al. in 1979 (Hall 1979; Hittner et al. 1979). However, the acronym "CHARGE association" was coined by Pagon in 1981 (Pagon et al. 1981). At present, with its recognizable pattern and definition, CHARGE is referred to as a syndrome (Pampal 2010; Zentner et al. 2010). The prevalence is estimated to be approximately 1 in 10,000 (Jongmans et al. 2006; Lalani et al. 2006).

Synonyms and Related Disorders

CHARGE association; Coloboma, heart defects, atresia of choana, retardation of growth and/or development, genitourinary defects, and ear anomalies and/or deafness; Hall-Hittner syndrome (Graham 2001)

Genetics/Basic Defects

1. Sporadic in almost all cases (Zentner et al. 2010)
2. Familial in a small number of cases with parent-to-child transmission of *CHD7* mutations (Mitchell et al. 1985; Metlay et al. 1987; Lalani et al. 2006; Delahaye et al. 2007; Jongmans et al. 2008; Vuorela et al. 2008; Wincent et al. 2008; Pauli et al. 2009)
    1. Parents generally have a mild CHARGE phenotype or are asymptomatic
    2. Their children display more severe defects (a full spectrum of CHARGE features)
    3. Somatic mosaicism for a CHD7 mutations has been described in an asymptomatic mother of two affected siblings (Jongmans et al. 2008)
    4. Germ-cell mosaicism has also been described in an asymptomatic father of two affected children (Pauli et al. 2009)
3. Cause: De novo mutations in the gene encoding chromodomain helicase DNA

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binding protein 7 (*CHD7*), located on chromosome 8q12.1, are the major cause of CHARGE syndrome.

4. Individuals with *CHD7* mutations: more commonly have the following findings compared to those without the mutations:
    1. Ocular colobomas
    2. Temporal bone anomalies (semicircular canal hypoplasia/dysplasia)
    3. Facial nerve paralysis
5. Pathogenetic mechanism: Haploinsufficiency for *CHD7* is the most likely pathogenic mechanism underlying CHARGE syndrome:
    1. Nonsense or frameshift mutations: majority of *CHD7* disruptions
    2. Chromosomal abnormalities (Sanlaville et al. 2002)
        1. Interstitial deletion of 8q11.2-q13 (Arrington et al. 2005)
        2. A balanced translocation disrupting 8q12 (Hurst et al. 1991; Johnson et al. 2006)
        3. Several chromosomal abnormalities not involving CHD7 have been reported to confer a phenotype similar to those seen in CHARGE patients (Clementi et al. 1991; North et al. 1995; Wieczorek et al. 1997; Lev et al. 2000)
    3. Recently, CHARGE patients without detectable single-base mutation were found to have heterozygous deletions of CHD7 (Wincent et al. 2009). In fact, CHD7 deletion was originally detected by array-CGH (Vissers et al. 2004). Alterations in copy number have been reported but represent only a small fraction of the reported disruptions of CHD7 (Bergman et al. 2008).
    4. Other conditions with CHD7 mutations having significant clinical overlap with CHARGE syndrome
        1. Kallmann syndrome (Ogata et al. 2006; Kim et al. 2008; Jongmans et al. 2009)
        2. Omenn-like syndrome (Gennery et al. 2008)
        3. 22q11.2 deletion syndrome: more often than anticipated (Sanka et al. 2007; Corsten-Janssen et al. 2013)

Clinical Features

1. Major criteria (Lalani et al. 2012)
    1. Eye anomalies (Chestler and France 1988; Russell-Eggitt et al. 1990)
        1. *C*oloboma (80–90%) of the iris, choroid disc, and optic nerve
        2. Microphthalmia/anophthalmia
        3. Secondary retinal detachments and cataracts
        4. Total or partial vision loss
        5. Superior palpebral ptosis, epicanthus, and telecanthus
    2. Choanal *a*tresia (50–60%) (Kaplan 1985; Harris et al. 1997)
    3. *E*ar anomalies/deafness (90%) (Morgan et al. 1993)
        1. External ears (Dhooge et al. 1998)
            1. Asymmetry
            2. Posteriorly rotated
            3. Dystopia
            4. Prominent
            5. Increased width
            6. Decreased height
            7. Cup-shaped
            8. "Snipped-off" helical fold
            9. Prominent antihelix discontinuous with the antitragus
            10. Triangular concha
            11. Small or absent lobes
        2. Middle ears
            1. Chronic serous otitis media approaching 100%
            2. Eustachian tube anomalies associated with choanal atresia or palatal cleft
            3. Ossicular malformations
            4. Conductive hearing loss
        3. Inner ears
            1. Cochlear defects
            2. Sensorineural hearing loss (Thelin et al. 1986; Edwards et al. 1995)
        4. Temporal bone malformations
    4. Cranial nerve dysfunction (70–90%)
        1. Cranial nerve I: anosmia
        2. Cranial nerve II: unilateral or bilateral facial palsy
        3. Cranial nerve VIII: sensorineural deafness and vestibular problems

4. Cranial nerves IX and/or X: velopharyngeal incoordination and swallowing problems with aspiration

2. Minor criteria
   1. *H*eart disease (cardiovascular malformations) (75–85%)
      1. Conotruncal defects (e.g., tetralogy of Fallot)
      2. AV canal defects
      3. Aortic arch anomalies
      4. Others
         1. Double outlet right ventricle
         2. Hypoplastic left/right heart
   2. Growth and mental *r*etardation (70–100%)
      1. Growth deficiency
      2. Short stature
      3. Delayed motor milestones
      4. Hypotonia
      5. Mental retardation
   3. *G*enital anomaly (70–80%)
      1. Hypogonadotropic hypogonadism and delayed puberty
      2. Males: micropenis, cryptorchidism, delayed/incomplete pubertal development
      3. Females: hypoplastic labia, delayed/incomplete pubertal development
   4. Orofacial cleft (15–20%)
      1. Cleft lip/palate
      2. Laryngeal cleft
   5. Tracheoesophageal fistula/esophageal atresia (15–20%)
   6. Distinctive face (70–80%)
      1. Broad forehead
      2. Square face
      3. Facial asymmetry
      4. Ptosis
      5. Arched eyebrows
      6. Shallow supraorbital ridges
      7. Iris coloboma
      8. High nasal bridge
      9. Full nasal tip
      10. Microretrognathia
      11. Cleft lip/palate
      12. Laterally protruding ears
      13. Prognathism, prominent mandibular mentum, and generalized facial narrowing with advancing age
      14. Occasional broad or webbed neck with sloping shoulders
3. Occasional findings
   1. Thymic/parathyroid hypoplasia: DiGeorge sequence without chromosome 22q11 deletion (rare)
   2. Renal anomalies (15–25%)
      1. Dysgenesis
      2. Horseshoe/ectopic kidney
      3. Hydronephrosis
   3. Hand anomalies
      1. Polydactyly, ectrodactyly, thumb hypoplasia (rare)
      2. Altered palmar flexion creases (50%)
   4. General appearance
      1. Webbed neck (rare)
      2. Sloping shoulders (occasional)
      3. Accessory or hypoplastic nipples (rare)
   5. Abdominal defects
      1. Omphalocele (rare)
      2. Umbilical hernia (15%)
   6. Spine anomalies (rare)
      1. Scoliosis
      2. Hemivertebrae
   7. CNS malformations
      1. Midline defects (corpus callosum agenesis, arhinencephaly, septal agenesis, meningoencephalocele, partial vermis agenesis) (22%)
      2. Asymmetry (cerebral, ventricular, cerebellar) (18%)
      3. Hindbrain anomalies (brain stem hypotrophy demonstrated by CT scan or MRI, vermian agenesis) (14%)
4. Different diagnostic criteria for CHARGE syndrome (Sanlaville and Verloes 2007; Pampal 2010)
   1. Clinical criteria (Pagon et al. 1981): presence of four criteria out of six, and at least one major
      1. Major criteria
         1. Choanal atresia
         2. Ocular coloboma
      2. Minor criteria
         1. Heart defects of any type
         2. Retardation (of growth and/or of development)
         3. Genital anomalies

4. Ear anomalies (abnormal pinnae or hearing loss)

2. Diagnosis criteria of CHARGE (Verloes 2005): typical CHARGE (presence of either all three major signs or two major signs with two minor signs), partial CHARGE (two majors plus one minor), and atypical CHARGE (two majors but no minors or one major plus two minors)
    1. Major signs
        1. Ocular coloboma
        2. Choanal atresia
        3. Hypoplastic semicircular canals
    2. Minor signs
        1. Rhombencephalic dysfunction (brain stem and cranial nerve III-XII anomalies, including sensorineural deafness)
        2. Hypothalamo-hypophyseal dysfunction (including growth hormone and gonadotrophin defects)
        3. Mental retardation
        4. Malformation of mediastinal organs (heart, esophagus)
        5. External or middle ear malformations
3. Diagnostic criteria of CHARGE (Blake et al. 1998; Blake and Prasad 2006): presence of either all four major signs or three major signs plus three minor signs
    1. Major signs (classical four Cs)
        1. Coloboma (of iris, retina, choroid, disc, microphthalmia)
        2. Choanal atresia/stenosis (unilateral or bilateral, membranous, or bony)
        3. Cranial nerve dysfunction: facial palsy (unilateral or bilateral), sensorineural deafness, and/or swallowing problems
        4. Characteristic ear anomalies: external ear (lop or cup-shaped); middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects
    2. Minor signs
        1. Characteristic CHARGE facies (sloping forehead, flattened nasal tip)
        2. Orofacial cleft (cleft lip and/or palate)
        3. Cardiovascular malformations: all types, especially conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch
        4. Tracheoesophageal fistula: all types
        5. Genital hypoplasia: males (micropenis, cryptorchidism); females (hypoplastic labia); both males and females (delayed, incomplete pubertal development)
        6. Developmental delay: delayed motor milestones, language delay, mental retardation
        7. Growth deficiency: short stature, growth hormone deficiency
    3. Occasional signs
        1. Renal anomalies: duplex system, vesicoureteric reflux
        2. Spinal anomalies: scoliosis, osteoporosis
        3. Neck/shoulder anomalies: sloping, Sprengel deformity, kyphosis
        4. Hand anomalies: fifth finger clinodactyly, camptodactyly, cutaneous syndactyly
4. Another major diagnostic criteria by Amiel et al. (2001): emphasized the importance of temporal bone imaging in the diagnosis of the disease along with characteristic clinical findings
5. Neonatal brain dysfunction (Tellier et al. 1998)
    1. Severe sucking and swallowing problems
    2. Pharyngo-esophageal dysmotility
    3. Respiratory problems
    4. Cranial nerve palsies or anomalies (VI, VII, VIII, IX, X)

Diagnostic Investigations

1. Audiology, tympanometry, BAER, and CT of temporal bones for evaluation of hearing loss (Blake and Prasad 2006)
2. Auditory brain stem responses (ABR): an effective tool for early assessment of hearing function in children with multisystem involvement (Edwards et al. 2002)

3. Visual analysis and electroretinogram and functional vision testing: to identify and document severity of visual loss
4. Dilated fundoscopic exam for colobomas
5. Nasal pharyngeal feeding tube passage and CT scan of upper airway for evaluation of choanal atresia
6. Blood urea nitrogen, creatinine, electrolytes, and calcium: to evaluate renal function and exclude hypocalcemia (if present, evaluate T-cells for signs of DiGeorge sequence)
7. Hormonal studies (Hsu et al. 2014)
    1. Luteinizing hormone-releasing hormone and human chorionic gonadotropin tests in cases of hypogenitalism
    2. Growth hormone (GH) stimulation levels to exclude GH deficiency as a cause of growth retardation
    3. Prepubertal bone age X-ray, followed by screening for hypogonadotrophic hypogonadism in early puberty for growth
8. Echocardiography for cardiovascular malformations
9. Holter monitoring: to detect cardiac rhythm abnormalities
10. Abdominal ultrasound and voiding cystourethrogram: to exclude renal anomalies
11. Skeletal survey: to exclude skeletal anomalies, especially cervical spine anomalies, and scoliosis
12. Head CT scan and/or MRI for brain malformations and defective formation of the ossicles of the middle ear, cochlear, and semicircular canals. Olfactory bulbs and tracts imaging may be pathognomonic for CHARGE syndrome (Chalouhi et al. 2005).
13. Chromosome analysis for associated chromosomal anomalies
14. FISH to exclude 22q11 deletion
15. *CHD7* gene mutation testing available clinically
16. Multiple ligation-dependent probe amplification (MLPA) and comparative genomic hybridization (CGH): for patients with clinical suspect of CHARGE syndrome (Pisaneschi et al. 2015)
17. Whole exome sequencing (Martin et al. 2016)
    1. Identification of CHD7 mutations in some cases
    2. Other genes: likely to be the underlying cause of their CHARGE-like syndrome
    3. May be helpful to some patients, particularly those who are negative for CHD7 mutations and present with atypical findings
18. Strongly recommend performing *CHD7* analysis in any patients with a 22q11.2 deletion phenotype but without TBX1 haploinsufficiency and performing a genome-wide array for 22q11.2 deletions in clinical CHARGE patients without a *CHD7* mutation (Corsten-Janssen et al. 2013)

Genetic Counseling

1. Recurrence risk (Lalani et al. 2012)
    1. Patient's sib
        1. A parent affected or with a CHD7 mutation: a 50% risk
        2. Neither parent affected: the empiric risk is approximately 1–2% due to germ-line mosaicism. Typically, CHARGE syndrome is caused by a *CHD7* de novo mutation; the risk to the sibs is small. However, several sib pairs born to unaffected parents have been reported (Jongmans et al. 2006; Lalani et al. 2006), likely due to germ-line mosaicism confirmed in a report (Pauli et al. 2009).
    2. Patient's offspring
        1. Severely affected individuals do not reproduce
        2. Each child of a mildly affected individual: a 50% risk of inheriting the mutations
2. Prenatal diagnosis (Lalani et al. 2012)
    1. Ultrasonography: difficult unless in the pregnancy at risk
    2. Molecular genetic testing: possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis or CVS, provided the disease-causing allele of an affected family

member has been identified prior to prenatal diagnosis
3. Preimplantation genetic diagnosis: possible for families in which the disease-causing mutation has been identified

3. Management
   1. Neonatal brain stem dysfunction (Tellier et al. 1998)
      1. Feeding problems/failure to thrive (use of antispasmodics, Nissen fundoplication, gastrostomy tube feeding, gastrostomy)
      2. Oxygen therapy
      3. Tracheostomy
   2. Developmental delay/mental retardation
      1. Early infant intervention
      2. Special education
   3. Neonatal surgeries (Morgan et al. 1993)
      1. Respiratory problems: may require tracheostomy for aspiration of secretions
      2. Choanal stenosis/atresia (choanoplasty): airway stabilization and circulatory support; requires surgical opening for the posterior choanae by placing stents to keep the nasal passages open if there is obstructed breathing
      3. Laryngotracheal abnormalities (tracheoesophageal fistula, laryngomalacia, tracheomalacia, subglottic stenosis, laryngeal clefts, vocal cord/bulbar palsy)
      4. Congenital heart defects: corrective surgery when indicated
      5. Inguinal hernia
      6. Imperforate anus
   4. Colobomas: requires ophthalmologic care
   5. External ear anomalies/hearing loss
      1. Hearing aids for deafness
      2. Surgery for ear canal and temporal bone abnormalities
   6. Congenital absence of vestibular function: gradually develop motor function, and presumably improve equilibrium by using visual and proprioceptive inputs (Murofoshi et al. 1997)
   7. Cochlear implant surgery: an effective technological resource to provide information on hearing as one source for language construction (Cardoso et al. 2013)
   8. Management of other associated anomalies

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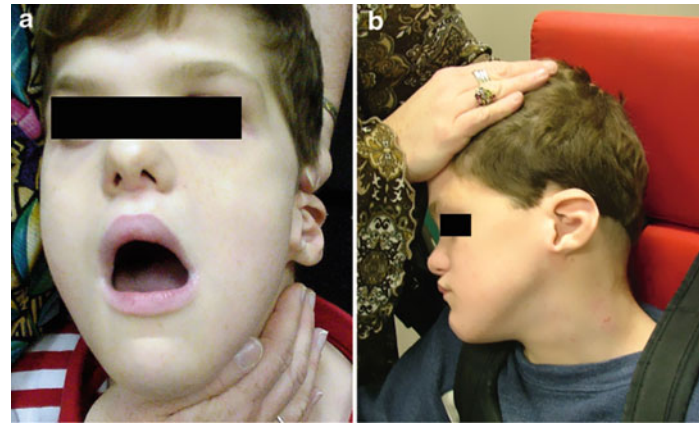

Fig. 1 (**a**, **b**) A boy with typical CHARGE association at ages 11 (*front view*) and 15 (*lateral view*). The patient had bilateral colobomas, choanal atresias, growth and mental retardation, hypogonadism, and ear anomalies with hearing loss

Cherubism

Contents

In 1933, Jones (1933) first described familial occurrence of painless enlargement of the jaws in three siblings. Later in 1938, Jones (1938) reported observations on the same family under the title "familial multilocular cystic disease of the jaws" and coined the term "cherubism" after the cherubs of Renaissance art for the full round cheeks and the upward cast of the eyes giving the children a peculiarly grotesque, cherubic appearance.

Cherubism is a benign maxillary bone dysplasia of childhood, usually showing an autosomal dominant inheritance with variable penetrance and spontaneously resolving after puberty. The prevalence of cherubism is 1 or less in 10,000.

Genetics/Basic Defects

1. Inheritance (Faircloth et al. 1991):
    1. Autosomal dominant with variable penetrance (Peters 1979; Caballero Herrera and Vinals Iglesias 1998; Zohar et al. 1989; Kömerik et al. 2014)
    2. Familial (Jones et al. 1950, 1965; Caffey and Williams 1951) in 80% of cases
    3. Males affected twice as often as females
    4. 80% overall penetrance:
        1. 100% in males
        2. 50–70% in females
    5. Variable expressivity
2. Cause (Ueki et al. 2001; Lo et al. 2003):
    1. Gene responsible for cherubism: mapped to chromosome region 4p16.3 (Southgate et al. 1998; Mangion et al. 1999).
    2. Caused by mutations in the gene encoding SH3-binding protein *SH3BP2*:
        1. Familial cherubism: all mutations are present in exon 9 and affect three amino acids within a conserved six amino acid sequence (Hatani and Sada 2008).
        2. Sporadic cherubism: description of a *SH3BP2* mutation in a case of nonfamilial case (Imai et al. 2003) and in an aggressive case of sporadic cherubism (Carvalho et al. 2008).
        3. Novel mutations in the *SH3BP2* gene have been described in sporadic central giant-cell lesion (which is indistinguishable histologically from cherubism), suggesting that both conditions share the same genetic alteration (Carvalho et al. 2009).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_39

3. SH3BP2 cherubism mutation potentiates TNF-α-induced osteoclastogenesis via NFATc1 and TNF-α-mediated inflammatory bone loss (Mukai et al. 2014).

Clinical Features

1. Variable size of the jaw lesions in cherubism:
    1. Minor lesions of both jaws
    2. Massive involvement of both jaws
2. Natural history:
    1. Classically normal at birth.
    2. Onset usually between 14 months and 5 years. However, the severe cases are evident at birth.
    3. Progresses until puberty.
    4. Usually progression stops after puberty.
    5. Regression of the bone lesions (involution of the disease) without treatment in some cases.
    6. Rapidly growing and extensively deforming lesions of the maxilla and the mandible including the coronoids and condyles in severely affected individuals.
3. Characteristic "eyes raised to heaven" cherubic appearance: an appearance of the cherubs portrayed in Renaissance art:
    1. Fullness of the lower half of the face (cheeks and jaw).
    2. Retraction of the lower lids by the stretched skin over the cheeks pulling down the lower eyelids. Consequently, a thin line of sclera is exposed beneath the iris, and the eyes appear to be raised heavenward in a manner reminiscent of "the cherubs in Renaissance paintings."
4. Painless hard enlargement of the jaws
5. Exclusively affecting the maxilla and mandible:
    1. The mandible usually involved.
    2. Involvement of the maxilla in 60% of cases.
    3. Painless lesions.
    4. Bilateral enlargement with loss of bone in the jaws and its replacement with large amount of fibrous tissue.
    5. Dental effect by bone lesion:
        1. Premature loss of deciduous teeth
        2. Displacement of permanent dentition
    6. Swelling usually abates by the third decade, whereas radiographic changes commonly persist into the fourth decade.
6. Submandibular lymph node enlargement in 45% of cases
7. Ocular manifestations (Carroll and Sullivan 2001; Yoo et al. 2015):
    1. Lower lid retraction
    2. Proptosis
    3. Strabismus with diplopia
    4. Globe displacement
    5. Visual loss due to compressive optic neuropathy (optic nerve atrophy)
    6. Retinal vein occlusion
    7. Macular folds and scarring (Ahmadi et al. 2003)
    8. Rare extension of lesion into the orbits (Colombo et al. 2001)
8. Rare upper airway involvement:
    1. Displaced tongue affecting speech, mastication, swallowing, and respiration
    2. Obstructive apnea (complete nasal obstruction) (Battaglia et al. 2000)
9. Extremely rare extrafacial skeletal involvement:
    1. Upper humerus
    2. Bilateral triquetral bones
    3. Anterior ribs
    4. Upper femoral necks
10. Modified clinical classification for cherubism (Raposo-Amaral et al. 2007; Pérez-Sayáns et al. 2013; Jiao et al. 2015):
    1. Grade 0: existence of the mutation without expression of the disease
    2. Grade I: lesion of the mandible without signs of root resorption
    3. Grade II: lesions involving the mandible and maxilla without signs of root resorption
    4. Grade III: aggressive lesion of the mandible with signs of root resorption
    5. Grade IV: lesions involving the mandible and maxilla with signs of root resorption
    6. Grade V: the rare, massively growing, aggressive, and extensively deforming

juvenile lesions involving the maxilla and mandible
7. Grade VI: the rare, massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla, mandible, and orbits

11. Rare associated syndromes:
    1. Noonan syndrome
    2. Ramon syndrome (Baskin et al. 2011):
        1. Cherubism
        2. Short stature
        3. Mental retardation
        4. Gingival fibromatosis
        5. Epilepsy
    3. Fragile X syndrome
    4. Craniosynostosis
12. Functional impairment (Tiziani et al. 1999):
    1. Mastication problems
    2. Speech difficulty
    3. Tooth alteration
    4. Loss of normal vision
13. Psychological consequences
14. Prognosis:
    1. Normally a self-limiting condition.
    2. Unusually extensive cases of cherubism have been reported (Ramon and Engelberg 1986), and even a fatal case is reported due to pulmonary and gastrointestinal infection as a result of aspiration given the gross deformity of the child (Silver et al. 2002).
15. Differential diagnosis (Baskin et al. 2011):
    1. Four main types of fibrous dysplasia:
        1. Monostotic fibrous dysplasia: only one bone is affected.
        2. Polyostotic: multiple bones are affected.
        3. McCune-Albright syndrome:
            1. Polyostotic form
            2. Accompanied by pigmentary lesions
            3. Endocrine dysfunction presenting as precocious puberty in females
        4. Craniofacial form of fibrous dysplasia:
            1. Only bones of the craniofacial complex are affected.
            2. Onset in the second decade in majority of patients.
            3. Generally unilateral lesions tend to become static once skeletal maturity is reached.
            4. Clinically difficult to differentiate from cherubism if the skeletal abnormalities are localized to the jaws.
            5. Molecularly different from cherubism.
    2. Infantile cortical hyperostosis:
        1. Diagnosed in the first 6 months of life
        2. Radiographically does not produce cystic areas
        3. Characterized by thickening of the mandibular lower border
        4. Does not have bilateral expression
    3. Osteitis fibrosa cystica secondary to hyperparathyroidism:
        1. Increased serum alkaline phosphatase
        2. Increased serum calcium
        3. Decreased serum phosphorus
        4. Increased urinary phosphorus
    4. Congenital infiltrating lipomatosis of the face (please see the chapter "► Congenital Infiltrating Lipomatosis of the Face")
    5. Noonan-like/multiple giant-cell lesion syndrome (Dunlap et al. 1989; Jafarov et al. 2005; Lee et al. 2005):
        1. Phenotypic overlap and frequently misdiagnosed with cherubism.
        2. Mutations in PTPN11 and SOS1 have been described in both familial and simplex cases (Hanna et al. 2009).
    6. Central giant-cell granuloma:
        1. Histologically cannot be distinguished from cherubism (Kaugars et al. 1992; De Lange and Van den Akker 2005)
        2. A somatic mutation in SH3BP2: identified in one individual (Carvalho et al. 2009)
    7. Odontogenic myxoma of the face: mimicry of cherubism (Kleiber et al. 2014)
    8. Ramon syndrome:
        1. Cherubism: a part of the syndrome
        2. Short stature
        3. Intellectual disability
        4. Gingival fibromatosis

Diagnostic Investigations

1. Orthodontic assessment, commonly required as the jaw distortion leads to permanent dental abnormalities:
   1. Malocclusive bite
   2. Premature loss of deciduous teeth
   3. Wide-spaced, misplaced, unerupted, or absent permanent teeth
2. Ophthalmologic examination, for rare individuals who may have:
   1. Lower lid retraction
   2. Proptosis
   3. Diplopia
   4. Globe displacement
   5. Visual loss caused by optic atrophy
3. Serum alkaline phosphatase levels may be elevated (Kozakiewicz et al. 2001).
4. Radiography (Jones et al. 1950; Hitomi et al. 1996; Tiziani et al. 1999; Agrawal et al. 2014):
   1. Extensive involvement of the mandible and the maxilla
   2. Multilocular radiolucent areas in the mandible and maxilla with expansion of the bony cortex:
      1. Often very extensive
      2. With a few irregular bony septa
      3. Multilocular rarefactions replaced by sclerosis with progressive calcification in the adult
   3. Absent and displaced teeth in the involved areas
5. CT scan:
   1. Superior in making the diagnosis
   2. Determining the degree of severity
6. Histological changes in cherubism:
   1. Replacement of the normal bony architecture with proliferating fibrous tissue containing numerous giant cells (Ayoub and El-Mofty 1993)
   2. Mononuclear fibroblastic stroma:
      1. Nonneoplastic fibrous lesions rich in multinucleated giant cells identified as osteoclasts
      2. Irregular bone formation
   3. A peculiar perivascular cuffing of collagen: considered by some to be pathognomonic for the condition (Adante and Breen 1996)
   4. Histological resemblance to the following disorders (Mangion et al. 1999):
      1. Giant-cell tumor
      2. Giant-cell granulomas
      3. Ossifying fibroma
      4. Fibrous dysplasia of the jaw
      5. Paget disease of bone
7. Molecular genetic testing (Baskin et al. 2011):
   1. To confirm the diagnosis in a proband with the suggestive clinical findings and typical radiologic and/or histologic manifestations.
   2. Sequence analysis: *SH3BP2* sequence variants in exon 9 detect an estimated 80% of mutations.

Genetic Counseling

1. Recurrence risk (Baskin et al. 2011):
   1. Patient's sib. The risk depends on the genetic status of the parents:
      1. An affected parent: a 50% risk
      2. Clinically unaffected parents and/or the parents not detected to have a disease-causing mutation: a low recurrence risk but greater than that of the general population because of the possibility of germ-line mosaicism
   2. Patient's offspring: a 50% risk of inheriting the mutation.
2. Prenatal diagnosis (Baskin et al. 2011):
   1. Ultrasonography: not possible since the lesion is postnatal in nature
   2. Molecular analysis possible on fetal DNA obtained by amniocentesis or CVS if the disease-causing mutation (*SH3BP2*) has been identified in an affected family member
   3. Preimplantation genetic diagnosis: possible for families at risk in which the disease-causing mutation has been identified
3. Management:
   1. Although cherubism represents a benign and localized maxillary dysplasia, it requires prompt surgical but conservative treatment and careful follow-up to avoid permanent lesions (malocclusion and/or edentulism) (Mortellaro et al. 2009).

2. Observation:
    1. Generally self-limiting lesions and subside with age (Katz et al. 1992)
    2. Surgical intervention required only in cases with esthetic or functional problems
3. Tracheostomy to secure the airway for upper airway obstruction.
4. Teeth extraction from the sites of fibrous changes.
5. Curettage alone or in combination with surgical contouring: considered the treatment of choice.
6. Resection of the orbital lesions may be required to improve visual impairment.
7. Prompt recurrence is likely if surgery is performed at an early age.
8. Radiation therapy is ineffective and contraindicated in view of the following risks:
    1. Osteoradionecrosis
    2. Interference with dentofacial growth and development
    3. Effect on future surgical procedures
9. Tacrolimus (calcineurin inhibitor) as a new therapy for cherubism enhances bone formation by stimulating osteogenesis and inhibiting osteoclastogenesis (Kadlub et al. 2015).

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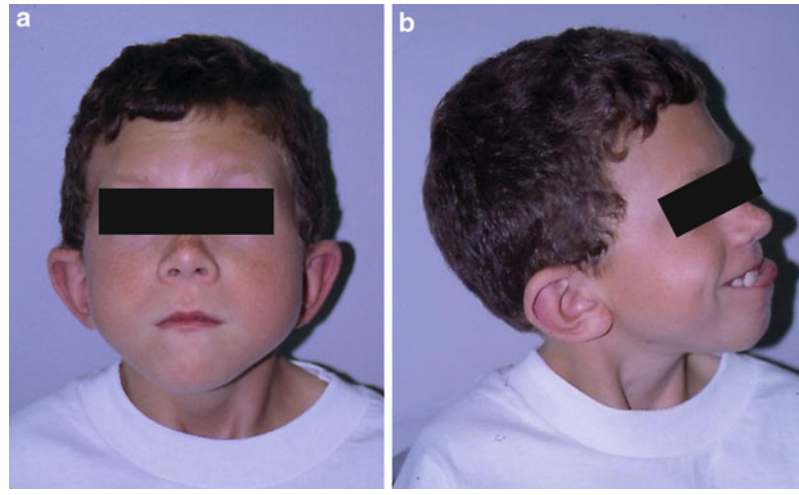

Fig. 1 (**a**, **b**) A boy with cherubism showing full cheeks and jaw and the retraction of the lower eyelids with symmetrical augmentation on both mandibular angles

Chiari Malformation

Contents

In 1891, Chiari first described a dysplasia of the nervous system consisting of herniation of the cerebellar tonsils into the foramen magnum. There are three types of Chiari malformations. The commonest ones are type I and type II, and the latter has been named the Arnold-Chiari malformation (De Reuck and Theinpont 1976).

Synonyms and Related Disorders

Chiari malformation type I with syringomyelia; Chiari malformation type II (Arnold-Chiari malformation); Chiari malformation type III

Genetics/Basic Defects

1. Classification of Chiari malformations according to the severity (Cesmebasi et al. 2015)
    1. Chiari type I (CMI) malformations (the milder malformation)
        1. Ectopia of the cerebellar tonsils (caudal herniation of the cerebellar tonsils and inferior cerebellum through the foramen magnum).
        2. Usually an isolated feature encountered in adults.
        3. The anomaly occurs sporadically but can be transmitted genetically in some families (Milhorat et al. 1999; Schanker et al. 2011).
    2. Chiari type II (CMII) malformations (also called the Arnold-Chiari malformation) (the more severe malformation)
        1. Downward displacement of the cerebellar medulla and fourth ventricle into the spinal canal
        2. Almost always associated with meningomyelocele
        3. May be associated with polygyria, cortical heterotopia, and dysgenesis of the corpus callosum
    3. Chiari type III (CMIII) malformations (the most severe malformation) (Caldarelli et al. 2002)
        1. Downward displacement of most of the cerebellum into a high cervical/low occipital encephalocele
        2. Malformation consisting of anatomical anomalies typical of Chiari type II malformation with those of a high cervical/occipital encephalocele

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Chiari type IV (CM IV) malformations
    1. Absence of hindbrain herniation
    2. Defined as hypoplasia or aplasia of the cerebellum
    3. Occasionally associated with tentorial hypoplasia (Wellons et al. 2005)
5. Chiari type 1.5 (CM 1.5) malformations
    1. Recently coined to specifically address patients with Chiari type I malformation with an added component of brainstem and fourth ventricle elongation/caudal descent (Iskandar and Oakes 1999)
    2. Have symptoms similar to Chiari type I patients
    3. May have a higher incidence of developing syringomyelia
6. Chiari type 0 (CM 0) malformations
    1. Used to describe a particular subset of patients.
    2. Have syringomyelia but no associated findings of hindbrain herniation.
    3. Patients' symptoms improve following posterior cranial fossa decompression.
    4. Presence of craniocervical anomalies such as those seen in Chiari type I malformation in many patients.
    5. Crowding of the foramen magnum and obstruction of the median aperture (of Magendie) by arachnoid veils and adhesions are seen (Wellons et al. 2005).
    6. By definition, Chiari type 0 patients present with symptoms associated with syringohydromyelia (these symptoms are like those seen in patients with Chiari type I malformation and syringomyelia).

2. Acquired Chiari I malformation caused by conditions leading to increased intracranial pressure
    1. Head injury
    2. Hydrocephalus
    3. Craniosynostosis
3. Brainstem dysfunction, sensory disturbance, and motor loss caused by impaction of the tonsils against the cervicomedullary structures

Clinical Features

1. Patients with Chiari I malformation
    1. Asymptomatic in majority of patients
    2. General symptoms (Thomas et al. 1999)
        1. Headache (Weinberg et al. 1998)
        2. Fatigue
        3. Memory loss
        4. Pressure on the neck
        5. Back pain
        6. Insomnia
        7. Poor circulation
        8. Nausea
        9. Menstrual problems
        10. Sexual alterations
        11. Hypothermia
        12. Bronchial aspirations
        13. Respiratory alterations
        14. Drop attacks
        15. Rare reports of sudden death
    3. Ocular symptoms
        1. Loss of vision
        2. Intolerance of bright light
        3. Diplopia
    4. Otolaryngologic symptoms (Naya Galvez et al. 2002)
        1. Vestibular manifestations
            1. Imbalance
            2. Swaying
            3. Dizziness
            4. Positional vertigo
            5. Spontaneous vertigo
            6. Nystagmus
            7. Hearing loss
            8. Tinnitus
        2. Alterations of cranial pairs
            1. Dysphagia
            2. Dysphonia
            3. Alterations in tongue mobility
            4. Loss of smell
            5. Facial hypoesthesia
        3. Sleep apnea
    5. Cerebellum compression symptoms
        1. Ataxia
        2. Nystagmus
        3. Gait difficulties
        4. Opisthotonos

5. Horner's syndrome
6. Paralysis of the last cranial nerves
7. Hypotonia
8. Trembling
9. Dysarthria
10. Dysmetria

6. Associated CNS anomalies
    1. Stenosis of the aqueduct of Silvia
    2. Meningomyelocele
    3. Syringomyelia (cystic dilation of the spinal cord)
7. Symptoms associated with syringomyelia
    1. Known to accompany 50–70% of patients with Chiari I malformations.
    2. Obstructed cerebrospinal fluid at the site of cerebellar tonsillar herniation shows perivascular movement of CSF from the spinal subarachnoid space into the spinal cord with each Valsalva maneuver and causes syringomyelia.
    3. Tingling, hypoesthesia, and burning sensation in the extremities.
    4. Thermalgesic anesthesia.
    5. Alteration in muscular reflexes.
    6. Areflexia.
    7. Alteration of kinesthesia.
    8. Motor skill dysfunction.
    9. Headache or nonradicular pain in the shoulder, back, and limbs
    10. Headache usually suboccipital and upper cervical in location and is exacerbated by Valsalva maneuvers.
    11. Associated with the development of a painful, rapidly progressive, or left-curving scoliosis.
    12. Recent reports of spontaneous radiographic improvement of childhood Chiari malformations and syringomyelia.
8. Chiari I malformation in children and adolescents (Genitori et al. 2000)
    1. Natural history of an asymptomatic Chiari I malformation in children
        1. Not well understood
        2. Rarely reported to resolve spontaneously
        3. Asymptomatic at the time of diagnosis in many children
        4. Degree of tonsillar ectopia correlating well with the presence of neurologic signs and symptoms
        5. Rare reports of sudden death
    2. Group I (asymptomatic)
        1. Age at diagnosis: 3 months to 17 years
        2. Associated conditions: hydrocephalus, craniofacial syndromes, epilepsy, and occult spinal dysraphism
    3. Group II (brainstem compression)
        1. Age at diagnosis: 7 months to 26 years
        2. Associated conditions: craniofacial syndromes, hydrocephalus (Di Rocco et al. 2011), and precocious puberty
        3. Symptoms: neck pain, vertigo, headache, numbness, swallowing difficulties, apnea, opisthotonos, brachialgia, hyposthenia, spasticity, and hemifacial pain
    4. Group III (presence of syringomyelia) (Paul et al. 1983; Dauser et al. 1988; Dure et al. 1989; Dyste et al. 1989). Symptoms are:
        1. Numbness
        2. Sensory loss
        3. Neck pain
        4. Vertigo
        5. Scoliosis
        6. Hyposthenia
        7. Headache
        8. Muscle hypotrophy
        9. Swallowing difficulties
        10. Limb pain
    5. Associated disorders of Chiari type I malformations (Loukas et al. 2011)
        1. Craniostenosis (e.g., Apert syndrome)
        2. Endocrinopathy (e.g., acromegaly)
        3. Hyperostosis (e.g., craniometaphyseal dysplasia)
        4. Bone mineral deficiency (e.g., familial vitamin D-resistant rickets)

5. Cutaneous disorders (e.g., acanthosis nigricans)
6. Spinal defects (e.g., atlantoaxial assimilation)
7. Space-occupying lesions (e.g., brain tumors)
8. Others (e.g., Beckwith-Wiedemann syndrome)

6. Prognosis (Nagib 1994)
   1. The clinical presentation of younger children (less than 6 years old) appeared similar to older children (over 6 years of age), except for sleep apnea, which was limited to the younger age group.
   2. Patients with pronounced motor and sensory deficits had the worst prognosis for recovery.

2. Patients with Chiari II malformation (Rauzzino and Oakes 1995)
   1. Almost invariably associated with myelomeningocele (90%)
   2. Brainstem signs in 20% of patients with Chiari II malformation in children and adolescence
      1. Vertigo
      2. Bioccipital headache
      3. Cerebellar dysfunction
      4. Progressive paresis of the arms
3. Patients with Chiari III malformation (Caldarelli et al. 2002)
   1. Rarest of the Chiari malformations
   2. Associated with a high cervical or occipital encephalocele (Häberle et al. 2001; Ivashchuk et al. 2015)
   3. Prognosis for nearly all reported patients
      1. Various degree of developmental delay
      2. Epilepsy
      3. Hypotonia
      4. Spasticity
      5. Upper and/or lower motor neuron deficits
      6. Lower cranial nerve dysfunction
   4. CNS anomalies usually observed in an occipital encephalocele
      1. A small cranial fossa
      2. Caudal displacement of cerebellar tonsils and vermis
      3. Medullary kinking
      4. Tectal beaking
      5. Obvious hydrocephalus

Diagnostic Investigations

1. CT or MRI
   1. Chiari I malformation
      1. Incidental detection in asymptomatic individuals (Elster and Chen 1992)
      2. Herniation of the tonsils >5 mm below the foramen magnum on MRI considered diagnostic
   2. Chiari II malformation (Naidich 1981; El Gammal et al. 1988; Chapman et al. 2015)
      1. Caudal cerebellum (100%)
      2. A small posterior fossa and pointed morphology of the herniating inferior cerebellar tonsil, cervical cord syrinx, and corpus callosal dysgenesis
         1. Kinking of medulla on spinal cord (79%)
         2. Elongation of brainstem and low medulla, stretched aqueduct, and fourth ventricle (75%)
         3. Beaking of quadrigeminal plate (60%)
         4. Large massa intermedia (55%)
         5. Large fourth ventricle (25%)
         6. Hydromyelia (15%)
         7. Calvarial three-dimensional surface-shaded reconstructions from a CT: lacunar skull seen in Chiari II malformation with numerous calvarial pits and thinning
   2. Chiari III malformation (Castillo et al. 1992; Aribal et al. 1996; Caldarelli et al. 2002)
      1. An occipitocervical meningoencephalocele protruding through a bony defect involving the lower occipital squama and/or the posterior arch of the first cervical vertebrae
      2. A small posterior cranial fossa with low tentorial attachment
      3. Scalloping of the clivus

4. Massive herniation of the hypoplastic cerebellar structures into the malformation
5. Beaking of the tectal plate
6. Dysgenesis of the corpus callosum
7. Severe ventricular dilatation (hydrocephalus)

2. Cranial and spinal magnetic resonance (MR) imaging: used to identify the degree of tonsillar descent and document the presence of syringohydromyelia (McVige and Leonardo 2014)
3. Cine flow MRI (Ventureyra et al. 2003)
   1. Understand the dynamics of cerebrospinal fluid at the craniocervical junction
   2. Understand pathophysiology of the Chiari I malformation
4. Brainstem auditory evoked potentials (BAEP) (Koehler et al. 2001)
   1. Consistently abnormal in symptomatic Chiari II malformation
   2. Showing a positive predictive value of 88% in predicting central neurologic sequelae in newborns and infants

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased
   2. Patient's offspring: not increased
2. Prenatal diagnosis
   1. Prenatal ultrasound diagnosis of Chiari I malformation (Iruretagoyena et al. 2010).
      1. A lip of cerebellum is downwardly displaced with the tonsils, but the fourth ventricle remains in the posterior fossa.
      2. Enlarged third ventricle.
      3. Cerebellar hypoplasia with marked cystic enlargement of the fourth ventricle.
      4. This condition may coexist with syringomyelia, which is a cyst formation on the cervical portion of the spinal cord.
   2. Prenatal diagnosis of Chiari II malformation (Chapman et al. 2015).
      1. Fetal ultrasound
         1. "Lemon sign": altered fetal calvarium with concave scalloping of the frontal bones
         2. "Banana sign": effaced cisterna magna and compressed fetal cerebellum which has an unusual elongated morphology
         3. Classic "lemon and banana" signs: the gold standard in the early screening of Chiari II malformation
         4. Demonstrate the myelomeningocele, occurring most often in the lumbar region
         5. A triangular shaped of the posterior horn of the lateral ventricle in coronal plane imaging
         6. Ventriculomegaly
      2. Fetal MR imaging: will show following additional key prognostic factors (Righini et al 2011)
         1. Degree of herniation
         2. Brainstem dysmorphology
         3. Corpus callosal dysgenesis
         4. Cerebral cortical or white matter abnormalities
   3. Strategy for fetal sonographic and MRI diagnosis of CMII when ultrasound study shows ventriculomegaly/hydrocephalus
      1. Presence of myelomeningocele by ultrasound: suspect CMII
      2. Absence of myelomeningocele by ultrasound: proceed to MRI
      3. Presence of tight posterior fossa by MRI (Ando et al. 2007)
         1. Presence of myelomeningocele: suspect CMII
         2. Absence of myelomeningocele: suspect CMII (with open defect) or conditions other than CMII, such as craniosynostosis, swollen hindbrain, and tumor
      4. Absence of tight posterior fossa by MRI: CMII not likely
   4. Prenatal ultrasound/MRI diagnosis of Chiari III malformation (Smith et al. 2007)
      1. Repeat US at 19 weeks demonstrated neural tissue in the cyst, consistent with an encephalocele.

2. MR imaging at 23 weeks confirmed the presence of an occipital encephalocele, demonstrated additional bony defect in the upper cervical spine, and identified abnormal morphology and position of the brainstem consistent with the diagnosis of Chiari III.
3. Postnatal MRI and CT confirmed the fetal MRI findings and demonstrated the utility of fetal MRI in the early evaluation of sonographically detected posterior fossa abnormalities.

3. Management
   1. Chiari I malformation (Bindal et al. 1995; Siasios et al. 2012)
      1. Conservative treatment for asymptomatic patients.
      2. Surgical treatment should be individualized for each patient.
      3. Main treatment consisting of decompressing the structures trapped in the foramen magnum.
         1. Suboccipital craniectomy with or without dural patch grafting and cervical laminectomies: the most often used procedure
         2. Syringosubarachnoid shunt when indicated
      4. Posterior fossa decompression as first-line treatment in symptomatic syringomyelia patients.
      5. Shunting of hydrocephalus.
      6. Major preexisting sensory or motor deficits: poor prognosticators for functional recovery.
   2. Chiari II (Arnold-Chiari) malformation
      1. Seen most often in children with myelomeningocele.
      2. Shunting of hydrocephalus often resolves brainstem symptoms and surgical decompression may not be necessary.
      3. Surgical decompression of posterior fossa and upper cervical spine may be required if brainstem compression symptoms remain after shunting.
      4. Surgical intervention indicated to prevent further deterioration of the motor function and to diminish the progress of spasticity and scoliosis from tethered cord syndrome.
   3. Chiari III malformation (Caldarelli et al. 2002)
      1. Primary closure of the malformation: usually the treatment of choice.
      2. CSF shunting of the associated hydrocephalus postponed to a later phase.
      3. Neonates often require intensive care treatment for the associated severe respiratory distress.

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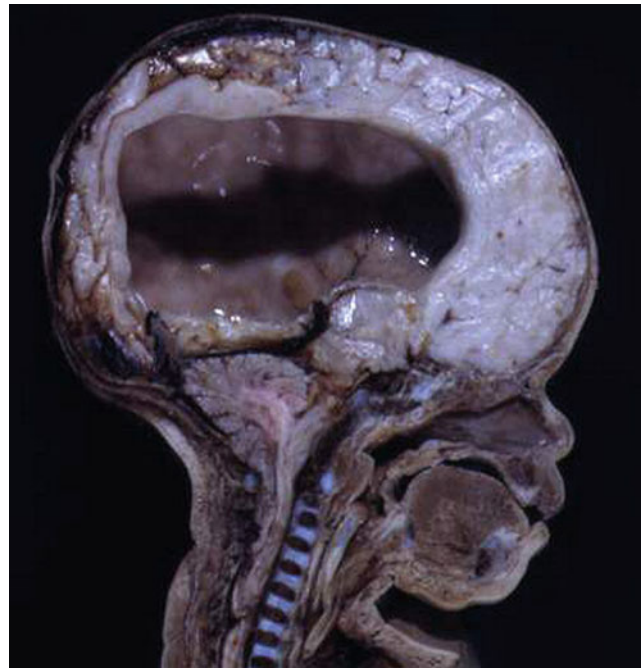

Fig. 1 Sagittal section of a neonate with a large ruptured lumbar meningomyelocele. Arnold-Chiari malformation is evident: the brainstem and lower portion of cerebellum herniate through the foramen magnum and overlap the cervical cord which is severely flattened. The brain shows hydrocephalus

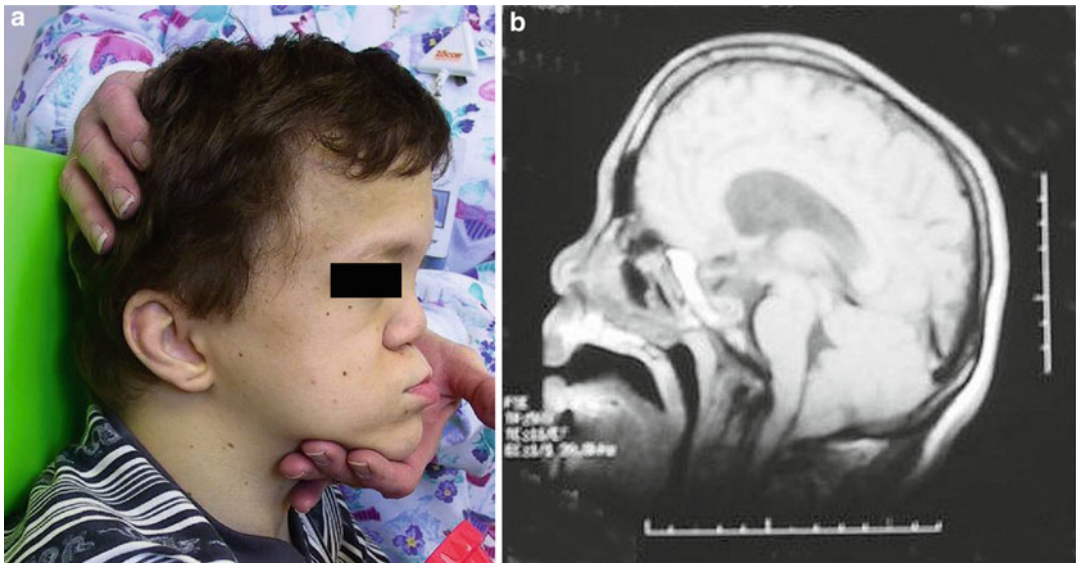

Fig. 2 (**a**, **b**) A patient with multiple congenital anomalies (mental retardation, flat facial plane, epicanthus inversus, blepharophimosis, cataracts, nystagmus, elbow flexion contractures, and vertical talus) with Chiari I malformation (MRI of the brain)

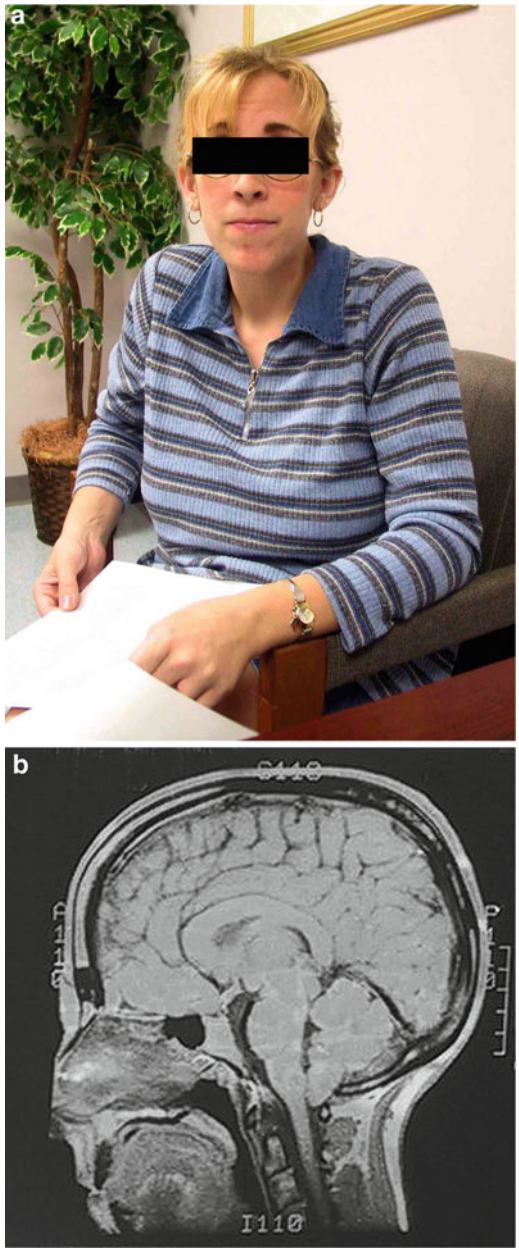

Fig. 3 (**a**, **b**) A 28-year-old female with Chiari I malformation with normal phenotype but complaining headache, dizziness, and neck pain worsened by pregnancy

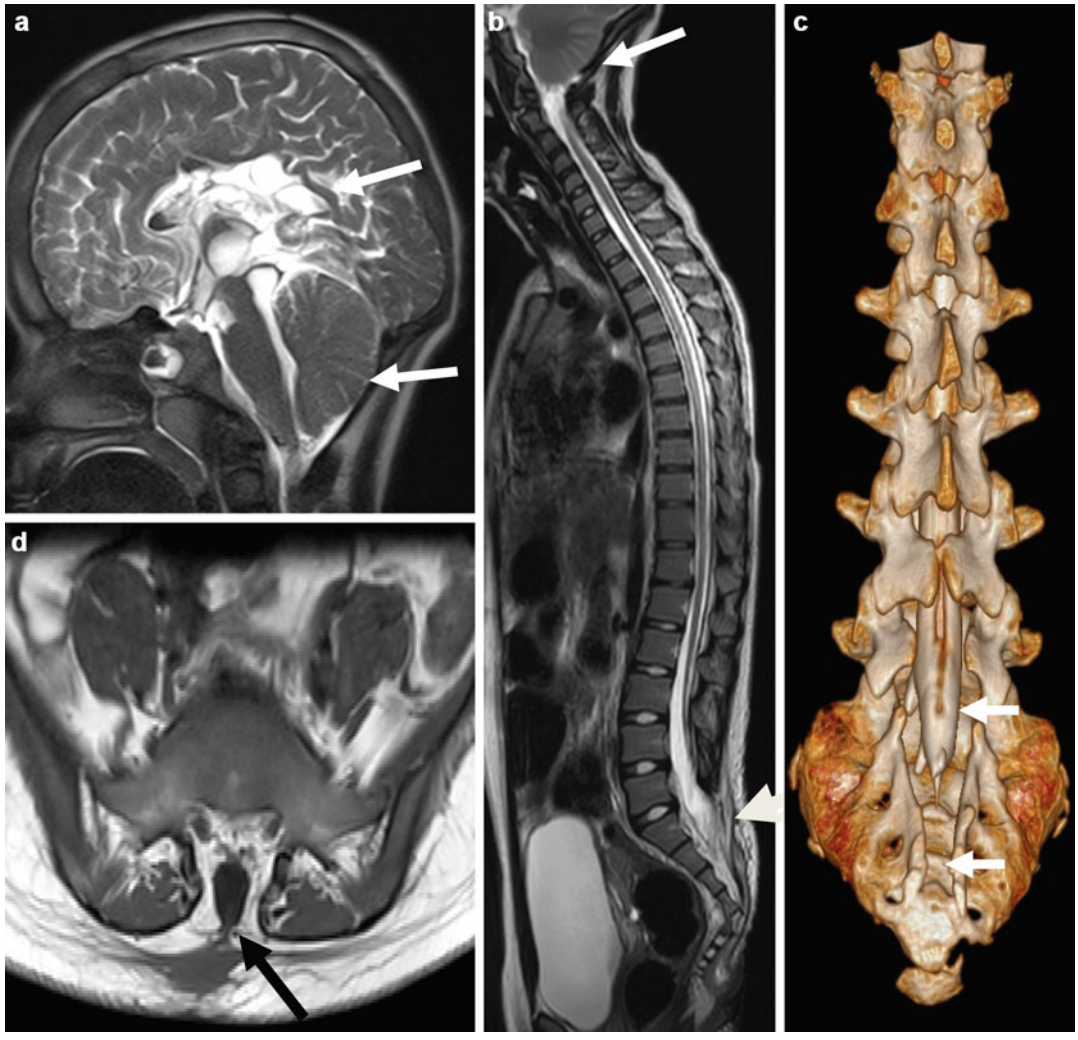

Fig. 4 (**a**–**d**) An 11-year-old female with Chiari II malformation. MRI images of the brain showed cerebellar tonsil located below the foramen of magnum (**a**) (*lower arrow*) and (**b**) (*upper arrow*) with absent corpus callosum (**a**) (*upper arro*w) and mild ventriculomegaly. There is a syrinx from T2–L4 (**b**) (lower arrow) and posterior spinal defect at L5/sacrum (b) (*lower arrow*) and (**d**) (*arrow*). CT 3D reconstruction image (**c**) showed the spina bifida (*arrows*) (Courtesy of Dr. Grace Guo)

Chondrodysplasia Punctata

Contents

Chondrodysplasia punctata (CDP) refers to the radiographic appearance of punctate calcifications, due to abnormal cartilaginous stippling, the result of calcium deposition in the areas of enchondral bone formation, described in a variety of chondrodysplasias.

Synonyms and Related Disorders

Chondrodystrophia calcificans punctata; Conradi-Hünermann syndrome; Conradi-Hünermann-Happle syndrome; Happle syndrome; Rhizomelic form of chondrodysplasia punctata

Genetics/Basic Defects

1. Genetic heterogeneity of chondrodysplasia punctata
    1. Rhizomelic chondrodysplasia punctata type I (RCDP1) (Braverman et al. 1997, 2002)
        1. Autosomal recessive disorder
        2. Caused by mutations in peroxisome biogenesis factor 7 (*PEX7*) gene, mapped at 6q22-q24, which encodes the cytosolic peroxisomal targeting signal type 2 (PTS2)-receptor protein peroxin 7
        3. Genotype-phenotype correlations
            1. Classic RCDP1: all patients homozygous for the L292X mutation (Brites et al. 1998)
            2. Phenotype determined by the other allele if the patients are compound heterozygotes for L292X and another mutation
            3. A milder phenotype associated with several *PEX7* alleles
    2. Rhizomelic chondrodysplasia punctata type 2 (RCDP2)
        1. Autosomal recessive disorder
        2. Caused by mutations in the gene that encodes peroxisomal dihydroxyacetone phosphate acyltransferase (DHAPAT) (Barr et al. 1993)
    3. Rhizomelic chondrodysplasia punctata type 3 (RCDP3)
        1. Autosomal recessive disorder
        2. Caused by mutations in the gene (mapped at 2q31) that encodes peroxisomal alkyl-dihydroxyacetone phosphate synthase (ADHAPS)
    4. Rhizomelic chondrodysplasia punctata type 4 (RCDP4)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. *FAR1* encodes fatty acyl-CoA reductase 1, producing fatty alcohols used in plasmalogen biosynthesis
2. Mutations in *FAR1* were recently shown to cause peroxisomal fatty acyl-CoA reductase 1 disorder (MIM 616154) (Buchert et al. 2014), also referred to as RCDP4 (Wanders and Poll-The 2015)

5. Rhizomelic chondrodysplasia punctata type 5 (RCDP5) (Barøy et al. 2015)
   1. Mutations in *PEX5* resulting in a selective loss of PEX5L isoform represent a fifth type of RCDP
   2. A novel c.722dupA mutation in *PEX5* gene, the first to exclusively affect PEX5Lexpression, and that unlike previous mutations in *PEX5* gene, results in RCDP instead of Zellweger spectrum disorders
   3. The peroxisomal dysfunction: due to an isolated defect in import of peroxisomal targeting signal 2 (PTS2)-tagged proteins, previously described from mutations in *PEX7* only
6. Relatively mild autosomal dominant Conradi-Hünermann syndrome
   1. Chondrodysplasia punctata, tibia-metacarpal type
   2. Chondrodysplasia punctata, humero-metacarpal type
7. X-linked dominant type only seen in females (Conradi-Hünermann-Happle syndrome) (CDPX2) (Braverman et al. 1999; Kelley et al. 1999; Has et al. 2000; Ikegawa et al. 2000; Becker et al. 2001; Herman et al. 2002)
   1. Lethal in males
   2. Caused by mutations of the 3β-hydroxysteroid-Δ^8-Δ^7-isomerase (also called emopamil-binding protein, EBP)
   3. The gene encoding EBP mapped to Xp11.22-p11.23
   4. EBP: which catalyzes an intermediate step in the conversion of lanosterol to cholesterol
   5. Presence of gonadal and somatic mosaicism in CDPX2
   6. Single gene mosaicism giving rise to CDPX2 in a male (Aughton et al. 2003)
8. X-linked recessive type (Parenti et al. 1997; Brunetti-Pierri et al. 2003) with a deletion of the short arm of the X chromosome (CDPX1)
   1. Caused by defects in arylsulfatase E, a vitamin K-dependent enzyme
   2. The locus of the disease identified through the characterization of patients with chromosomal abnormalities involving the Xp22.3 region
   3. The gene of CDPX1, named *ARSE*, encoding a new sulfatase (arylsulfatase E), showing a high-sequence homology to steroid sulfatase
   4. Point mutations of the *ARSE* gene detected in the DNA of karyotypically normal patients with chondrodysplasia punctata

2. Causes of stippled cartilaginous calcifications (Borochowitz 1991)
   1. Peroxisomal disorders
      1. Zellweger syndrome
         1. A peroxisomal disorder
         2. An autosomal recessive inheritance
         3. Associated stippled calcifications of the epiphyses, particularly common in the patella
         4. Severe hypotonia
         5. Characteristic facies with a high forehead, hypertelorism, epicanthal folds, Brushfield spots, and shallow supraorbital ridges
         6. Club foot deformity
         7. The affected infants that usually die early in infancy
         8. Involvement of other organ systems, especially the brain (migrational disorders) and kidneys (cortical cystic disease of the kidneys)
      2. Rhizomelic chondrodysplasia punctata
   2. Genetic disorders
      1. Conradi-Hünermann chondrodysplasia punctata

2. X-linked dominant chondrodysplasia punctata
3. Smith-Lemli-Opitz syndrome
4. Greenberg dysplasia (cholesterol biosynthesis disorder)
    1. An autosomal recessive disorder
    2. Appears to be caused by an error of sterol metabolism at the level of 3β-hydroxysteroid-Δ14 reductase
    3. Nonimmune hydrops fetalis
    4. Midface hypoplasia
    5. Micrognathia
    6. Rhizomesomelic dwarfism with relatively long and broad hands and feet
    7. Narrow thorax
    8. Protuberant abdomen
    9. Radiographic findings of grossly irregular and deficient ossification of the short tubular bones, fragmented ossification at the ends of the long tubular bones, small pelvic bones with irregular "moth-eaten" contours, platyspondyly with multiple ossification centers of the vertebral bodies, and deficient ossification of the calvaria
5. CHILD syndrome
    1. Congenital hemidysplasia
    2. Ichthyosiform erythroderma
    3. Limb defects (unilateral hypomelia with ipsilateral epiphyseal stippling)
6. Dappled diaphyseal dysplasia (lethal short-limbed dysplasia, type Carty) (Carty 1989)
    1. An autosomal recessive disorder
    2. All cases stillborn or died in utero
    3. Fetal hydrops
    4. Polyhydramnios
    5. Short limbs with relatively long hands and feet
    6. Small thorax
    7. Protuberant abdomen
    8. Radiographic findings of fragmented appearance of the ribs, small islands of ossification from disruption of the facial bones, axial and appendicular skeleton, and absent ossification of the calvaria
7. Acrodysostosis
8. Binder syndrome
9. De Barsy syndrome
    1. Cutis laxa
    2. Corneal clouding
    3. Mental retardation
    4. Stippled epiphysis
10. GM1 gangliosidosis
11. Galactosialidosis
12. Fibrochondrogenesis
13. Mucolipidosis II
14. De Lange syndrome
15. X-linked ichthyosis
16. Keutel syndrome
    1. Stippled epiphysis (knees, elbows)
    2. Brachytelephalangism
    3. Pulmonary stenosis
17. Osebold-Remondini syndrome
18. Hypothyroidism
19. Chromosome translocation
20. Trisomy 21 and 18
21. Turner syndrome
22. Brachytelephalangic chondrodysplasia punctata (CDP-B)
    1. An X-linked recessive disorder
    2. Male infants affected with a very small nose, anteverted and grooved nares
    3. Benign type of chondrodysplasia punctata
    4. Also observed in a patient with Xp terminal deletion with ichthyosis and mental retardation
    5. Distal phalangeal hypoplasia: the most characteristic radiological sign of this form
    6. Cervical canal stenosis with cervical cord compression leading to

serious morbidity and early mortality in a small number of patients (Ochiai et al. 2013)

23. Chondrodysplasia punctata, metacarpal type
    1. Including tibia-metacarpal type and humero-metacarpal type
    2. An autosomal dominant disorder
    3. Named for a specific long bone but with overlap in the long bone involved
    4. All having short metacarpals
    5. Affected children with a hypoplastic midface, a depressed nasal bridge, small mouth, micrognathia, short neck, and short limbs
    6. Radiographically, with short metacarpals associated with short tibias in the tibia-metacarpal type and short humeri in humero-metacarpal type
24. Sheffield-type chondrodysplasia punctata
    1. Heterogeneous group of patients with punctate epiphyses, particularly in the calcaneus and spine
    2. A benign course
    3. Distal phalangeal hypoplasia
    4. Probably not a specific entity but rather a heterogeneous group of disorders that can be included in other entities
25. Pacman dysplasia
    1. A single-case report with peculiar bone dysplasia, stippling in many areas, short bowed bones, and periosteal cloaking
    2. Osteoclasts with an unusual appearance reminiscent of the Pacman figures in computer games on bone histology
    3. The entire coccygeal and sacral regions replaced by stippling
    4. Dense stippling also observed in the thoracic region
    5. Considerable stippling also observed in the epiphyses of the proximal femur, talus, calcaneus, cuboid, and the bones of the hand
    6. Wide periosteal cloaking of many bones and poor ossification
    7. Bowed femora
    8. Superior inferior sagittal clefting in the AP views in the upper spine

3. Vitamin K disorders
    1. Warfarin embryopathy (Collins et al. 1977; Pauli et al. 1987)
        1. Associated with maternal use of warfarin sodium
        2. Consistent features: saddle nose deformity, hypertelorism, frontal bossing, high-arched palate, short neck, and short stature
        3. Other features: rhizomelia, micromelia, flexion contractures, optic atrophy, psychomotor retardation, cataracts, congenital heart disease, and renal anomalies
    2. Vitamin K epoxide reductase deficiency
4. Acquired in utero
    1. Fetal alcohol syndrome
    2. Phenacetin intoxication
    3. Fetal hydantoin syndrome
    4. Femoral hypoplasia unusual facies syndrome
    5. Maternal diabetes
    6. Maternal systemic lupus erythematosis
    7. Febrile illness
5. Other conditions involving unusual calcification that may be confused with punctata
    1. Amelia and other absence deficiencies
    2. Cerebrocostomandibular syndrome
    3. Dysplasia epiphysealis hemimelica
    4. Calcifying arthritis
    5. Metachondromatosis

3. Etiological classification of chondrodysplasia punctata to aid clinician to reach an accurate diagnosis when CDP is detected (Irving et al. 2008)

1. Group 1 (inborn errors of metabolism)
    1. Group 1a (abnormalities of peroxisomal function)
        1. Rhizomelic CDP1 (*PEX7*, 6q22-q24)
        2. Rhizomelic CDP2 (*DHAPAT*, 1q42)
        3. Rhizomelic CDP3 (*AGPS*, 2q31)
        4. Zellweger syndrome (*PEX1*, *PEX2*, *PEX3*, *PEX5*, *PEX6*, *PEX10*, *PEX12*, *PEX13*; 7q21, 8q, 6q, 12p13.3, 6p21.1, 1p36, 17q11.2, 2p15 respectively)
    2. Group 1b (abnormalities of cholesterol synthesis)
        1. Greenberg dysplasia/HEM (*LBR*, 1q42.1)
        2. CDP Conradi-Hunermann (CDPX2) (*EBP*, Xp11.23-p11.22)
        3. CHILD syndrome (*NSDHL*, *EBP*; Xq28, Xp11.23-p11.22 respectively)
    3. Group 1C (other metabolic disorders)
        1. Mucolipidosis type II
        2. Mucopolysacharidosis type III
        3. GM1 gangliosidosis
2. Group 2 (disruption of vitamin K metabolism)
    1. Warfarin embryopathy
    2. Familial multiple coagulation factor deficiency (*VKORC1*, *GGCX*: 16p11.2, 2p12, respectively)
    3. Maternal vitamin K deficiency
    4. Fetal phenytoin exposure
    5. Keutel syndrome (Keutel et al. 1972; Monroe et al. 1999) (*MGP*, 12p13.1-p12.3)
        1. Abnormal calcification with cartilaginous calcification of the ears, nose, trachea, bronchi, and ribs
        2. Peripheral pulmonary stenosis
        3. Sensorineural hearing loss
        4. Short-terminal phalanges
        5. Developmental delay and seizures, secondary to intracerebral calcification
    6. CDP X-linked recessive/brachytelephalangic (CDPX1) (*ARSE*, Xp22.3)
3. Group 3 (chromosomal abnormalities)
    1. Trisomy 21
    2. Trisomy 18
    3. Other chromosomal aberrations
4. Unknown etiology
    1. Maternal systemic lupus erythematosus
    2. Fetal alcohol syndrome
    3. CDP-TM (tibia-metacarpal type) (Rittler et al. 1990)
    4. Dappled diaphyseal dysplasia
    5. Astley-Kendall dysplasia (Astley and Kendall 1980)
    6. Pacman dysplasia (Miller et al. 2003)

Clinical Features

1. Recessive rhizomelic form
    1. Classic RCDP1
        1. Skeletal abnormalities
            1. Severe symmetric shortening of the proximal limb segments (more severe in humeri than femora)
            2. Stippled (punctate) epiphyses involving knees, hips, elbows, shoulders, hyoid bone, larynx, sternum, and ribs
        2. Peripheral calcifications
        3. Facial dysmorphism
            1. Frontal bossing
            2. A short, saddle nose
        4. Ocular features
            1. Cataracts: the most common ocular defect developing in virtually all patients, usually present at birth or appear in the first few months of life and are progressive
            2. Optic atrophy
            3. Posterior embryotoxon
            4. Strabismus
            5. Adhesions between iris and cornea in the ring of Schwabe
        5. Severe failure to thrive with profound postnatal growth deficiency
        6. Gross developmental retardation
        7. Contractures and stiff, painful joints, causing irritability in infancy
        8. Other complications

1. Seizures
2. Recurrent respiratory tract infections caused by neurological compromise, aspiration, immobility, and a small chest with restricted expansion
3. Spastic quadriplegia
4. Ichthyotic skin changes
5. Cleft soft palate
6. Cervical spine stenosis
7. Congenital heart disease
8. Ureteropelvic junction obstruction

9. A high mortality
    1. About 60% survive the first year.
    2. About 39% survive the second year.
    3. Only a few survive beyond age 10.

2. Mild RCDP1
    1. Only a few patients reported
    2. Consistent features
        1. Chondrodysplasia
        2. Cataracts
    3. Variable expression
        1. Punctate calcifications
        2. Rhizomelia
        3. Mental and growth deficiency

2. X-linked dominant form (CDPX2) (Happle 1979; DiPreta et al. 2000)
    1. Phenotype
        1. Usually a mild form of the disease identified in adult females
        2. May be a stillborn
        3. Occurring almost only in females
        4. Presumably lethal in males, although a few affected males have been reported
    2. Lyonization (skewed X-chromosome inactivation) in females resulting in phenotypic variability and asymmetric findings (Shirahama et al. 2003)
    3. Showing increased disease expression in successive generations (anticipation): another striking clinical feature of CDPX2 that may be associated with skewed methylation
    4. Skin lesions
        1. The hallmark of the X-linked dominant form
        2. Congenital ichthyosiform erythroderma, distributed in a linear or blotchy pattern
        3. Systematized atrophoderma mainly involving the fair follicles
        4. Circumscribed alopecia
        5. Sparse eyebrows and lashes
        6. Nails: flattened and split into layers
    5. Epiphyseal calcification in the first year of life
    6. Limb shortening
        1. Rhizomesomelic
        2. Usually asymmetric
        3. Severely affected infants with bilateral findings resembling those of RDCP1
    7. Other later signs
        1. Palmoplantar keratosis
        2. Follicular atrophoderma
        3. Cataracts (Happle 1981): usually asymmetric and often unilateral- versus rhizomelic-type cataracts tend to be symmetric and bilateral
        4. Tooth and bone abnormalities
3. X-linked recessive chondrodysplasia punctata, brachytelephalangic type (CDPX1) (Braverman et al. 2014)
    1. Clinical reports available so far are mainly those of patients who are nullisomic for Xp22.3 in which chondrodysplasia punctata is part of a complex phenotype due to a "contiguous gene syndrome"
    2. Wide spectrum of manifestations, ranging from aborted fetus, neonatal death, midfacial hypoplasia, and brachytelephalangy (Brunnetti-Brunetti-Pierri et al. 2003)
    3. Facial anomalies with severe nasal hypoplasia
    4. Short stature
    5. Cardinal manifestations
        1. Epiphyseal stippling
        2. Hypoplasia of the distal phalanges
    6. Abnormalities of proximal and middle phalanges after healing of the punctate calcifications: typical diagnostic signs
    7. Without limb shortening or cataracts
    8. Presence of ichthyosis attributed to the involvement of the STS gene in the patients with Xp deletion
    9. Mild ichthyosis that improves with age: may be part of the CDPX phenotype

4. Chondrodysplasia punctata, tibia-metacarpal type (Rittler et al. 1990; Shukla and Phadke 2015)
    1. Short tibia
    2. Sort metacarpals
    3. Punctate epiphyseal calcifications noted at birth
    4. Abnormal face (flattened midface and nose)
    5. Short hands
    6. Normal height
    7. Normal mentation

Diagnostic Investigations

1. Radiography (Spranger et al. 2002)
    1. Classic RCDP1
        1. Bilateral shortening of the humerus and to a lesser degree the femur
        2. Punctate calcifications in the epiphyseal cartilage at the knee, hip, elbow, shoulder, hyoid bone, larynx, sternum, and ribs
        3. Radiolucent coronal clefts of the vertebral bodies that represent unossified cartilage
        4. Abnormal epiphyses and flared and irregular metaphyses secondary to resolved punctate calcification after age 1–3 years
    2. Tibia-metacarpal type
        1. Shortened and bowed tibia and radii
        2. Overgrowth of the fibulae
        3. Ulnar hypoplasia
        4. Calcific stippling of the proximal bones
        5. Punctate calcifications of the trachea, thyroid cartilage, entire spine, and sacrum
        6. Clefting (coronal and/or sagittal) of the vertebral bodies
        7. Symmetrical brachymetacarpy: shortened 2nd, 3rd, and 4th metacarpals
        8. Shortened radial head
        9. Patella dislocation
    3. Chondrodysplasia punctata brachytelephalangic type (Ochiai et al. 2013)
        1. Skeletal survey
            1. Hypoplastic distal phalanges
            2. Diffuse stippling of the spine and proximal femora
        2. 3D CT scan: subluxation and multiple punctata in the cervical spine and atlantoaxial subluxation
    4. X-linked recessive CDPX2 (Mundinger et al. 2009; Jurkiewicz et al. 2013)
        1. Chondrodysplasia (symmetrical or asymmetrical shortening of long bones)
        2. Nasal/midface hypoplasia
        3. Epiphyseal stippling
            1. Punctate calcification of cartilage, including airway
            2. Diffuse paravertebral calcifications as well as around joints, in the cartilages of larynx, trachea, and nose
        4. Articular contractures
        5. Scoliosis
        6. Vertebral anomalies
        7. Platyspondylia
        8. Deformed feet
        9. Distal phalangeal hypoplasia
2. Biochemical/molecular studies
    1. RCDP1 (Braverman et al. 2010)
        1. Deficiency of red blood cell plasmalogens
        2. Increased plasma concentration of phytanic acid
        3. Deficiencies in plasmalogen biosynthesis and phytanic acid hydroxylation in cultured skin fibroblasts
        4. PEX7 receptor defect in RCDP1 predicted by the following:
            1. Deficiency of plasmalogens in red blood cells
            2. Increased plasma concentration of phytanic acid
            3. Normal plasma concentration of very long-chain fatty acids
        5. Molecular genetic analysis: *PEX7* gene mutation analysis and sequencing (Motley et al. 2002)
    2. RCDP2
        1. Deficiency of the peroxisomal enzyme dihydroxyacetone phosphate acyltransferase (DHAPRT) in cultured skin fibroblasts
        2. *DHAPRT* gene mutation analysis by sequencing of coding regions
    3. RCDP3: deficiency of the peroxisomal enzyme, alkyl-dihydroxyacetone phosphate

synthase (ADAPS) in cultured skin fibroblasts
1. Deficiency of the peroxisomal enzyme, alkyl-dihydroxyacetone phosphate synthase (ADAPS) in cultured skin fibroblasts
2. *ADHAPS* gene mutation analysis

4. X-linked dominant form (CDPX2)
1. Diagnosis confirmed by measuring the plasma concentration of sterols which show accumulation of precursors, 8(9)-cholesterol and 8-dehydrocholesterol
2. Identify molecular defect in human *EBP* in CDPX2 patients

5. X-linked recessive form (CDPX1): ARSE gene mutation analysis

Genetic Counseling

1. Recurrence risk
1. Patient's sib
1. Autosomal recessive RCDP1: 25%
2. Autosomal dominant form: not increased unless one of the parents is affected
3. X-linked recessive form: 50% of brothers affected when the mother is a carrier (Braverman et al. 2014)
4. X-linked dominant form
1. 50% of sisters and brothers (lethal) affected when the mother is a carrier
2. Possibility of an apparently normal mother being a carrier to be considered when examining seemingly sporadic cases

2. Patient's offspring
1. Autosomal recessive RCDP1: do not reproduce
2. Autosomal dominant form: 50%
3. X-linked recessive form: 50% risk of daughters to be carriers; none of sons will be affected
4. X-linked dominant form: affected mother; 50% of sons affected (lethal in male), 50% of daughters affected

2. Prenatal diagnosis
1. Radiography
1. Stippling of the bones of the extremities and pelvis
2. Abnormalities of the vertebral bodies

2. Ultrasonography (Argo et al. 1996)
1. Rhizomelic form
1. Severe rhizomelic limb shortening
2. Punctuate epiphyseal calcifications
3. Associated sonographic findings: profound hypoplasia of the humeri, metaphyseal flaring, a flattened midface, joint contracture, clubfoot deformity, and hydramnios

2. Nonrhizomelic form (Pradhan et al. 2002)
1. Asymmetric, variable limb shortening without a clear pattern of rhizomelia or mesomelia
2. Calcifications in the long-bone epiphyses, which may be recognizable in the second trimester or may not be recognizable even in the third trimester
3. Other sonographic findings: spinal deformities, frontal bossing, a depressed nasal bridge, ascites, and polyhydramnios

3. X-linked dominant form
1. Polyhydramnios
2. Growth retardation
3. Prenatal detection of asymmetric shortening and bowing of the long bones and cartilage stippling should raise the possibility of CPDX2 in female fetuses, especially because the majority of such cases involve de novo mutations (Lefebvre et al. 2015)

3. Biochemical studies
1. Assays of plasmalogen biosynthesis in cultured chorionic villi or amniocytes for pregnancies at 25% risk for RCDP1
2. Enzyme activity of alkyl-dihydroxyacetone phosphate synthase (ADHAPS) and subcellular localization of peroxisomal thiolase performed on uncultured chorionic villi

3. Biochemical test of DHAPAT synthase deficiency in amniotic fluid at 13 weeks gestation in RCDP family (Brookhyser et al. 1999)
4. Fetal MRI: shows cervical spinal cord compression in a fetus with CDP-B (Ochiai et al. 2013)
5. Molecular prenatal diagnosis in X-linked dominant chondrodysplasia punctata to identify disease-causing *EBP* mutation in the fetus (Whittock et al. 2003)

3. Management
   1. Health supervision for children with rhizomelic chondrodysplasia congenita (White et al. 2003)
   2. Mainly supportive
   3. G-tube placement for poor feeding and recurrent aspiration
   4. Cataract extraction to preserve vision
   5. Orthopedic procedures to correct contractures to improve function
   6. X-linked dominant form
      1. Emollients for ichthyosis
      2. Splinting for clubbed feet
      3. Surgery for polydactyly
      4. Ophthalmological care for cataracts

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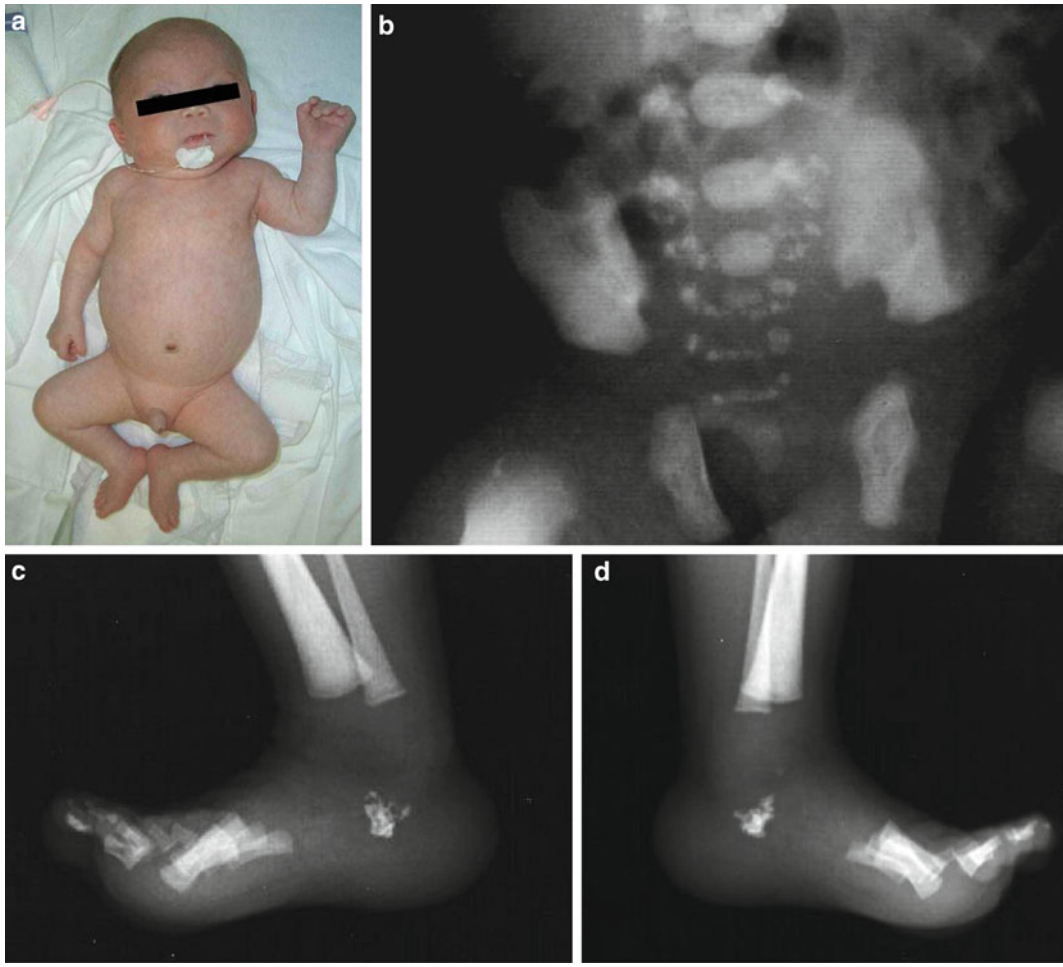


Fig. 1 (**a**–**d**) Patient 1 (a Japanese newborn boy) with X-linked recessive form of chondrodysplasia punctata. Radiographs show paravertebral and calcaneus punctate calcification

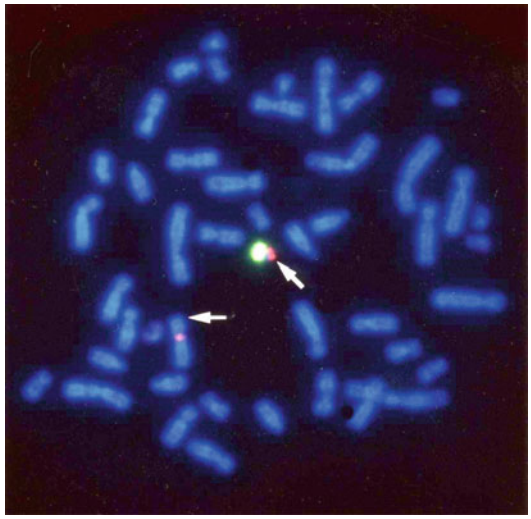


Fig. 2 FISH (patient 1) with a SHOX (short stature homeobox-containing gene) probe for Xp22.3 (*a pink signal*) and Yp11.3 (*a pink signal*) showing a deleted pink Xp22.3 signal. The *pink signal* in the X chromosome is an X peri-centromere probe (SXZ1) and the *green signal* is a Yq12 probe (DXZ1)

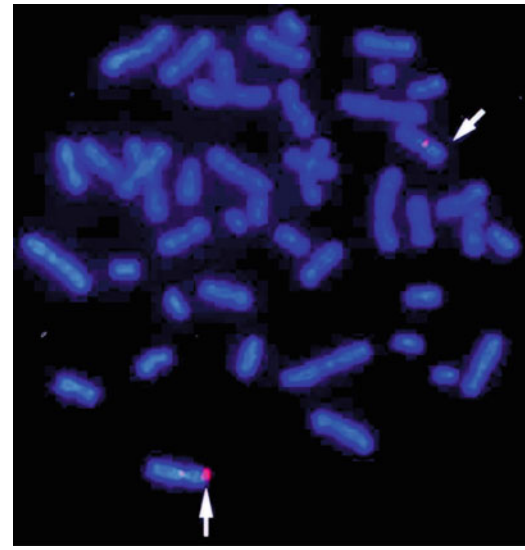


Fig. 3 The mother of patient 1 is a carrier of del(X) (p22.3p22.3) (SHOX-). Her FISH showed that a red signal (a probe for Xp22.3; SHOX gene) is deleted in one of her X chromosomes

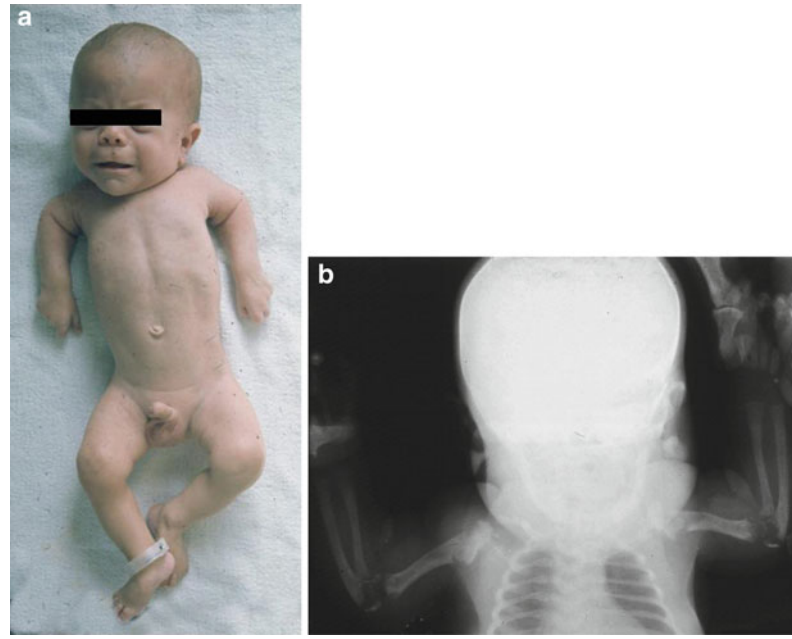


Fig. 4 (**a**, **b**) A neonate with rhizomelic form of chondrodysplasia punctata, showing short humeri and punctate calcifications in the shoulder and/or elbow joints illustrated by radiograph

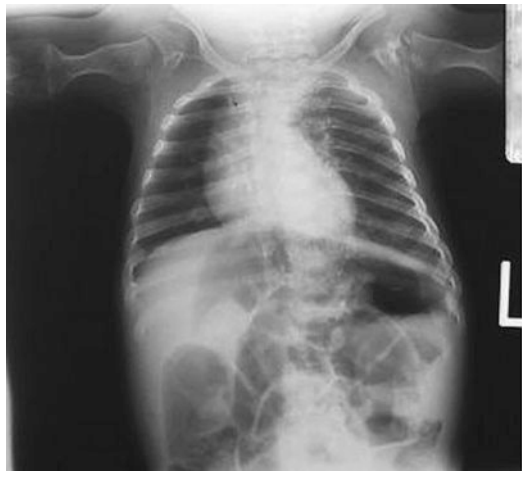


Fig. 5 Radiograph of another neonate with rhizomelic form of chondrodysplasia punctata, showing similar radiographic features

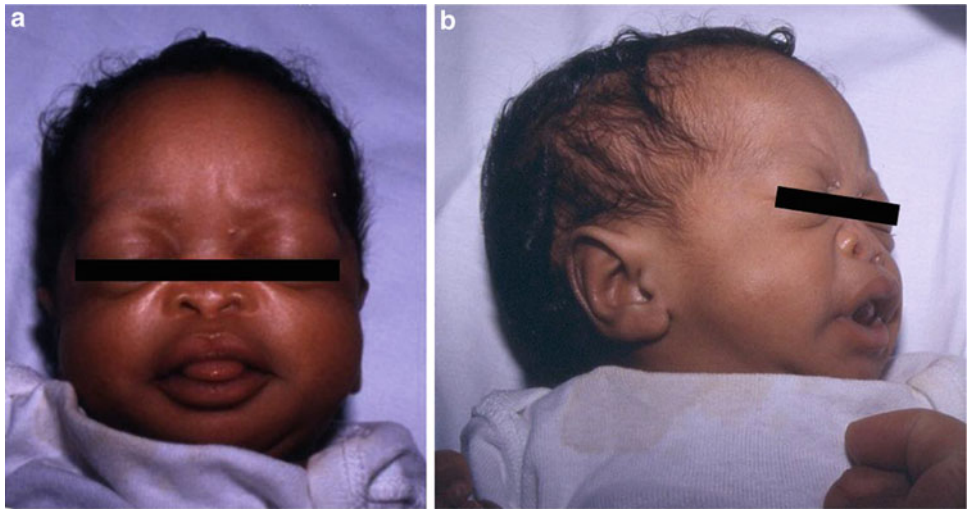
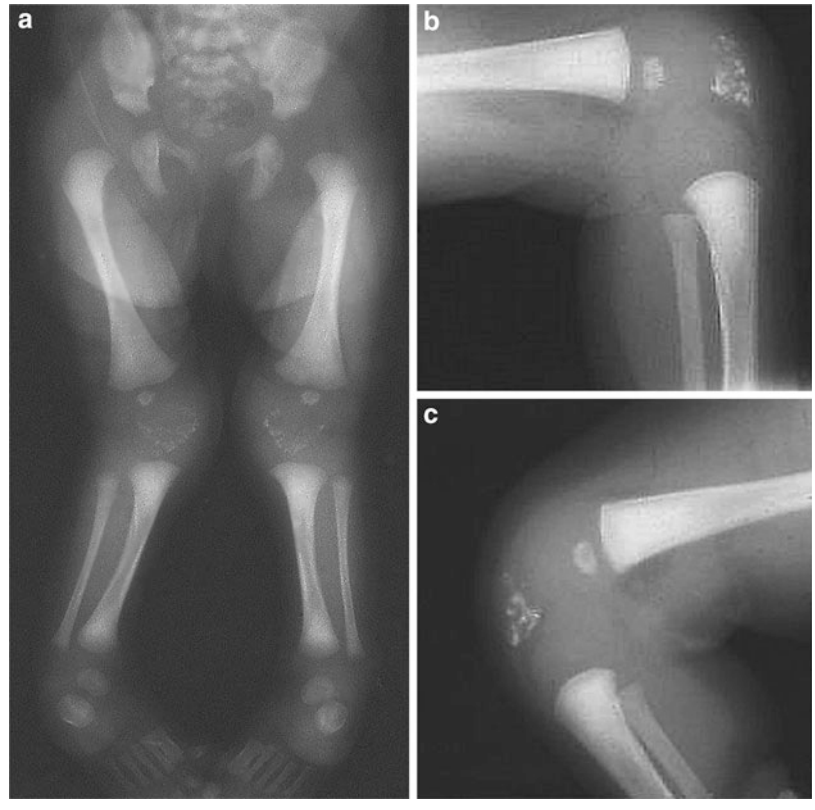


Fig. 6 (**a**, **b**) Another neonate with chondrodysplasia punctata showing depressed nasal bridge and underdeveloped nasal cartilage. The infant has punctate calcifications in the proximal femoral heads



Figs. 7 (**a**–**c**) Radiographs of a child with an autosomal dominant chondrodysplasia punctata showing punctate calcifications in the knees

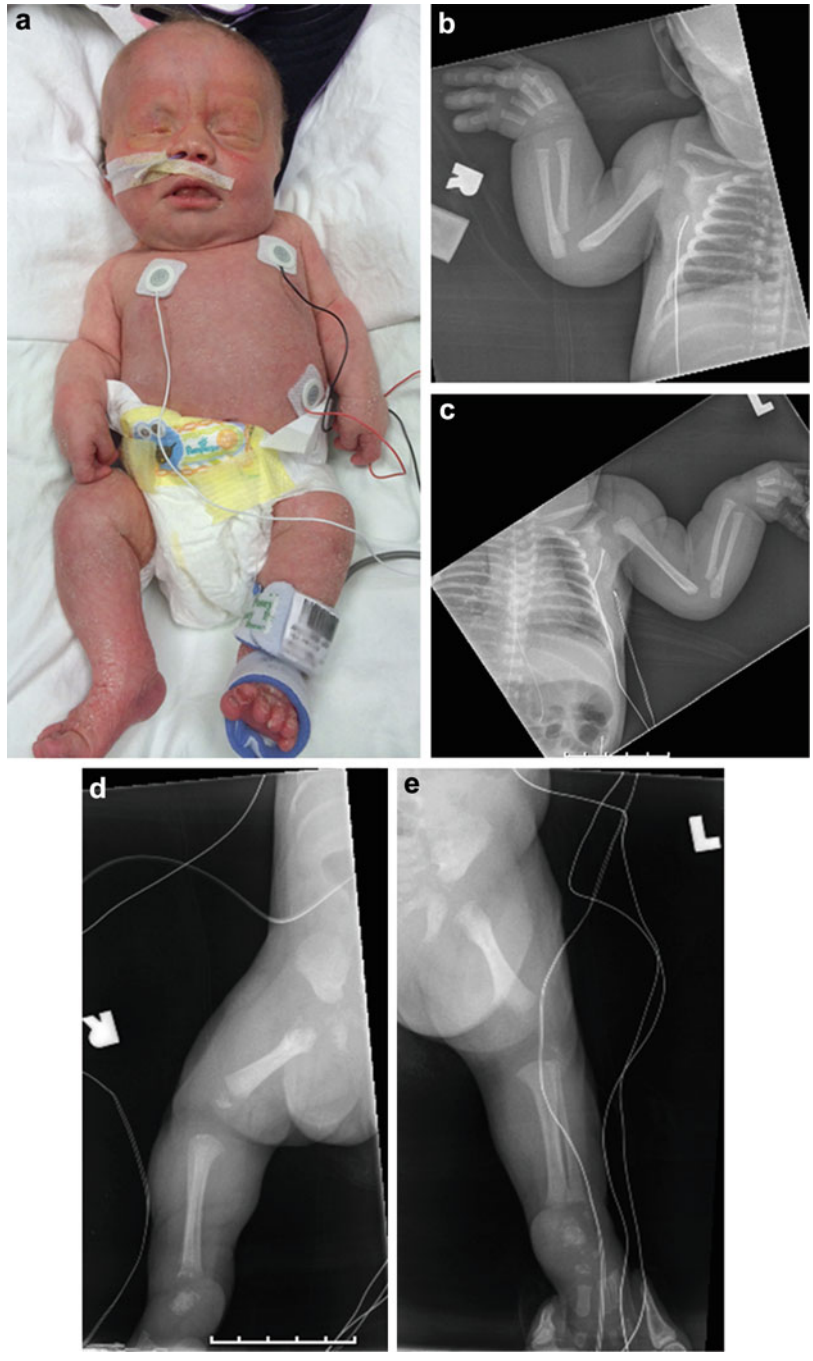


Fig. 8 (**a**–**e**) This Caucasian newborn baby girl (**a**) was born at 36 weeks' gestation secondary to polyhydramnios. The baby was noted to have rhizomelic shortening of the extremities. The radiographs (**b**–**e**) showed multiple punctuate calcifications (stipplings) throughout spinal column and in the epiphyses of the long bones such as proximal humerus and proximal and distal femurs and calcaneus and other tarsal bones. The skin showed congenital ichthyosiform erythroderma. EBP sequencing performed by Prevention Genetic Laboratory showed that the patient is heterozygous in the *EBP* gene for a sequence variant defined as c.328 C > T that is predicted to result in the premature protein termination (p.R110X). This variant was previously reported to be pathogenic for chondrodysplasia punctata (Grange et al. 2000; Hellenbroich et al. 2007). EBP is the only gene currently known to be associated with Conradi-Hunermann syndrome (CDPX2) (chondrodysplasia punctata X-linked dominant form) (Courtesy of Dr. Gerald Whitton)

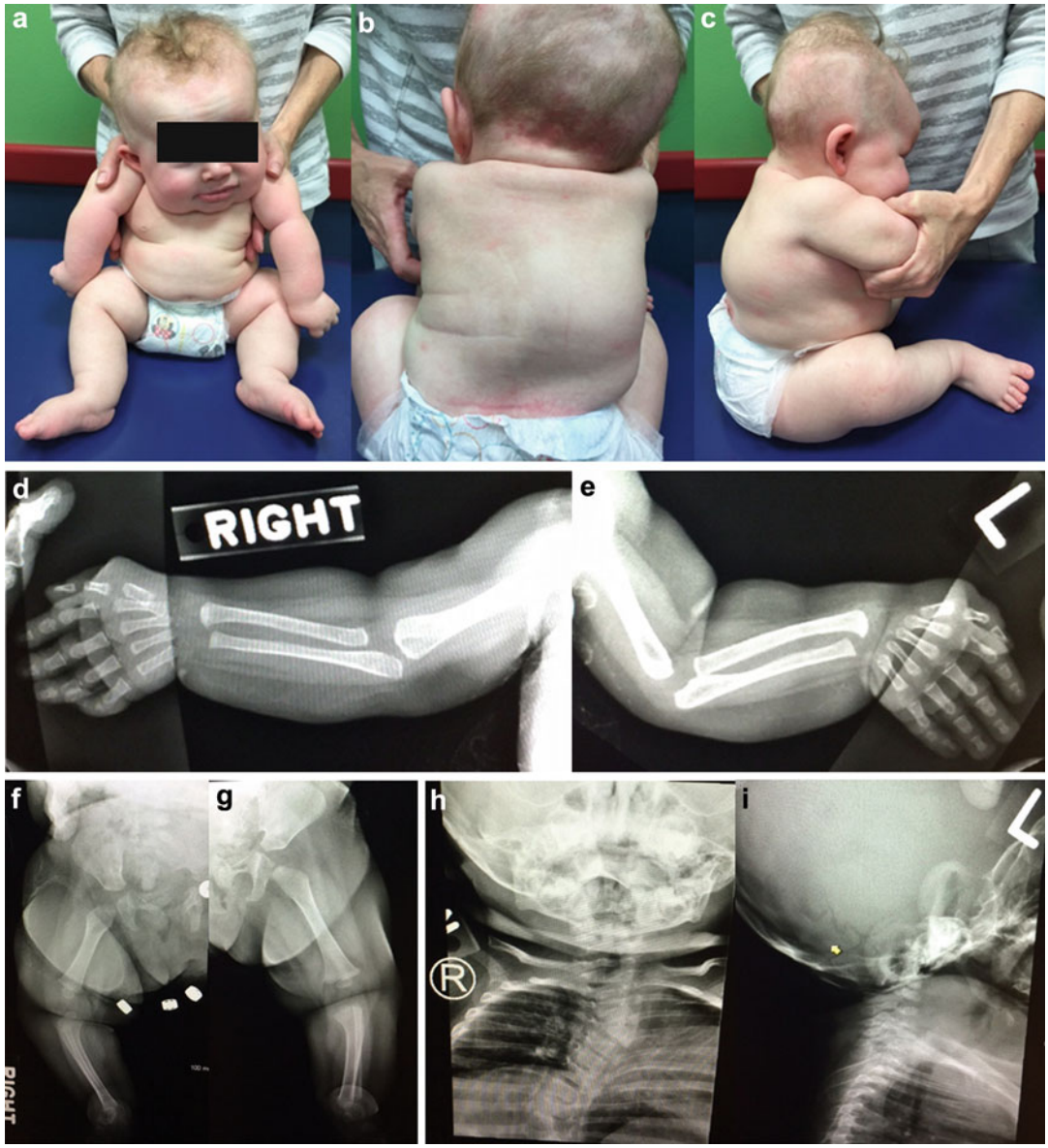


Fig. 9 (**a**–**i**) The infant was evaluated again at 10 months of age with the surrogate mother who had implanted an embryo from an unknown couple donor. She was short with rhizomelic shortening of the extremities, extremely short neck, and severe kyphoscoliosis. The wrists were pronated with ulnar deviation. The head was large and misshaped (plagiocephaly) with frontal bossing, flat and broad nasal root, and a large occipital hemangioma. The scalp hairs were coarse and twisted (**a**–**c**). Radiographs at 10 months of age showed rhizomelic shortening of the long bones, short neck, kyphoscoliosis, and loss of characteristic stippled epiphyses (**d**–**i**)

Chromosome Abnormalities in Pediatric Solid Tumors

Contents

Consistent chromosome abnormalities have been described in many pediatric solid tumors. These findings led to direct molecular investigation and a better understanding of tumor pathogenesis. Clinical correlation often produced useful prognostic information (Karnes et al. 1992).

Synonyms and Related Disorders

CNS primary tumor; Ewing sarcoma; Fibrosarcoma; Neuroblastoma; Osteosarcoma; Other pediatric solid tumors; Rhabdomyosarcoma; Retinoblastoma; Sarcomas; Wilms' tumor

Genetics/Basic Defects

1. Somatic mutation theory of cancer (Mertens et al. 1994):
    1. Resulting from the accumulation of specific genetic changes
    2. Several lines of evidence:
        1. Monoclonal origin of most tumors, suggesting that they derive from a single progenitor cell
        2. Several tumors occurring not only sporadically but also as familial hereditary traits
        3. Mutagenic nature of most carcinogenic agents, at least in experimental systems
        4. Acquired genetic changes in the tumor cells, many of which are detectable at the chromosome level and several of these mutations have been shown to be tumorigenic in experimental animals
2. Chromosome abnormalities in neoplastic cells:
    1. Technical improvement in basic cytogenetic techniques:
        1. Use of colchicine to arrest dividing cells in metaphase and hypotonic solutions to improve spreading of the chromosomes:
            1. Description of the correct chromosome number in humans
            2. The first specifically neoplasia-associated chromosome aberration, the Ph1 chromosome in chronic myeloid leukemia
        2. Introduction of chromosome banding techniques:
            1. Possible to identify individual chromosome pairs
            2. To detect and characterize even subtle rearrangements

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Clonal chromosome aberrations in neoplasms:
    1. Primary aberrations:
        1. Nonrandomly associated with particular tumor types.
        2. Sometimes observed as the sole karyotypic deviation.
        3. Thought to constitute early and essential events in carcinogenesis.
        4. Increased genomic instability thought to be one of the consequences of the acquisition of a primary cancer chromosome rearrangement.
        5. Many primary aberrations affect cellular oncogenes, often fusing them with other genes to encode hybrid proteins or disrupting the normal control sequences of the oncogene, causing its inappropriate expression.
    2. Secondary aberrations:
        1. Occurrence of new abnormalities facilitated by primary aberrations
        2. Nonrandom
        3. Distribution of the secondary aberrations dependent on both the primary abnormality and the tumor type in which they occur
    3. Cytogenetic noise:
        1. Resulting from acquired instability
        2. Random changes with little or no selective value
3. Mechanisms by which chromosomal aberrations arise (Albertson et al. 2003):
    1. Aberrations that lead to aneuploidy:
        1. Polyploidy
        2. Aneuploidy
        3. Reciprocal translocation
        4. Nonreciprocal translocation
        5. Amplification (double minutes)
        6. Amplification (HSR)
        7. Amplification (distributed insertions)
    2. Aberrations that leave the chromosome apparently intact:
        1. Loss of heterozygosity (LOH) (somatic recombination)
        2. Loss of heterozygosity (duplication/loss)
4. Identification of specific chromosome rearrangements in neoplasms:
    1. Leukemia and lymphoma:
        1. Crucial for more detailed studies utilizing molecular genetic techniques
        2. Possible to compare cytogenetic findings with morphologic, immunologic, and clinical parameters such as the response to therapy and survival
        3. Diagnostic and prognostic implications of karyotyping
    2. Solid tumors:
        1. In general, more complex karyotypes observed in solid tumors
        2. Have distinct patterns of primary and secondary aberrations closely associated with histopathologic entities
        3. Identification of only a few genes as a consequence of recurrent structural rearrangements
        4. Fusion of transcription factor gene with other loci, a common feature
        5. Tumor suppressor genes:
            1. Important in solid tumors
            2. Thought to encode inhibitors of unrestrained growth
            3. Behave in a recessive manner at the cellular level (i.e., loss or structural disruption of both wild-type alleles is required to unleash a neoplastic phenotype)
5. A new unifying concept called cellular pliancy as a possible explanation for susceptibility to cancer and the developmental origin of pediatric solid tumors (Chen et al. 2015):
    1. Diversity of pediatric solid tumors:
        1. Cellular diversity:
            1. Remarkably diverse in histologic features
            2. To define the genetic lesions in different pediatric solid tumors, the inter- and intra-tumor heterogeneity, and the order of events that cause malignant transformation during the development of the retina, bone, neural crest, muscle, and other cellular lineages
        2. Clinical diversity: can provide important clues about the developmental origins of pediatric solid tumors

3. Genetic diversity
4. Reprogramming the tumor genome: needs a detailed understanding of the genomic landscape of pediatric solid tumors that has emerged with next-generation sequencing over the past 5 years

2. Epigenetics: emerged as a major focus area in pediatric solid tumor research because of:
   1. Striking changes in the epigenetic landscape after inactivation of tumor suppressor genes such as *RB1*
   2. Identification of recurrent mutations in epigenetic modulators such as *BCOR* and *ATRX*
3. Cellular pliancy (unify the findings in pediatric solid tumor genomic and integrate them with our understanding of developmental competence and lineage specification)
4. Clinical genomics: important to incorporate whole-genome sequencing, whole-exome sequencing, and RNA sequencing in future clinical genomics efforts to identify potentially druggable mutations and to advance our understanding of the genetic underpinnings of pediatric solid tumors

6. Retinoblastoma (RB) (Mertens et al. 1994):
   1. A prototype tumor for understanding basic concepts in cancer genetics
   2. Genetics of retinoblastoma:
      1. Thought to be a single-gene disorder caused by mutation of the *RB1* gene (Carlson and Desnick 1979)
      2. Sporadic, nonhereditary form in most cases:
         1. Unilateral or unifocal retinoblastoma
         2. A mutation in the RB1 locus which occurred later in embryogenesis
      3. Hereditary form (one third of tumors):
         1. Bilateral or multifocal retinoblastoma
         2. Predisposition inherited as an autosomal dominant trait
         3. Mutations inherited from a carrier parent in 25% of the cases
         4. A new mutation occurring very early in embryogenesis in 75% of cases
         5. Overall estimates of the penetrance of the trait: 85–95%
   3. Retinoblastoma gene, *RB1*:
      1. The first cancer predisposition gene to be cloned
      2. Chromosome map: 13q14
      3. More than 100 different mutations reported to date:
         1. Missense mutations
         2. Nonsense mutations
         3. Splice-site mutations
         4. Small and large deletions
   4. Knudson's "two-hit hypothesis" of tumorigenesis (Knudson 1971; Horsthemke 1992):
      1. In the unaffected individual, both RB1 genes are intact and serve as guardians of the retina.
      2. Retinoblastoma develops as a result of two separate mutations.
      3. Sporadic tumors: two separate mutations occurring somatically in the same retinal cell.
      4. Heritable retinoblastoma: the first mutation is germinal and the second somatic.
   5. Inherited form of retinoblastoma:
      1. Critical gene for retinoblastoma located in band 13q14, suggested by cytogenetic analyses of tumor cells and lymphocytes
      2. Homozygous loss of DNA markers from 13q14 in tumor cells from individuals with familial retinoblastoma versus heterozygous loss of these DNA markers in normal cells, suggested by molecular genetic investigations
7. Neuroblastoma (NB):
   1. A malignant tumor derived from undifferentiated neural crest cells that are committed to differentiate into the sympathetic nervous system
   2. Inheritance:
      1. Sporadic in most cases
      2. A few clustered familial cases reported indicating an autosomal dominant inheritance with incomplete penetrance
   3. Molecular biology (Lee et al. 2003):
      1. The amplification (i.e., increased number of DNA copies) of the oncogene MYCN (N-myc), located on

chromosome 2p24, and changes in the normal diploid chromosomal content:
1. Both are correlated with disease prognosis and disease recurrence.
2. The amplification can be in the form of the double-minute chromosomes, which are extragenomic segments of DNA, or in homogeneously staining chromosomal regions.

2. Variable DNA content of neuroblastoma:
1. Near-triploid DNA index regardless of any clinical or biologic features predicts a smaller risk of progression to higher-stage diseases.
2. Diploid/tetraploid index tends to predict higher risk of progression or multiple relapses.

3. Other molecular markers (receptors for nerve growth factors) associated with neuroblastoma:
1. Trk A: associated with favorable neuroblastomas
2. Trk B: expressed in unfavorable neuroblastomas

8. Wilms' tumor (WT):
1. Biological pathways leading to the development of Wilms' tumor:
1. Complex
2. Involvement of several genetic loci:
1. Two genes on chromosome 11p: one on chromosome 11p13 (the Wilms' tumor suppressor gene, *WT1*) and the other on chromosome 11p15 (the putative Wilms' tumor suppressor gene, *WT2*)
2. Loci at 1p, 7p, 16q, 17p (the *p53* tumor suppressor gene), and 19q (the putative familial Wilms' tumor gene, *FWT2*)

2. Inheritance:
1. Sporadic in majority of cases (>95%).
2. Familial predisposition to Wilms' tumor is rare, affecting only1.5% of patients with Wilms' tumor.

3. Association with specific genetic disorders or recognizable syndromes:
1. WAGR syndrome:
1. Large constitutional deletions of chromosome 11p13
2. Tumor suppressor gene: *WT1*
3. Mechanism of gene inactivation: hemizygous deletion
4. Wilms' tumor incidence: >30%
5. Associated features: aniridia and genitourinary abnormalities
6. Mental retardation
7. Associated aniridia: caused by deletion of the *PAX6* gene in the 11p13 region in close proximity to *WT1* gene

2. Denys-Drash syndrome:
1. Chromosomal loss: 11p13
2. Tumor suppressor gene: *WT1*
3. Mechanism of gene inactivation: mutation (DNA-binding domain)
4. Wilms' tumor incidence: >90%
5. Associated features: pseudohermaphroditism, mesangial sclerosis, and renal failure

3. Beckwith-Wiedemann syndrome:
1. Chromosomal loss: 11p15
2. Tumor suppressor gene: (*WT2*/*BWS*)
3. Mechanism of gene inactivation: unknown
4. Wilms' tumor incidence: 5%
5. Associated features: organomegaly, hemihypertrophy, umbilical hernia, neonatal hypoglycemia, and other tumors such as hepatoblastoma

4. Perlman syndrome:
1. Renal dysplasia
2. Multiple congenital anomalies
3. Gigantism
4. Wilms' tumor

5. X-linked Simpson-Golabi-Behmel syndrome:
1. Overgrowth disorder
2. Caused by mutations in the *GPC3* gene located on Xq26
3. Overlapping physical features with Beckwith-Wiedemann syndrome
4. Wilms' tumor and other embryonal tumors

9. Primary tumors of the central nervous system (Mertens 1994):
    1. Primitive neuroectodermal tumors (PNETs):
        1. Homozygous inactivation of the *TP53* gene, a tumor suppressor gene located in 17p, secondary to i(17p): implicated in the development of several tumor types
        2. Molecular analyses indicating the existence of a second tumor suppressor gene, distinct from and distal to the *TP53* locus, which might be pathogenetically involved in a subset of primitive neuroectodermal tumors
    2. Gliomas:
        1. A tumor suppressor gene in 22q implicated as an essential event in the genesis of a number of neurogenic neoplasms.
        2. A candidate for such a role is *NF2*, thought to be mutated in neurofibromatosis type 2, a dominantly inherited disorder predisposing for gliomas, neurinomas, and meningiomas.

Clinical Features

1. Only retinoblastoma, neuroblastoma, and Wilms' tumor will be discussed here:
2. Retinoblastoma (Mertens 1994; Aerts et al. 2006):
    1. The most common malignant ocular tumor in childhood that affects approximately 1 in 18,000 children under 5 years of age in the USA (Devesa 1975)
    2. A rare malignant tumor arising from cells of the embryonal neural retina
    3. Develops only in infants and young children
    4. Unifocal retinoblastoma: presence of a single retinoblastoma
    5. Multifocal retinoblastoma: presence of more than one tumor (Lohmann and Gallie 2013):
        1. Unilateral: occurrence of multiple RB tumors in one eye
        2. Bilateral: occurrence of RB tumors in both eyes
        3. "Trilateral" retinoblastoma: occurrence of bilateral retinoblastoma plus a pinealoma
    6. Presenting signs:
        1. White papillary reflex (leukocoria): the most common presenting sign
        2. Strabismus: the second most common presenting sign
        3. Less common signs:
            1. Poor vision
            2. Orbital swelling
            3. Unilateral mydriasis
            4. Heterochromia iridis
            5. Glaucoma
            6. Orbital cellulitis
            7. Uveitis
            8. Hyphema or vitreous hemorrhage
            9. Nystagmus
    7. Retinoma-associated eye lesions ranging from retinal scars to calcified phthisical eyes resulting from spontaneous regression of retinoblastoma (include benign retinal tumors called retinocytoma or retinoma)
    8. Patients with germline RB1 mutations: at an increased risk of developing tumors outside the eye:
        1. Pinealomas
        2. Osteosarcomas
        3. Soft tissue sarcomas
        4. Melanomas
3. Neuroblastoma (Davidoff and Hill 2001; Lee et al. 2003):
    1. The most frequently occurring solid tumor in children
    2. Responsible for 8–10% of all cancers in children and approximately 15% of all pediatric cancer deaths
    3. 40% of cases diagnosed in children under 1 year of age who have a very good prognosis
    4. 60% in older children and young adult who have a poor prognosis despite advanced medical and surgical management

5. Amplification of *MYCN* gene found in neuroblastomas:
    1. A powerful prognostic indicator
    2. Associated with:
        1. Advanced stages of disease
        2. Rapid tumor progression
        3. Poor outcome
6. Clinical presentation:
    1. Variable presentation (Brodeur et al. 1997):
        1. Localized disease (one third to one fourth of cases)
        2. Metastatic disease (two thirds to three fourths of cases)
        3. Asymptomatic in a small number of patients
    2. Retroperitoneal and abdominal tumors (62–65%):
        1. A palpable mass
        2. Abdominal pain (34%)
        3. Weight loss (21%)
        4. Anorexia
        5. Vomiting
        6. Symptoms related to mass effect
    3. Thoracic tumors (14%):
        1. Dysphagia
        2. Cough
        3. Respiratory distress
    4. Pelvis (5%) and paraspinal tumors that compress the spinal cord:
        1. Urinary dysfunction
        2. Constipation
        3. Fetal incontinence
        4. Lower extremity weakness
    5. Neck tumors:
        1. Horner syndrome: present in patients with lesions in the cervical or upper thoracic sympathetic ganglia (1.7%)
        2. Airway distress
    6. Liver metastasis:
        1. Hepatomegaly
        2. Jaundice
        3. Abnormal liver function tests
        4. Abdominal pain
    7. Bone metastases and bone marrow involvement:
        1. Bone pain
        2. Palpable bony nodules
        3. Anemia
        4. Purpura
    8. Fever (28%)
    9. Lymph node metastases: palpable lymphadenopathy
    10. Retrobulbar and orbital metastases: periorbital ecchymoses
    11. Severe diarrhea refractory to standard treatment due to production of vasoactive intestinal peptide by tumor cells (4%)
    12. Acute cerebellar encephalopathy (2%):
        1. Cerebellar ataxia
        2. "Dancing eyes and dancing feet syndrome" (involuntary eye fluttering and muscle jerking)
        3. Myoclonic jerks
    13. Symptoms related to high catecholamine levels (0.2%):
        1. Hypertension
        2. Palpitations
        3. Flushing
        4. Sweating
        5. Malaise
        6. Headache
4. Wilms' tumor (Mertens 1994):
    1. The most common kidney cancer in childhood
    2. Represents about 6% of all childhood cancers in the USA
    3. Clinical presentation (Paulino 2014):
        1. Presence of an asymptomatic abdominal mass – the most common presentation:
            1. Usually affects one kidney with multiple tumor foci in 8% of cases
            2. Bilateral in 6% of cases
        2. Hypertension, gross hematuria, and fever observed in 5–30% of patients
        3. Hypotension, anemia, and fever in a small number of patients who have hemorrhaged into their tumor
        4. Rare respiratory symptoms related to the presence of lung metastases in patients with advanced-stage disease
    4. Association with congenital malformations:
        1. Found in 60% of the bilateral cases and 4% of the unilateral cases
        2. WAGR

3. Denys-Drash syndrome
4. Beckwith-Wiedemann syndrome
5. Perlman syndrome
6. X-linked Simpson-Golabi-Behmel syndrome

5. Likelihood of developing Wilms' tumor in aniridia patients:
   1. Aniridia patients without other anomalies: 1–2%
   2. Aniridia patients with WAGR syndrome: 25–40%

Diagnostic Investigations

1. Cytogenetic and molecular genetic techniques used in analyzing tumor materials from patients (Cooley et al. 2009):
   1. Conventional and molecular cytogenetic techniques most commonly used (Varella-Garcia 2003):
      1. Metaphase cytogenetics or karyotyping (G-, Q-, and R-bandings):
         1. Protein digestion and/or special dye generating banding pattern specific for each chromosome
         2. Identification of numerical and structural chromosomal anomalies
      2. Fluorescence in situ hybridization (FISH):
         1. A small, labeled DNA fragment used as a probe to search for homologous target sequences in chromosome or chromatin DNA
         2. Identification of the presence, number of copies per cell, and localization of probe DNA
         3. Applicable to interphase cells
      3. Comparative genomic hybridization (CGH):
         1. Comparative hybridization of differentially labeled total genomic tumor DNA and normal reference DNA to normal human metaphases used as templates
         2. Detection of variant DNA copy numbers at the chromosome level
         3. Applicable to fresh or preserved specimens
      4. Multicolor karyotyping (M-FISH, SKY):
         1. Hybridization with 24 differentially labeled, chromosome-specific probes allowing the painting of every human chromosome in a distinct color
         2. Detection of rearrangements involving one or more chromosomes within individual metaphase spreads
         3. Accurate origin identification of all segments in complex rearrangements
         4. Clarification of marker chromosomes
   2. Other techniques:
      1. Flow cytometry
      2. Reverse transcriptase-polymerase chain reaction (RT-PCR)
      3. Quantitative PCR
      4. Southern blot analysis of gene rearrangements
      5. Loss of heterozygosity (LOH) analysis
      6. Clinical utilization of high-resolution single-nucleotide polymorphism (SNP)-based oligonucleotide arrays in diagnostic studies of pediatric patients with solid tumors (Dougherty et al. 2012)
      7. Restriction landmark genome scanning
      8. Representational difference analysis
      9. cDNA gene expression microarrays
      10. Proteomic methods:
          1. Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF)
          2. Surface-enhanced laser desorption/ionization-time of flight (SELDI-TOF)
2. Cytogenetic studies in retinoblastoma:
   1. Cytogenetically visible changes of 13q14: infrequent in retinoblastoma
   2. Deletions or unbalanced translocations leading to loss of 13q14 band (10%)
   3. Monosomy 13 (10%)

4. i(6p), mostly detected as a supernumerary isochromosome (one third of cases)
5. Gain of 1q material (one third of cases)
6. Bone marrow cytogenetic (Barros et al. 2012):
    1. Del(13q), i(6p), +1, monosomy 16, dup (5q), dic(15;22), and add(14q).
    2. These complex chromosome abnormalities may be related to the aggressiveness of the disease.
7. Cytogenetic aberrations in retinoblastoma:
    1. Secondary to *RB1* mutations
    2. More related to tumor progression than to tumor establishment

3. Other studies for retinoblastoma:
    1. Indirect ophthalmoscopy to examine the fundus of the eye to detect retinomas, preferably by a retinal specialist
    2. Imaging studies (CT, MRI, ultrasonography) to support the diagnosis and stage the tumor
    3. Histopathological examination to confirm the diagnosis
    4. Direct DNA testing of the RB1 gene in WBC DNA:
        1. Identify a germline mutation in about 80% of individuals with a hereditary predisposition to retinoblastoma
        2. Probability of detection of the RB1 gene mutation in an index case dependent on the following:
            1. Whether the tumor is unifocal or multifocal
            2. Whether the family history is positive or negative
            3. The sensitivity of the testing methodology
4. Cytogenetic studies in neuroblastoma (Maris and Matthay 1999; Davidoff and Hill 2001; Lee et al. 2003; Schwab et al. 2003):
    1. Identification of multiple cytogenetic abnormalities in neuroblastoma:
        1. Allelic losses on chromosomes 1p (particularly 1p36), 11q, 14q, 7q, 2q, 3p, and 19q.
        2. Allelic gains on chromosomes 17q, 18q, 1q, 7q, and 5q.
        3. Aberrations involving chromosomes X,3, 19, and del(1p) could be considered early events, whereas those involving chromosomes 9, 13, 15, 18, 20, and 21 were often late events (Betts et al. 2005).
    2. Hyodiploid, triploid, or "near-triploid", or "near-tetraploid" in modal chromosome number:
        1. Majority (55%) with triploid or "near-triploid" (a chromosome number between 58 and 80)
        2. Remainder with "near-diploid" (35–57 chromosomes) or "near-tetraploid" (81–103 chromosomes)
    3. Frequent partial 1p monosomy (70–80% of cases) with most commonly deleted region being between 1p32 and 1p36
    4. Gain on the long arm of chromosome 17 (17q):
        1. Probably the most common genetic abnormality in neuroblastomas
        2. Occurring in approximately 75% of primary tumors
        3. Most often resulting from an unbalanced translocation of this region to other chromosomal sites, most frequently 1p or 11q
        4. A powerful independent finding of adverse outcome
    5. Deletions of the long arms of chromosomes 11 (11q) and 14 (14q):
        1. Appears to be common in neuroblastomas
        2. Both inversely related to *MYCN* amplification
    6. Frequent presence of extrachromosomal double-minute chromatin bodies (DMs) or homogeneously staining regions (HSRs):
        1. Cytogenetic evidence of gene amplification
        2. Amplified region derived from the distal short arm of chromosome 2 (2p24) that contains the *MYCN* proto-oncogene
    7. Chromosome imbalances and alterations of AURKA and MYCN genes in children

with neuroblastoma (İnandıklıoğlu et al. 2012):

1. Some 72% of the cells had structural aberrations and only 28% had numerical changes in patients.
2. Structural aberrations consisted of deletions, translocations, breaks, and fragility in various chromosomes, 84% and 52% of the patients having deletions and translocations, respectively.
3. Among these expressed chromosome abnormalities, there was a higher frequency at 1q21, 1q32, 2q21, 2q31, 2p24, 4q31, 9q11, 9q22, 13q14, 14q11.2, 14q24, and 15q22 in patients.
4. Thirty two percent of the patients had chromosome breaks, most frequently in chromosomes 1, 2, 3, 4, 5, 8, 9, 11, 12, 19, and X.
5. Aneuploidies in chromosomes X, 22, 3, 17, and 18 were most frequently observed.
6. Numerical chromosome abnormalities were distinctive in 10.7% of sex chromosomes.
7. Fragile sites were observed in 16% of patients.

5. Other studies for neuroblastoma:
   1. Imaging studies:
      1. Chest radiography
      2. Ultrasound
      3. CT
      4. MRI
      5. Radionucleotide bone scan
   2. Blood tests:
      1. Elevated urinary and serum catecholamine metabolites:
         1. Homovanillic acid (HVA)
         2. Vanillylmandelic acid (VMA)
      2. Abnormal liver function tests
   3. Molecular genetic testing (Castel et al. 2007):
      1. Array CGH analysis: a pangenomic technique allowing insights into gains and losses with high resolution
      2. Multiplex ligation-dependent probe amplification (MILPA)

6. Cytogenetic studies in Wilms' tumor:
   1. A near-diploid chromosome count.
   2. Triploid-tetraploid karyotypes in a few cases with tendency to have an anaplastic morphology.
   3. Numerical aberrations:
      1. Trisomy 12: particularly frequent
      2. Followed by trisomies 8, 6, 7, 13, 20, and 17
   4. Structural rearrangements:
      1. Involve all chromosomes except the Y chromosome
      2. Recombinations of 11p (>20%):
         1. Vast majority of the breakpoints assigned to 11p13 and 11p15, indicating these loci are important in sporadic Wilms' tumor
         2. Loss of heterozygosity studies indicating that alleles from 11p13 and 11p15 are often lost in Wilms' tumor
      3. Loss of the long arm of chromosome 16 occurring in about 20% of Wilms' tumors: associated with poor prognosis independent of stage or tumor histology
   5. SNP-based arrays complement classic cytogenetics in the detection of chromosomal aberrations in Wilms' tumor (Zin et al. 2012).
7. Other studies in Wilms' tumor:
   1. Renal ultrasound to monitor Wilms' tumor
   2. Abdominal CT scanning to determine the tumor's origin, lymph node involvement, bilateral kidney involvement, and invasion into major vessels (e.g., inferior vena cava or liver metastases)
   3. Chest radiography to detect lung metastases
   4. Histopathological examination to confirm the diagnosis
   5. Further studies of certain patients with either Wilms' tumor or associated anomalies (Coppes and Egeler 1999):
      1. Hemihypertrophy/Beckwith-Wiedemann syndrome: uniparental disomy studies to evaluate constitutional or somatic alterations of 11p15.

2. WAGR syndrome: molecular evaluation of the 11p13 region if chromosomal studies do not reveal a deletion:
    1. Fluorescence in situ hybridization (FISH)
    2. Pulsed-field electrophoresis
3. Denys-Drash syndrome: molecular evaluation of *WT1* to determine whether the patient indeed carries a constitutional mutation. If the mutation is present, family members need to be screened.
4. Aniridia:
    1. Cytogenetic analysis and molecular evaluation of the WAGR region by FISH or pulsed field to rule out contiguous deletion of *Pax6* and *WT1*
    2. No further screening for Wilms' tumor if *Pax6* mutation is identified in isolated cases of aniridia

8. Cytogenetic studies of primary tumors of the central nervous system (Mertens 1994):
    1. Primitive neuroectodermal tumors:
        1. Near-diploid in most tumors
        2. I(17q): the most consistent rearrangement
    2. Gliomas:
        1. Mostly astrocytomas and ependymomas
        2. No specific structural rearrangement found
        3. Loss of 1p and gain of 1q found in a subset of tumors
        4. Loss of chromosome 22 common in childhood gliomas
        5. Loss of material from chromosome 22, either numeric or structural aberrations, found recurrently in rhabdoid tumors, meningiomas, and neurinomas
        6. Single-nucleotide polymorphism (SNP) arrays (Paxton et al. 2015):
            1. Allow for a whole-genome view of complex copy number changes and loss of heterozygosity
            2. Enable observations of the genomic landscape beyond 1p19q deletions and EGFR amplification
9. Cytogenetic studies in hepatoblastoma (Mertens et al. 1994):
    1. Trisomy 2 or duplications of part of 2q: detected in half of the cases
    2. Trisomy 20
    3. Duplication of 8q through either i (8q) formation or trisomy 8
10. Cytogenetic studies in sarcomas (Bennicelli and Barr 1999; Esparza 2012):
    1. Ewing sarcoma/primitive neuroectodermal tumor (Davidoff and Hill 2001):
        1. Reciprocal translocation t(11;22)(q24;q12):
            1. Characteristic primary rearrangement.
            2. Found in nearly 90% of the tumors.
            3. Causing a fusion of the transcription factor gene *FLI1* on chromosome 11 with *EWS* on chromosome 22 (*FLI1-EWS*, a fusion transcript). Only the chimeric gene expresses on the derivative chromosome 22 which contains a sequence encoding a DNA-binding domain from *FLI1*.
        2. t(21;22)(q22;q12) and *ERG-EWS*
        3. t(7;22)(p22;q12), *ETV1-EWS*
        4. t(17;22)(q12;q12), *E1AF-EWS*
        5. t(2;22)(q33;q12), *FEV-EWS*
    2. Additional chromosome changes:
        1. Trisomy 8
        2. Der(16)t(1;16)(a10-q21;q10-13), leading to gain of 1q and loss of 16q
    3. Congenital or infantile fibrosarcoma (Mertens et al. 1994):
        1. t(12;15)(p13;q25), *ETV6-NTRK3*
        2. Hyperdiploid with few or no structural rearrangements
        3. Nonrandom numerical changes:
            1. Trisomies 11 and 20, the most frequent changes
            2. Trisomies 17 and 8
    4. Osteosarcoma (Mertens et al. 1994):
        1. Highly complex karyotypes in the majority of cases
        2. Chromosome number in the triploid-tetraploid range
        3. Most common numeric aberrations involving −3, −10, −13, and −15

4. Structural rearrangements involving chromosome arms 1p, 1q, 3p, 3q, 7q, 11p, 17p, and 22q
5. Presence of many undefined chromosome markers

5. Rhabdomyosarcoma (Mertens et al. 1994):
   1. The most common soft tissue sarcoma in childhood
   2. Alveolar subtype:
      1. Most contain one or two recurring translocations, namely, t(2;13)(q35-37;q14) or the rare t(1;13)(p36;q14), shown to juxtapose the *PAX3* gene on chromosome 2 with the *FKHR* gene on chromosome 13, leading to the formation of a hybrid transcription factor (*PAX3-FKHR*).
      2. Found in about 70% of the alveolar tumors.
      3. Only occasionally described in other subtypes.
   3. Embryonal subtype: numerical changes with +2, +8, +11, and +20, found in 35–50% of cases

11. Other common, recurrent translocation/chromosome abnormalities in solid and soft tissue tumors of childhood (Davidoff and Hill 2001; Tien et al. 2014):
    1. Alveolar soft part sarcoma: t(X;17)(p11;q25), *ASPL-TFE3*
    2. Inflammatory myofibroblastic tumor: 2p23 translocations, *ALK-TPM3*
    3. Desmoplastic small round cell tumor:
       1. t(11;22)(p13;q12), *WT1-EWS*
       2. t(11;22)(q24;q12), *FLI1-EWS*, *ERG-EWS*
    4. Synovial sarcoma:
       1. t(X;18)(p11.23;q11.2), *SSX1-SSXT*
       2. t(X;18)(p11.21;q11), *SSX2-SSXT*
    5. Malignant melanoma of soft part (clear cell sarcoma): t(12;22)(q13;q12), *ATF1-EWS*
    6. Myxoid liposarcoma:
       1. t(12;16)(q13;p11), *CHOP-TLS*(*FUS*)
       2. t(12;22)(q13;q12), *CHOP-EWS*
    7. Ewing sarcoma:
       1. t(11;22)(q24;q12)
       2. t(2;11;22)(q35;q24;q12), add(17)(p11.2)
       3. +12
    8. Extraskeletal myxoid chondrosarcoma: t(9;22)(q22;q12), *CSMF-EWS*
    9. Dermatofibrosarcoma protuberans and giant cell fibroblastoma: t(17;22)(q22;q13), *COLIAI-PDGFB*
    10. Lipomas: t(2;12)(q23;q15)
    11. Leiomyomas: t(12;14)(q13;15), *HMGI-C* (Cooper 1996)

12. Other primary chromosome changes in solid tumors (Sandberg and Turc-Carel 1987; Sandberg 1988):
    1. Benign tumors:
       1. Meningioma and acoustic neuroma:
          1. −22
          2. 22q−
       2. Mixed tumors of salivary glands:
          1. t(3;8)(p21;q12)
          2. t(9;12)(p13-22;q13-15)
       3. Colonic adenomas:
          1. 12q− and/or +7
          2. 12q− and/or +8
       4. Cortical adenoma of the kidney:
          1. +7
          2. +17
          3. −Y
    2. Adenocarcinomas:
       1. Bladder:
          1. i(5p)
          2. +7
          3. −9/9q−
          4. 11p−
       2. Prostate: del(10)(q24)
       3. Lungs (small cell carcinoma): del(3)(p14p23)
       4. Colon:
          1. 12q−
          2. +7
          3. +8
          4. +12
          5. 17(q11)
          6. 17p-
       5. Kidney: del(3)(p11p21)
       6. Uterus: 1q−
       7. Ovary:
          1. 6q−
          2. t(6;14)(q21;q24)

8. Endometrium:
   1. Trisomy 1q
   2. +10
3. Embryonal and other tumors:
   1. Testicular (germ cell tumors): i(12p)
   2. Malignant melanoma:
      1. Del(6)(q11q27)
      2. i(6p)
      3. Del(1)(p11p22)
      4. t(1;19)(q12;q13)
   3. Mesothelioma: del(3)(p13p23)
   4. Glioma: −22

13. Potential prognostic markers of neoplastic disease (Barcus et al. 2000):
   1. Breast cancer: allelic loss at 1p22-p31 (lymph node metastasis and tumor size >2 cm)
   2. Bladder cancer:
      1. LOH RB (high grade/muscle invasion)
      2. Genomic alterations (2q−, 5p+, 5q−, 6q−, 8p−, 10q−, 18q−, 20q+) (higher grade)
   3. Cervical carcinoma: LOH on chromosome (advanced stage)
   4. Colorectal cancer:
      1. LOH at 18q21 or p53 expression (recurrence/poor survival)
      2. *MSI* (microsatellite instability) and *K-ras* mutations in normal-appearing colonic mucosa (predictive of colorectal cancer)
      3. P16 hypermethylation (shorter survival in Stage T3N0M0 tumors)
   5. Gastric cancer:
      1. LOH p53 (invasive disease)
      2. LOH of 7q (D7S95) (poor prognosis (in Stage III/IV))
   6. Glioma: chromosome 22q loss (astrocytoma progression)
   7. Head and neck squamous cell carcinoma:
      1. LOH of 14q (poor outcome)
      2. LOH on 2q (poor prognosis)
      3. LOH on 17p (chemoresistance)
   8. Melanoma: LOH in plasma (advanced stage/tumor progression)
   9. Neuroblastoma:
      1. N-myc amplification (poor prognosis)
      2. TrkA expression (good prognosis)
      3. High telomerase expression (aggressive behavior)
   10. Neuroblastomas, 4s: N-myc amplification, 1p deletion, 17q gains, and elevated telomerase activity (poor prognosis)
   11. Non-small cell lung cancer:
      1. Allelic imbalances on 9p (poor prognosis)
      2. LOH of 11p (poor prognosis)
   12. Primitive neuroectodermal tumor:
      1. LOH of 17p (metastatic disease)
      2. C-myc amplification (poor prognosis)
   13. Prostate cancer: LOH on 13q (advanced stage)
   14. Retinoblastoma: LOH at RB1 locus (tumoral differentiation, absence of choroidal invasion)

14. Chromosome abnormalities observed in some solid tumors (Cooley et al. 2009):
   1. Genitourinary:
      1. Renal:
         1. Renal cell carcinoma (RCC): −3 or del(3p), del(3p) with gain 5q, del (3p) with loss 5q, and −14/del(14q)
         2. Papillary RCC: +7, +17, −Y, and 9p−
         3. t(Xp11.2) RCC: (X;17)(p11.2;q25), t(X;17) (p11.2;q23), and t(X;1) (p11.2;p34)
         4. t(6;11) RCC: t(6;11)(p21;q12)
         5. Chromophobe RCC: losses 1, 2, 6, 10, 13, 17, and 21
         6. Oncocytoma: 1p− and t(11q13)
         7. Rhabdoid: −22/22q−
         8. Congenital mesoblastic nephroma: t(12;15)(p12;q25), +11, +17, and +20
      2. Bladder, papillary: del(9)(p21), 8p−, +7, and +17
      3. Wilms' tumor: 16q−, +1q, 1p−, −22, and 17p−
      4. Prostate: +17q31, 8p22−, +8q24, 10q−, and 17p13−
   2. Gastrointestinal:
      1. Liver:
         1. Hepatoblastoma: +20, +2, +8, and t(1q12q21)

2. Hepatic mesenchymal hamartoma: t(11;19)(q13;q13.4) and t(19q-13.4)
2. Salivary gland:
1. Pleomorphic adenoma: t(3;8)(p21;q12)
2. Mucoepidermoid cancer: t(11;19)(q21;p13)
3. Warthin tumor: t(11;19)(q21;p13)

3. Breast:
1. Invasive intraductal: dmin (double minute) and HSR (homogeneously staining region)
2. Secretory breast: t(12;15)(p13;q25)

4. CNS:
1. Astrocytic tumors: +7, −10/10q−, 9p21−, and 19q−
2. Glioblastoma: +7, 10q−, and 9p−
3. Anaplastic: 1p−, 19q−, and der(1;19)(q10;p10)
4. Mixed oligoastrocytoma: +7, −10/10q−, and 15q−
5. Oligoastrocytoma: 19q− and 1p−

5. Ependymoma:
1. Spinal: +7, −22q, and 14q−
2. Intracranial: +1q, 6q−, +7, and 9p−

6. Mudulloblastoma: i(17q), 17p−, −10/10q−, and +7
7. Supratentorial primitive neuroectodermal tumor: +1q, 16q−, and 19p−
8. Atypical teratoid/rhabdoid tumor: −22 or del(22q11.23)
9. Meningioma: −22 or del(22q11.2), 1p−, and −14/14q−
10. Choroid plexus tumors:
1. Carcinoma: losses 2, 3, 4, 5, 6, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19, and 22
2. Papilloma: gains 7, 8, 9, 12, 14, 15, 17, 18, 19, and 20

11. Small round cell tumors:
1. Alveolar RMS: t(2;13)(q37;q14), t(1;13)(p36;q14), t(X;2)(q13lq35), and t(2;2)(q35;p23)
2. Embryomal rhabdomyosarcoma: gains 2, 7, 8, 11, 12, 13, and 20; losses 1p, 3p, 9q, 10q, 16q, 17p, and 22
3. Neuroblastoma: del(1p), del(11q) without *MYCN* amp, del(1p), +17q, *MYCN* amp, and triploidy without above abnormalities
4. Ewing sarcoma/peripheral neuroectodermal tumor: t(11;22)(q24;q12) and variants, t(21;22)(q22;q12), del(9p), 17p−, and der(1;16)(q10;p10)
5. Desmoplastic small round cell tumor: t(11;22)(p13;q12)
6. Clear cell sarcoma: t(12;22)(q13;q12)
7. Retinoblastoma: del(13q14) and gains 1q and 6p
8. Lymphomas: specific translocations

12. Bone and soft tissue:
1. Congenital fibrosarcoma/congenital mesoblastic nephroma: t(12;15)(p12;q25), +11, +17, and +20
2. Synovial sarcoma: t(X;18)(p11.2;q11.2)
3. Lipoma: t(3;12)(q27-28;q14-15) and variants
4. Liposarcoma:
1. Myxoid, round cell: t(12;16)(q13;p11)
2. Myxoid: t(12;22)(q13;q12) and variant
3. Well differentiated: rings, markers, and dmin

13. Leiomyoma: t(12;14)(q15;q24):
1. Alveolar soft part sarcoma: der(17)t(X;17)(p11.2;q25)
2. Extraskeletal myxoid chondrosarcoma: t(9;22)(q22;q12), t(9;17)(q22;q11.2), t(9;15)(q22;q21), and t(3;9)(p11;q22)

14. Dermal tumors:
1. Dermatofibrosarcoma protuberans: der(22)t(17;22)(q22;q13.1) or r(22)t(17;22)
2. Giant cell fibroblastoma: t(17;22)(q22;q13.1)
3. Bednar tumor: der (22)t(17;22) (q22;q13.1) or r(22)t(17;22)
4. Hidradenoma: t(11;19)(q21;p13)

15. Non-small cell lung cancer: 3p−, +7, and *EGFR* high copy number or amplification
16. Dysgerminoma, ovary: i(12p) and 12p overrepresentation

17. Testicular germ cell tumors, seminoma, and nonseminoma: i(12p) and 12p amplification

Genetic Counseling

1. Recurrence risk:
    1. Retinoblastoma:
        1. Predisposition to retinoblastoma which is caused by germline mutations in the *RB1* gene: transmitted in an autosomal dominant fashion.
        2. Use *RB1* mutation analysis to clarify the genetic status of at-risk sibs and offspring when a previously characterized germline cancer-predisposing mutation is available.
        3. Use indirect testing using polymorphic loci linked to the *RB1* gene in some families to clarify genetic status of at-risk family members if *RB1* direct DNA testing is not available or is uninformative.
        4. Use empiric recurrence risk estimates in all families in which direct DNA testing of *RB1* and linkage analysis are unavailable or uninformative.
        5. Risk to patient's siblings:
            1. When there is an existing family history: a 45% chance for siblings of bilaterally affected cases and a 30% chance for siblings of unilaterally affected cases to develop disease.
            2. When there is absence of any family history: 2% risk for siblings of bilaterally affected cases and 1% for siblings of unilaterally affected cases to develop disease (Draper et al. 1992).
            3. There is an additional risk to siblings in the absence of any family history or documented mutation in parental leukocyte DNA because of germline mosaicism. If neither parent has the cancer-predisposing *RB1* germline mutation that was identified in the index case, germline mosaicism in one parent is possible, and the risk to each sib of having retinoblastoma is 3–5%.
            4. If the index case has mosaicism for an *RB1* cancer-predisposing mutation (the mutation arose as a post-zygotic event) and neither parent has an *RB1* germline mutation, the risk to the sibs is not increased, and thus it is not warranted to test the sibs for the *RB1* mutation identified in the index case.
        6. Risk for patient's offspring:
            1. About 45% by the age of 6 years (consistent with an autosomal dominant inheritance with 90% penetrance) for the offspring of survivors of hereditary (multifocal, bilateral) retinoblastoma.
            2. About 2.5% for the offspring of survivors of unilateral retinoblastoma.
            3. The low (~1%), but not negligible, risk to the offspring of index cases with unifocal disease and a negative family history reflect the possibility of a germline *RB1* mutation with low penetrance or mutational mosaicism.
    2. Implications of somatic and germline mosaicism in retinoblastoma for genetic counseling (Sippel et al. 1998):
        1. In a unilateral, simplex case of retinoblastoma, the absence of a detected mutation in leukocytes does not reliably predict that no tumors will arise in the fellow eye in the future.
        2. Some bilateral simplex retinoblastoma patients and unilateral, multifocal simplex retinoblastoma patients have a recurrence risk among their offspring that is much less than 45–50%.
        3. It is possible – but not yet proven – that every bilateral or unilateral retinoblastoma patient in whom an initial mutation is identified in tumor cells, but not in leukocytes, has a recurrence risk of zero.

4. If unaffected parents with no previous family history of retinoblastoma have an affected child, DNA-based estimates of the recurrence risk for future children should include, whenever possible, an analysis of paternal germline DNA.
5. The risk that a patient with unilateral simplex retinoblastoma will have mutant germ cells may be much higher than 12%; however, some will be mosaics, and <50% of their germ cells will be mutant.

3. Genetic counseling for retinoblastoma in the presence of positive family history (Vogel 1979; Isidro et al. 2011):
   1. Multiplex disease (>2 affected members) – the index patient had retinoblastoma and one or more close relatives are also affected:
      1. Affected individuals definitely carry a germline mutation.
      2. A 50% chance exists that a known carrier will pass the mutant copy of the retinoblastoma gene to each child and there is 50% penetrance and there is a 50% × 90% = 45% chance that each child will develop retinoblastoma.
   2. Multiplex disease (>2 affected members) – the index patient did not develop retinoblastoma as a child, but a parent is known to be a carrier:
      1. Approximately 10% risk that an asymptomatic son or daughter of a known carrier is also a carrier.
      2. The risk that his or her offspring will inherit a mutation is about 5%, and the risk of the disease is 90% × 5% = 4.5%.
   3. Simplex disease (only one family member affected) – the index patient had multifocal retinoblastoma:
      1. The patient very likely has a germline mutation.
      2. The risk to each offspring is 50% for being a carrier and 45% for developing the disease.
   4. Simplex disease (only one family member affected) – the index patient had unifocal retinoblastoma (one tumor in one eye only):
      1. A 12% risk exists that the patient carries a germline mutation (i.e., has hereditary retinoblastoma) and an 88% risk that he or she does not (nonhereditary retinoblastoma).
      2. The risk for the first child of the index patient is 6% for being a carrier and 5.4% for developing the disease.
      3. If the first child does not develop retinoblastoma, the risk for the next child is less.
      4. If at least one child develops retinoblastoma, the index patient definitely has the hereditary type of the disease, and the risk for family members is as described for multiplex families.
   5. Simplex disease (only one family member affected) – two unaffected parents have one child with retinoblastoma:
      1. The risk of the parents' second child's developing retinoblastoma is about 1% if the first child had unifocal disease and about 6% if the first child had multifocal disease.
      2. These risks decrease with every unaffected child that passes the years of highest risk (years 0–5) without developing the disease.
   6. Simplex disease (only one family member affected) – the index patient is an adult of childbearing age who did not develop retinoblastoma, but a sibling had retinoblastoma:
      1. A small risk exists that one of the parents is an asymptomatic carrier and the index patient is also an asymptomatic carrier.
      2. The carrier risk for the index patient is 0.1% if the affected sibling had unilateral retinoblastoma and 0.6% if the

affected sibling had bilateral retinoblastoma.
3. The risk that the first child of the index patient will develop retinoblastoma is approximately half of these numbers, i.e., 0.05% or 0.3%, respectively.

4. Neuroblastoma:
1. Risk for patient's sibling: low unless a parent has hereditary form of neuroblastoma
2. Risk for patient's offspring: 50%

5. Wilms' tumor:
1. Risk for patient's sibling: low unless a parent has hereditary form of Wilms' tumor
2. Risk for patient's offspring: 50%

2. Prenatal diagnosis:
1. Retinoblastoma:
1. Prenatal testing is possible if the germline *RB1* mutation in the parent is known or if *RB1* linkage analysis is informative in the family.
2. Mutation analysis on fetal DNA obtained from amniocentesis or CVS.
3. Use prenatal ultrasonography to detect intraocular tumors if the disease-causing RB1 mutation is identified in the fetus.

2. Adrenal neuroblastoma (Kesrouani et al. 1999):
1. Prenatal diagnosis adrenal neuroblastoma by ultrasonography usually made in the third trimester.
2. Sonographic appearance of the adrenal neuroblastoma varies:
1. Solid
2. Purely cystic (50%)
3. Mixed echo pattern (related to necrosis, hemorrhage, or spontaneous tumoral involution)
4. Fetal hydrops
5. Hydropic placenta with metastases in the placenta

3. Needle biopsy for selection of the group with favorable biological parameters (N-myc, DNA index).
4. Frequently producing catecholamines and hence maternal symptoms could aid the diagnosis.
5. Elevated catecholamines in the amniotic fluid.

3. Wilms' tumor (Vadeyar et al. 2000):
1. Prenatal ultrasonography:
1. Maternal hydramnios.
2. Fetal hydrops.
3. A solid echogenic mass with a clearly defined capsule.
4. Areas of hemorrhage and necrosis may be seen within the mass.

2. Fetal renal biopsy (nephroblastoma by histology)

3. Management:
1. Surgeries for most solid tumors
2. Determining the genetic changes present in the tumor of an individual patient: becoming increasingly important for managing the oncology patient
3. Retinoblastoma (Chintagumpala et al. 2007):
1. Goals of treatment: preservation of sight and life.
2. Management of intraocular disease:
1. Enucleation
2. External beam radiation (EBR) therapy
3. Brachytherapy: involves the placement of a radioactive implant
4. Thermotherapy
5. Chemothermotherapy
6. Laser photocoagulation
7. Cryotherapy
8. Chemotherapy

3. Management of extraocular disease: Patients with extraocular disease, having a very poor prognosis with respect to survival, may benefit from a combination of conventional chemotherapy and EBR, and those with distant metastatic disease may benefit from high-dose chemotherapy and EBR in conjunction with bone marrow stem cell transplantation.

4. Neuroblastoma (Lee et al. 2003):
1. Localized, low-risk disease:
1. Primary curative surgery
2. Minimal therapy: low-dose radiation or chemotherapy
3. Supportive care with surveillance

2. Intermediate-risk patients: combination therapy with radiation, chemotherapy, and surgery
3. High-risk patients:
   1. Combination of radiation, myeloablative chemotherapy, and surgery (delayed)
   2. Autologous bone marrow transplant
   3. Research protocols

5. Wilms' tumor: The usual approach in most patients is nephrectomy followed by chemotherapy with or without postoperative radiotherapy.

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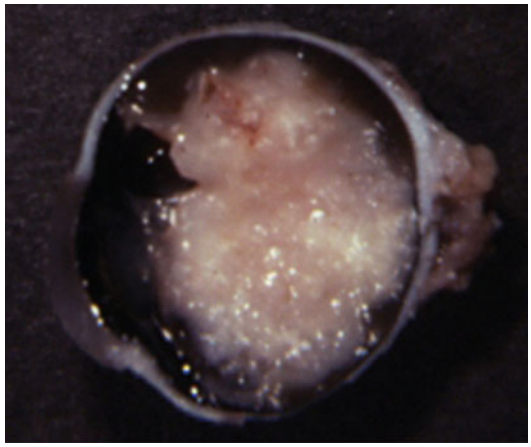

Fig. 1 Notice the *white* firm neoplasm (retinoblastoma) filling the vitreous space of the eye

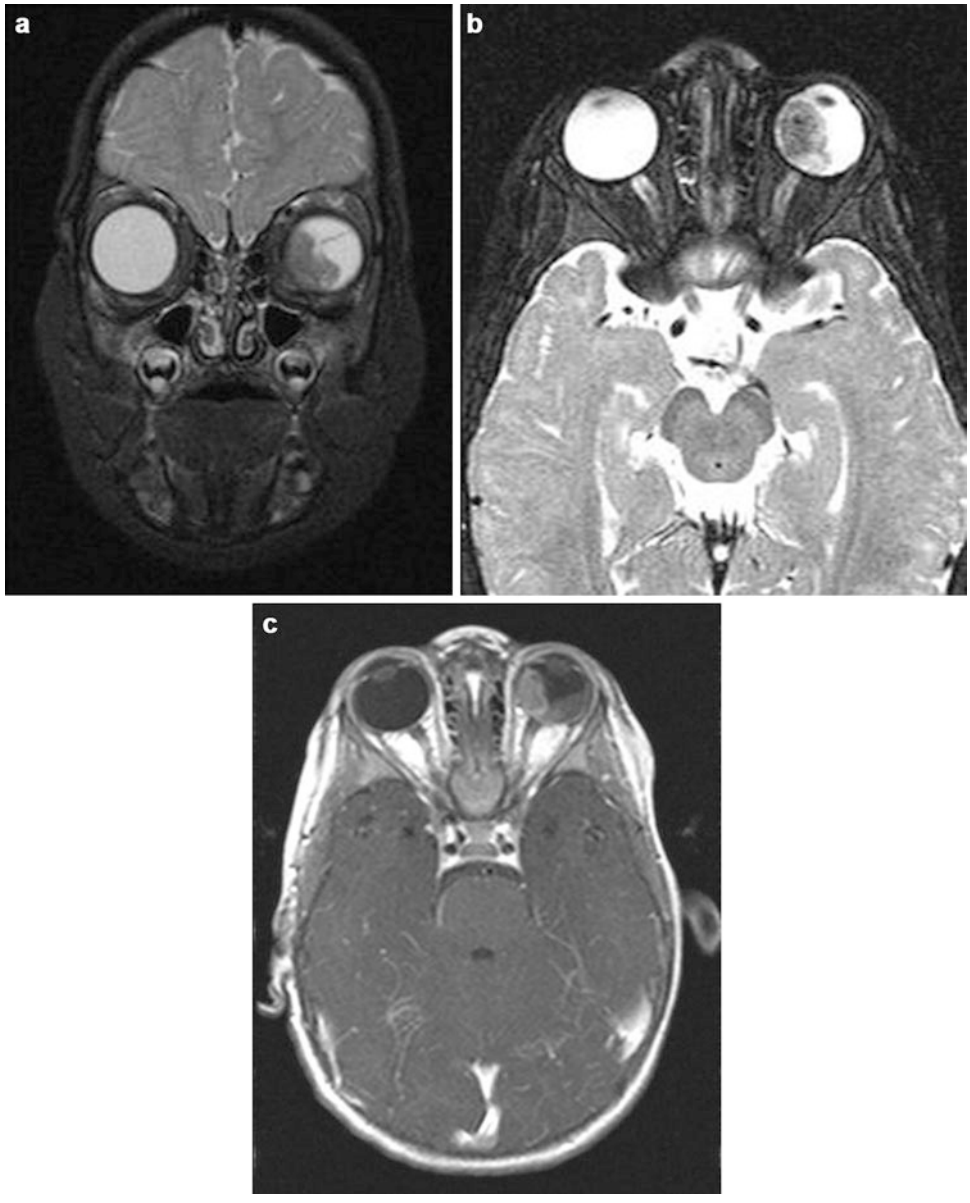

Fig. 2 (**a**–**c**) A 12-month-old boy was seen because of a 3-month history of a lazy left eye. One month previously, he was noted to have a white reflex in his left eye. He was seen by an ophthalmologist who diagnosed him to have group E retinoblastoma of the left eye. The right eye was normal. MRI of orbits demonstrated a calcified mass (**a**, **b**) with mild enhancement (**c**) in the posterior aspect of the left globe. The findings are compatible with retinoblastoma. Mutation screening of RB1 gene on DNA isolated from lymphocytes demonstrated heterozygous for a single-base substitution, g.162367G > A, in the last nucleotide of exon 23 of the coding sequence of the RB1 gene. This single-base substitution translates to a missense mutation, p.Arg830Lys. Although this novel change has not been reported in the RB1 mutation database, it has been seen in one other child with unilateral retinoblastoma in the performing molecular laboratory own database (Courtesy of Dr. Grace Guo)

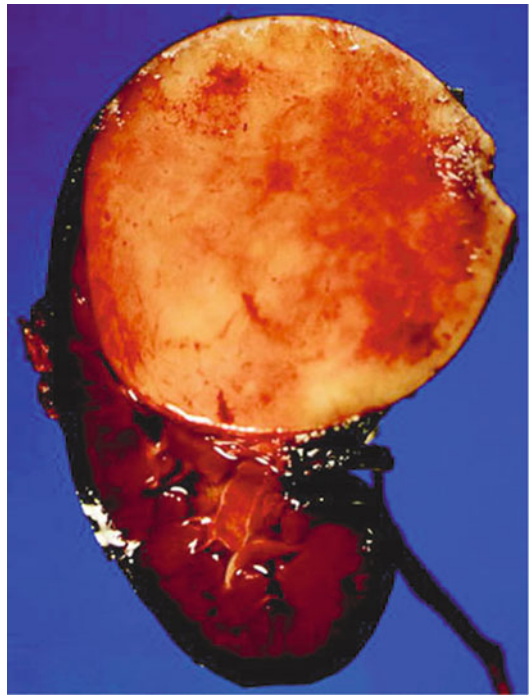

Fig. 3 Large, well-circumscribed ovoid Wilms' tumor in the upper pole of the kidney. Barely identifiable small areas of hemorrhage and necrosis are present

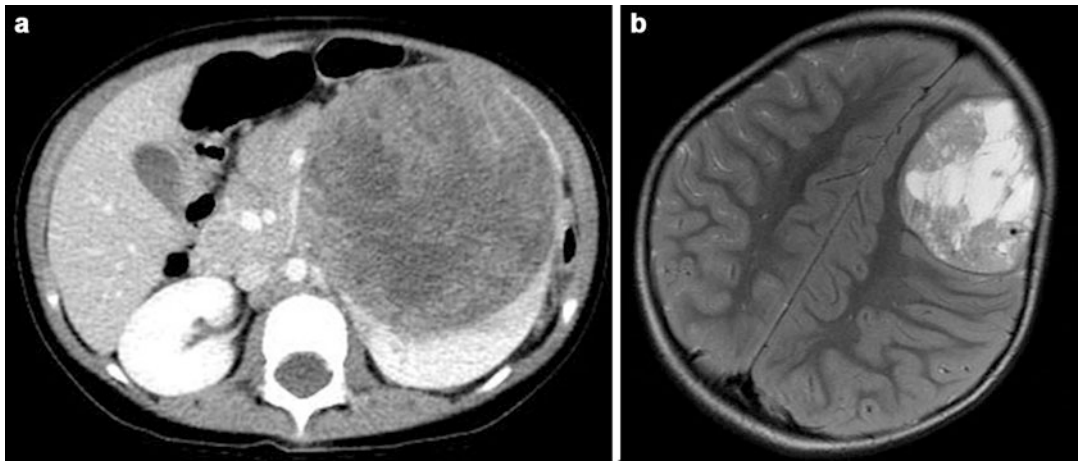

Fig. 4 (**a**, **b**) A 2-year-old female with a left renal mass was seen on the recent ultrasound. CT scan demonstrated a large heterogeneous mass arising from the left kidney (**a**). A heterogeneous metastatic lesion was present in the right front lobe of the brain (**b**). The masses were confirmed as Wilms' tumors (Courtesy of Dr. Grace Guo)

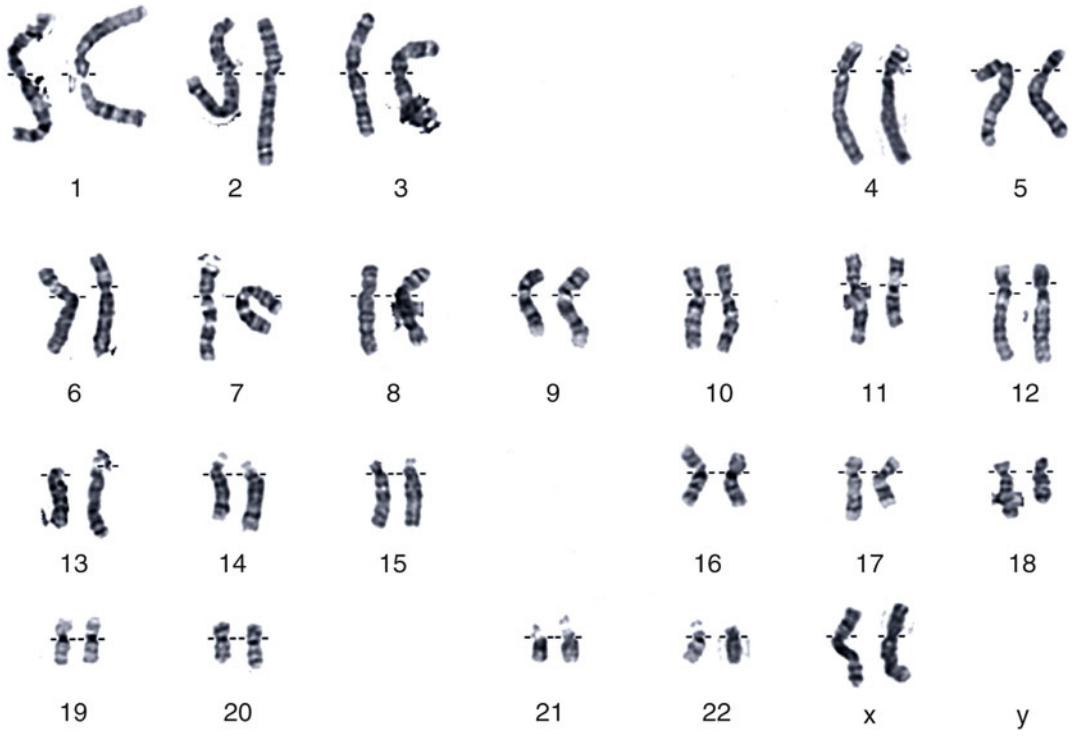

Fig. 5 Karyotype of a patient with Wilms' tumor showing 46,XY,der(11)(p11.2q13.5)del(11)(p13p15.1)

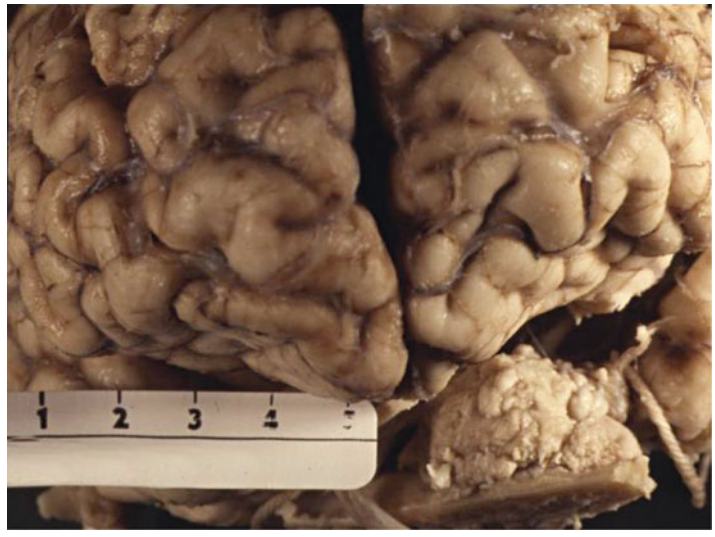

Fig. 6 Note a lobulated meningioma encroaching the brain at the inferior surface of the left frontal lobe

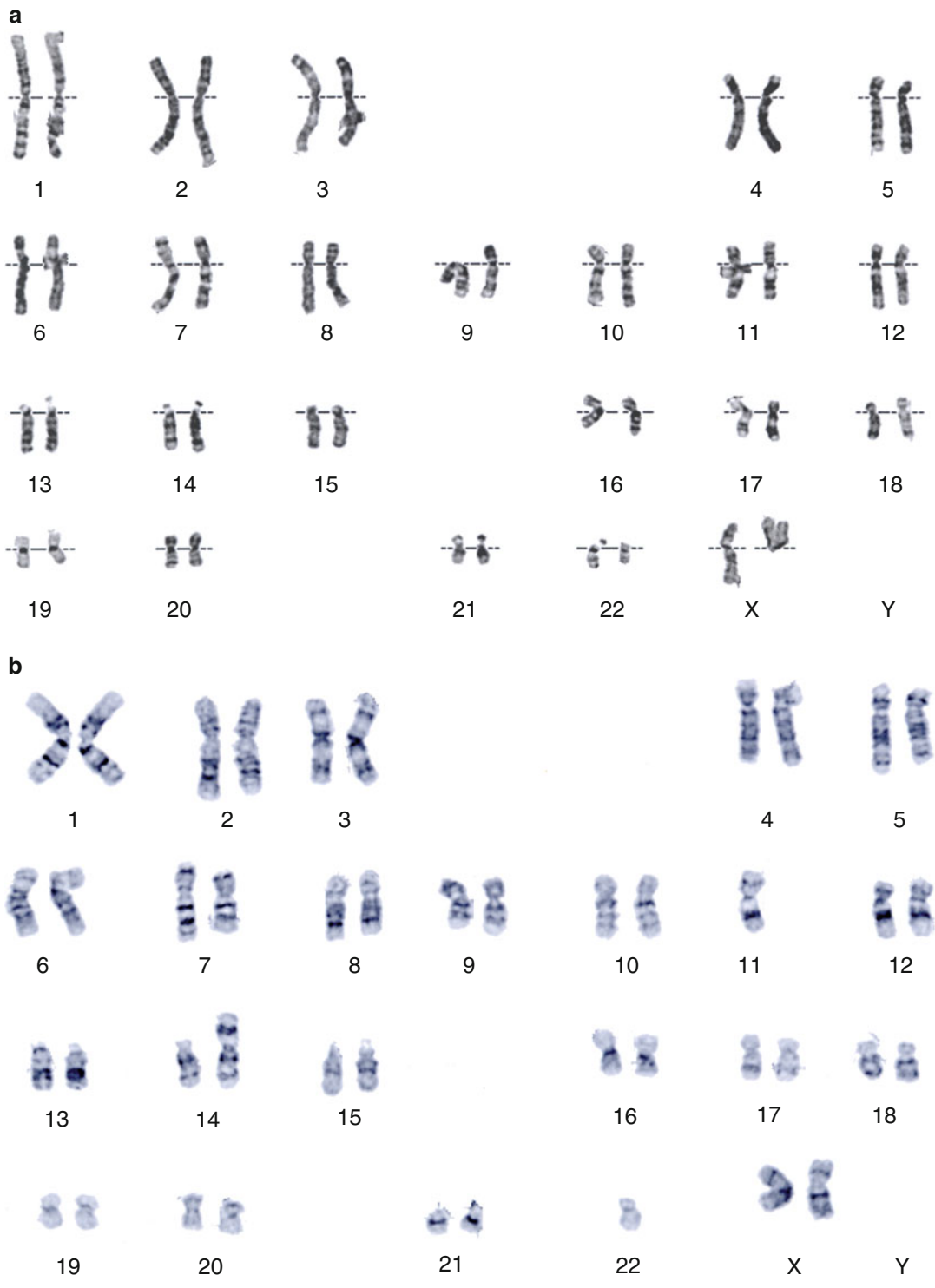

Fig. 7 (**a**, **b**) Karyotypes of two patients with meningioma showing 46,XX,del(22)(q12) (**a**) and 44,XX,del(7)(q32q36), -11,der(14)t(11;14)(q12;p11),-22 (**b**)

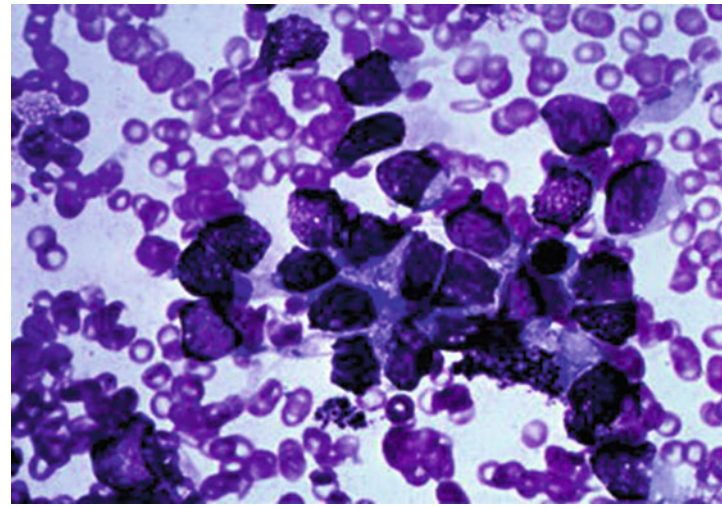

Fig. 8 Neuroblastoma smear. Note the anaplastic neuroblastic cells mixed with blood

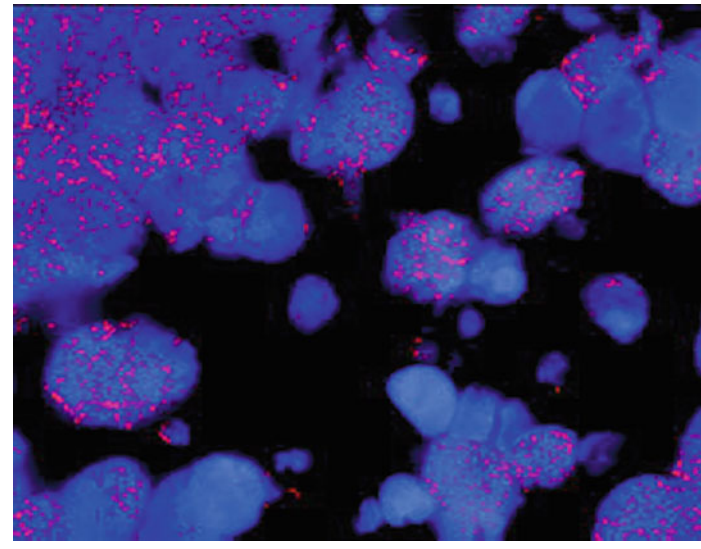

Fig. 9 N-myc amplification in a patient with neuroblastoma. Gross copy number of the orange signal is noted (LSI® N-MYC (2p24.1) SpectrumOrange TM probe)

Cleft Lip and/or Cleft Palate

Contents

Cleft lip and/or cleft palate (CL/CP) is the most common craniofacial malformation with an estimated incidence from approximately 1 in 700 to 1 in 1,000 live births among Caucasians (Carinci et al. 2000). CL/CP may occur as an isolated finding or may be found in association with other congenital malformations.

Genetics/Basic Defects

1. Etiological heterogeneity (Fraser 1970; Wyszynski et al. 1996)
2. Environmental agents (De La Pedraja et al. 2000):
    1. Cleft lip and cleft palate (Habib 1978a; Wyszynski and Beaty 1996):
        1. Alcohol
        2. Anticonvulsants (phenytoin, sodium valproate) (Jackson et al. 2015)
        3. Isotretinoin
        4. Steroids
        5. Methotrexate
        6. Maternal infections in the first trimester:
            1. Rubella
            2. Toxoplasmosis
        7. Maternal smoking
    2. Isolated clefts:
        1. Little evidence linking to any single teratogenic agent, except anticonvulsant phenytoin.
        2. Use of phenytoin during pregnancy is associated with a tenfold increase in the incidence of cleft lip.
    3. Cleft lip: incidence of cleft lip in infants in mothers who smoke during pregnancy is twice that of those born to nonsmoking mothers.
3. Genetic factors:
    1. Syndromic clefts associated with malformations involving other developmental regions:
        1. About 25% of neonates with CL/CP show associated malformations, syndromes, or aneuploidy (Bergé et al. 2001).
        2. Van der Woude syndrome (van der Woude 1954): the most commonly recognized syndrome associated with CL/CP, an autosomal dominant disorder characterized by CL/CP and blind sinuses or pits of the lower lip.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Microdeletion of chromosome 22q11.2 (velocardiofacial syndrome, DiGeorge syndrome, and conotruncal anomaly face syndrome): currently the most common syndromic diagnosis among patients with clefts of the secondary palate alone.
4. Other syndromes associated with clefts of the secondary palate alone:
    1. Stickler syndrome
    2. Ectrodactyly-ectodermal clefting (EEC) syndrome
    3. Popliteal pterygium syndrome

2. Nonsyndromic cleft of the lip and/or palate (Carinci et al. 2000; Mehrotra 2015):
    1. An embryopathy derived from failure in fusion of the nasal process and/or palatal shelves.
    2. Genetic factors play an important role in the etiology of cleft lip and/or palate since one in five patients in different populations has a positive family history of CL/CP.
    3. Isolated CL/CP is considered multifactorial in origin and demonstrates strong familial aggregation with a significant genetic component.
    4. No evidence of classic Mendelian inheritance attributable to any single gene, although a number of genes or loci have been implicated, including transforming growth factor-alpha (*TGFA*, 2p13), *TGFB3* (14q24), retinoic acid receptor alpha (*RARA*, 17q12), B-cell leukemia/lymphoma 3 (*BCL3*, 19q13) (Stein et al. 1995), *MSX-1* (4p16, 4q31, 6p23), interferon regulatory factor-6 (*IRF6*), runt-related transcription factor 2 (*RUNX2*), and several regions on chromosomes 1p36 (*SKI*/*MTHFR*), 6p23-24 (*OFC1*), 2q13 (*OFC2*), and 19q13.2 (*OFC3*) and other loci such as 4q25-4q31.3 and 17q21 (Hibbert and Field 1996; Prescott et al. 2001; Murray 2002; Mehrotra 2015).

3. Molecular signaling events in embryonic palatal development (Yu et al. 2009):
    1. Failure of palatal shelf formation:
        1. Recent studies have identified several molecular networks operating between the palatal shelf epithelium and mesenchyme during different steps of palatogenesis.
        2. These networks include signaling molecules and growth factors such as sonic hedgehog (Shh); members of the transforming growth factor-β (TGFβ) superfamily, including bone morphogenetic proteins (BMPs) and TGFβs; and fibroblast growth factors (FGFs) and their receptors (FGFR), effectors, and targets.
    2. Fusion of the palatal shelf with the tongue or mandible:
        1. Severe reduction of the expression of *Jagged 2* (*Jag2*), thereby encoding a ligand for the Notch family receptors and ectopic TGFβ3 production in the nasal epithelia of mice.
        2. Mutations in TBX22 have been reported in families with X-linked cleft palate and ankyloglossia.
    3. Failure of palatal elevation:
        1. Mutations of *Pax9, Pitx1*, or *Osr2* can lead to failed palatal shelf elevation and cleft palate defect.
        2. The implication of GABA in palate development was demonstrated by genetic studies of mice lacking the β3 subunit of the GABA receptor that developed CP without other craniofacial malformations.
    4. Failure of palatal shelves to meet after elevation: mutations in *Msx1* and *Lhx8* and conditional inactivation of *TGFbr2* in CNC cells or *Shh* in the epithelium all result in retarded palatal shelf development.
    5. Persistence of the middle edge epithelium: mutations of *CDH1*/E cadherin, which deletes the extracellular cadherin repeat domains required for cell–cell adhesion, have recently been associated with CL/CP in families with hereditary diffuse cancer.

Clinical Features

1. Classification of different types of orofacial clefting:
   1. Cleft lip with or without cleft palate (CL/CP):
      1. Unilateral cleft lip
      2. Unilateral cleft lip and cleft palate
      3. Bilateral cleft lip
      4. Bilateral cleft lip and cleft palate
   2. Cleft palate only:
      1. Cleft palate
      2. Submucous cleft palate
      3. Velopharyngeal insufficiency
      4. Robin sequence and robin complexes
   3. Median clefts:
      1. Median cleft lip
      2. Persistent infranasal furrow
      3. Median frenular cleft
      4. Median mandibular cleft
   4. Alveolar (oral–facial–digital syndromes)
   5. Tessier-type clefts including lateral and oblique facial clefts
2. Racial difference in CL/CP (De La Pedraja et al. 2000):
   1. Whites: approximately 1 in 1,000 births
   2. African Americans: 0.41 per 1,000 births
   3. Asians: approximately twice of whites
3. Sex difference in CL/CP and isolated clefts of the secondary palate (De La Pedraja et al. 2000):
   1. Children born with CL/CP: 60–80% are males.
   2. Isolated clefts of the secondary palate: more frequently in females.
4. Sites of clefts:
   1. Isolated cleft lip: 21%
   2. CL/CP: 46%
   3. Clefts of the secondary palate alone: 33%
   4. Unilateral clefts:
      1. More common in the left than the right (2:1)
      2. Much more common than bilateral (9:1)
      3. Associated with palatal clefts in 68% of cases
   5. Bilateral clefts of the lip: associated with palatal clefts in 86% of cases
5. Types of cleft lip:
   1. Microform:
      1. Presence of a vertical groove and vermilion notching
      2. Associated with varying degrees of lip shortening
   2. Unilateral incomplete cleft lip:
      1. Present with varying degrees of lip disruption
      2. Associated with an intact nasal sill or Simonart band (a band of fibrous tissue from the edge of the red lip to the nostril floor)
   3. Complete cleft lip: characterized by disruption of the lip, alveolus, and nasal sill
6. Incidence of cleft lip +/− palate (CL/CP) and cleft palate alone (CPA) (Robin et al. 2006):
   1. Overall incidence of CL/CP and CPA: 1–2/1,000 children.
   2. CPA incidence is about 1/1,500:
      1. More common if submucous CP/CA is included.
      2. Bifid uvula occurs in 1 of 80 patients and often occurs in isolation, with no clefting of the palatal muscles.
   3. Incidence of CL/CP varies by race:
      1. Highest among American Indians, at 3.6 cases per 1,000 live births.
      2. Lowest among African Americans, with 0.3 cases per 1,000 live births.
      3. The incidence of CPA does not vary by race.
   4. Of all CL/CP and CPA:
      1. Twenty percent of all clefts are isolated cleft lip (18% unilateral, 2% bilateral).
      2. Fifty percent are CL/CP (38% unilateral, 12% bilateral).
      3. Thirty percent are CPA.
   5. CL/CP is twice as common in males; CPA is twice as common in females.
7. Secondary medical problems with the presence of cleft palate:
   1. Difficulty in sucking
   2. Inadequate intake of formula
   3. Aspiration
   4. Deviated nasal septum (airway obstruction)
   5. Hearing impairment
   6. Recurrent ear infections

7. Malocclusion
8. Abnormal craniofacial growth
9. Inability to generate a pressure gradient between the oral and nasal chambers (hinders sucking in most infants)
10. Speech dysfunction:
    1. The most serious untoward consequence associated with cleft palate
    2. Hypernasality or escape of sound into the nasal cavity associated with the production of many consonant phonemes and vowels in the English language except m, n, and ng
11. Cosmetic disfigurement associated with orofacial clefting

Diagnostic Investigations

1. Speech and hearing evaluation
2. Echocardiography for associated cardiac anomalies
3. Karyotyping if indicated, especially to detect del(22)(q11.2)
4. Molecular genetic analysis for a known mutation in a syndromic CL/CP
5. Multiple ligation probe-dependent amplification (MLPA) analysis: to detect chromosomal rearrangements (22q11.2 microduplications among patients with cleft lip and/or cleft palate) (Sedghi et al. 2015)

Genetic Counseling

1. Recurrence risk (Chen 1988; Tolarova 1972):
    1. Recurrence risk for nonsyndromic CL +/− CP (Curtis et al. 1961; Cockell and Lees 2000):
        1. Unaffected parent:
            1. No previously affected child: about 0.1% (general population risk) (Bonaiti-Pellie and Smith 1974; Kirschner and LaRossa 2000)
            2. With one previously affected child: about 4%
            3. With two previously affected children: about 9%
        2. One affected parent:
            1. No previously affected child: about 4%
            2. With one previously affected child: about 17%
            3. With two previously affected children: about 25%
        3. Two affected parents:
            1. No previously affected child: about 35%
            2. With one previously affected child: about 45%
            3. With two previously affected children: about 50%
        4. Risks to first-, second-, and third-degree relatives: 4%, 0.7%, and 0.4%, respectively (Habib 1978b)
    2. Recurrence risk for nonsyndromic CP:
        1. Unaffected parent:
            1. No previously affected child: about 0.04% (general population risk) (Kirschner and LaRossa 2000)
            2. With one previously affected child: about 3.5%
            3. With two previously affected children: about 13%
        2. One affected parent:
            1. No previously affected child: about 3.5%
            2. With one previously affected child: about 10%
            3. With two previously affected children: about 24%
        3. Two affected parents:
            1. No previously affected child: about 2.5%
            2. With one previously affected child: about 40%
            3. With two previously affected children: about 45%
3. Van der Woude syndrome (presence of lip pits in addition to the cleft anomaly): if lip pits are identified in either parent, the recurrence risk would increase to 50% (Cockell and Lees 2000).

4. Presence of a microform such as a forme fruste cleft lip, submucous cleft palate, or bifid uvula suggests genetic factors within the family, which would alter the inheritance risks (e.g., striking association with lower-lip pits in the van der Woude syndrome).
5. Recurrence risk for CL/CP with associated anomalies:
    1. Mendelian diseases and syndromes:
        1. Autosomal dominant inheritance (e.g., Apert syndrome)
        2. Autosomal recessive inheritance (e.g., Smith–Lemli–Opitz syndrome)
        3. X-linked inheritance (e.g., oto-palato-digital syndrome)
    2. Chromosome disorders (e.g., trisomy 13)

2. Prenatal diagnosis:
    1. Prenatal ultrasonography (2D, 3D) (Lee et al. 2000):
        1. 3D ultrasonography:
            1. Enhances 2D ultrasonography
            2. Provides more precise image of the defect
        2. CL/CP not reliably diagnosed until the soft tissues of the fetal face become distinct by 13–14 weeks by transabdominal (TA) sonography and by transvaginal (TV) sonography slightly earlier
        3. Fetal palate best seen in the axial plane
        4. Fetal lips optimally visualized in the coronal view
        5. To demonstrate isolated cleft lip (Mulliken and Benacerraf 2001):
            1. Unilateral versus bilateral
            2. Incomplete (the labial cleft does not extend through the nasal still or floor) versus complete (no tissue connection between the alar base and medial labial element or premaxilla)
            3. Microform (tiny) cleft on the "normal" side of a unilateral labial cleft
            4. Alveolar cleft: extent and degree of premaxillary proclination
            5. Cleft of the secondary palate if any
        6. To demonstrate associated anomalies (limb and spine anomalies, most common with 33%; cardiovascular anomalies, 24%)
    2. Fetal MRI: useful for detecting fetal deformities with valuable information and supplying higher diagnostic accuracy (Wang et al. 2011; Kim et al. 2015)
    3. Fetal echocardiography in case of fetal cardiac anomalies
    4. Fetal karyotyping in case of associated fetal anomalies
3. Management:
    1. Medical:
        1. A highly specialized multidisciplinary approach from birth to adulthood
        2. Airway management
        3. Establishment of feeding
        4. Speech, hearing, and language therapies
    2. Cleft lip repair (Shaye 2014; Shaye et al. 2015):
        1. Timing of repair: usually carried out around at the age of 3 months followed by palatal repair at around 6 months
        2. Unilateral cleft lip:
            1. Objectives: to approximate the medial and lateral lip elements with preservation of natural landmarks, to align a functional concentric orbicularis, and to establish symmetry and proportionality
            2. Straight-line closure
            3. Triangular (geometric) cleft lip repair
            4. Rotation-advancement technique
        3. Bilateral cleft lip:
            1. Two-stage repair with columellar elongation as the second procedure between the ages of 1 and 5 years.
            2. One-stage approach with primary rhinoplasty at the time of cleft lip repair.
            3. Nasoalveolar molding.
            4. Lip adhesion surgery.
            5. Alveolar bone grafting.
            6. Primary cleft rhinoplasty: improves nasal appearance and possibly decreases the number of revision surgeries in the future.

7. Postoperative nasal stents.

3. Cleft palate repair (Shaye 2014; Shaye et al. 2015):
   1. Goals: closure of the soft palate and reorientation of the levator veli palatini to obtain normal velopharyngeal closure and speech.
   2. Closure of the hard palate cleft separates the oral and nasal cavities.
   3. Palatoplasty:
      1. Von Langenbeck palatoplasty
      2. Veau–Wardill–Kilner palatoplasty
      3. Two-flap palatoplasty
      4. Furlow double-opposing Z-plasty
   4. Preventative and restorative dental care
   5. Orthodontics
   6. Pharyngeal flap or sphincter pharyngoplasty for velopharyngeal incompetence
4. Psychological issues (Endrica and Kapp-Simon 1999):
   1. Parental stress
   2. Parent–child relationship
   3. Behavioral and emotional adjustment
   4. Self-concept and personality
   5. Cosmetic disfigurement
   6. Social functioning
   7. Cognitive development and adjustment
   8. Cleft Lip and Palate Association (CLAPA), a helpful source of support and information for both families and professionals
5. Recent observation suggests beneficial effects of folic acid supplementation during pregnancy in the prevention of facial clefting (Tolarova and Harris 1995; Hartridge 1999).

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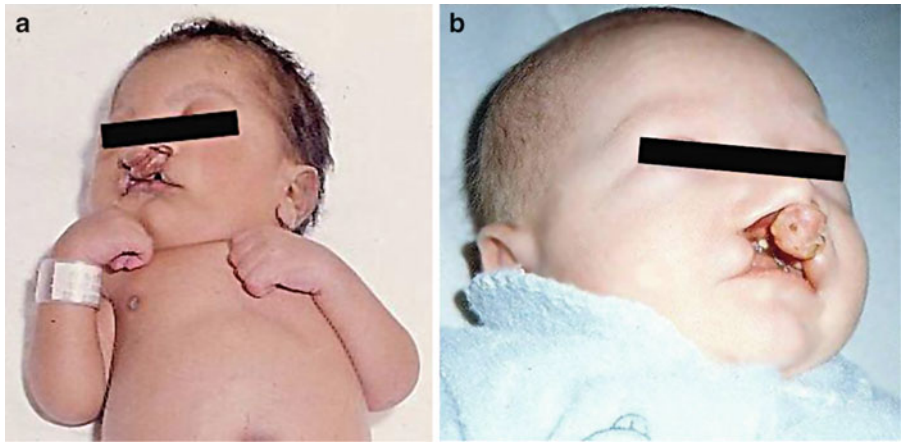

Fig. 1 (**a**, **b**) Two infants with bilateral cleft lips and cleft palate

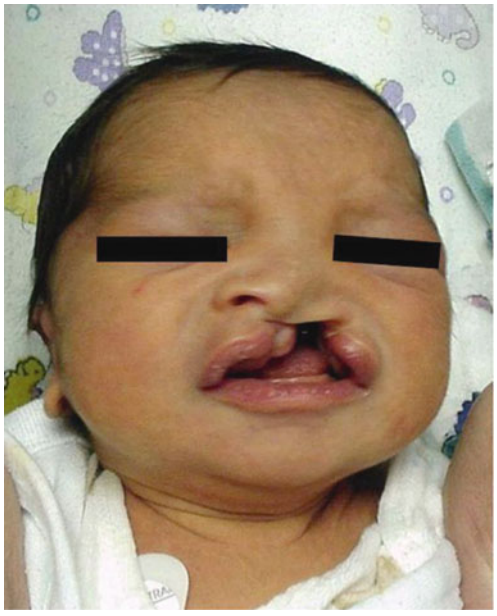

Fig. 2 An infant with unilateral cleft lip and cleft palate

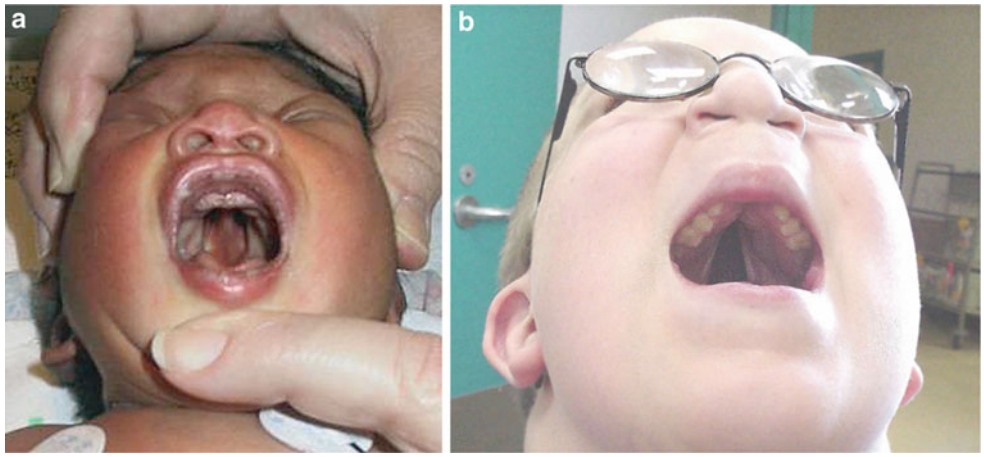

Fig. 3 (**a**, **b**) An infant and a boy with cleft palate

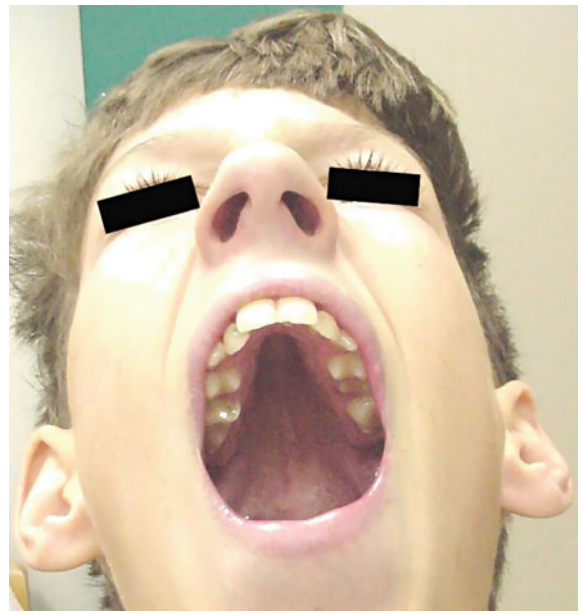

Fig. 4 A boy with high-arched palate

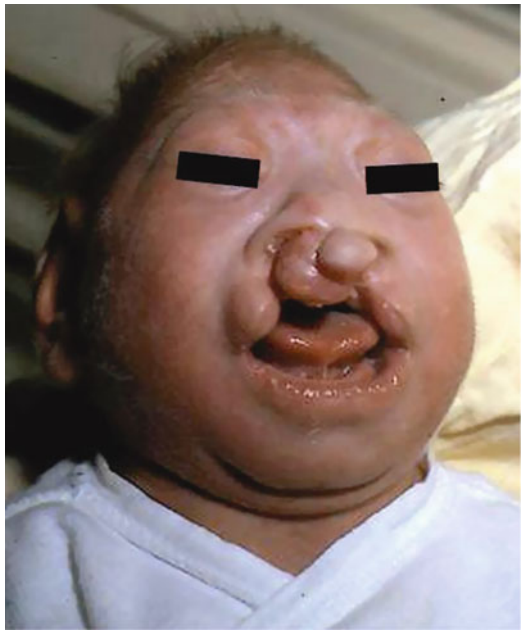

Fig. 5 An infant with bilateral CL/CP associated with trisomy 13

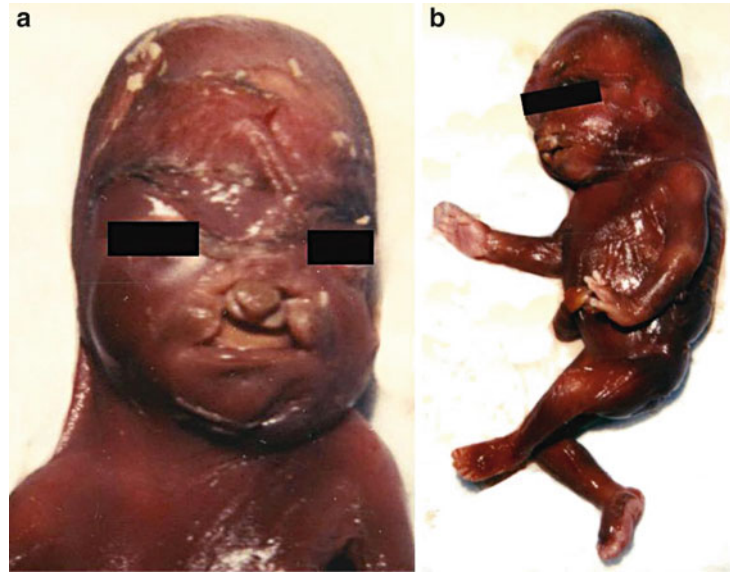

Fig. 6 A stillborn with CL/CP and other multiple congenital anomalies including massive cystic hygroma

Cleidocranial Dysplasia

Contents

Cleidocranial dysplasia is a generalized skeletal dysplasia affecting not only the clavicles but almost the entire skeletal system. It is characterized by aplasia or hypoplasia of the clavicles, enlarged calvaria with frontal bossing, multiple Wormian bones, delayed tooth eruption, supernumerary unerupted teeth, distal phalanges with abnormally pointed tufts, hypoplasia of the pelvis, and numerous other abnormalities (Jensen 1990).

Synonyms and Related Disorders

Cleidocranial dysostosis

Genetics/Birth Defects

1. Inheritance: autosomal dominant
2. About 20–40% of cases represent new mutations (Martinez-Frias et al. 1988)
3. Cause (Mundlos et al. 1997; Quack et al. 1999; Cohen 2001)
    1. Caused by mutations in *CBFA1* (*RUNX2*) gene resulting in haploinsufficiency. Types of mutations identified are:
        1. Deletion
        2. Insertion
        3. Missense (Golan et al. 2000)
        4. Nonsense
    2. The gene for cleidocranial dysplasia called core-binding factor A1 (*CBFA1*) (a member of the runt family of transcription factors), mapped to 6p21 (Feldman et al. 1995; Gelb et al. 1995). The alternative gene name is called *RUNX2*
    3. *CBFA1* encodes a transcription factor that activates osteoblast differentiation and plays a role in differentiation of chondrocytes (Otto et al. 1997)
4. Germline mosaicism has been reported (Zackai et al. 1997; Pai et al. 2007)
5. No significant genotype/phenotype correlations observed

Clinical Features

1. Significant intra- and interfamilial variability of phenotypic expression (Chitayat et al. 1992; Mundlos 1999)
2. Abnormal craniofacial growth
    1. The head

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Abnormally large, wide-open fontanels at birth
2. A large brachycephalic head
3. A broad forehead with frontal bossing
4. Delayed closure of the fontanels and sutures
5. Poorly developed midfrontal area showing a frontal groove owing to incomplete ossification of the metopic suture
6. Soft skull in infancy

2. The face
   1. Frontal and parietal bossings, separated by a metopic groove
   2. A depressed nasal bridge
   3. Hypertelorism with possible exophthalmos
   4. A small, flattened facial appearance (midface hypoplasia) with mandibular prognathism
   5. An anatomic pattern of dentofacial deformity consistent with the diagnosis of vertical maxillary deficiency (short face syndrome, type 2)
3. Oral/dental (Jensen and Kreiborg 1990)
   1. High-arched palate
   2. Clefts involving soft and hard palates
   3. Persistence of the deciduous dentition with delayed eruption of the permanent teeth: a relatively constant finding
   4. Impaction of supernumerary permanent teeth
   5. Crowding/malocclusion
   6. Dentigerous cysts
3. Otolaryngologic manifestations (Segal and Puterman 2007)
   1. Hypoplasia of the maxilla and zygoma resulting in small face and sometimes asymmetric.
   2. Small or absent mastoid air cells.
   3. A high rate of Eustachian tube dysfunction.
   4. A higher prevalence of submucosal cleft palate.
   5. Narrow external auditory canals.
   6. Increase rates of recurrent childhood ear infections and various degrees of hearing loss.
   7. Clumping of the ossicles, stapes fixation, and sclerosis of the footplate have been described (Hawkins et al. 1975).
4. Shoulders and thorax
   1. Ability to bring shoulders together.
   2. Dimplings in the skin secondary to mild hypoplasia of the clavicles.
   3. Sloping, almost absent shoulders secondary to severe hypoplasia or the absence of the clavicles.
   4. A narrow thorax may lead to respiratory distress during early infancy.
5. Mildly disproportionate short stature with short limbs comparing to the trunk and more apparent in the upper limbs than the lower
6. The spine
   1. Scoliosis
   2. Kyphosis
7. Hands
   1. Brachydactyly
   2. Short distal phalanges
   3. Tapering fingers
   4. Nail dysplasia/hypoplasia
   5. Short, broad thumbs
   6. Clinodactyly of the fifth fingers
8. Other abnormalities
   1. Hearing loss (Dhooge et al. 2001)
   2. Abnormal gait
   3. Joint hypermobility
   4. Muscular hypotonia
9. Intelligence: normal
10. Cesarean section often required in the pregnant female due to dysplastic pelvis

Diagnostic Investigations

1. Radiographic findings: generalized failure of midline ossification (Jarvis and Keats 1974).
   1. The skull
      1. Delayed closure of the anterior fontanel (open fontanel) and sagittal and metopic sutures, often open for life
      2. Unossified areas of the skull becoming smaller with increasing age
      3. Multiple Wormian bone formation, particularly around the lambdoid suture
      4. Small or absent nasal bones

5. Segmental calvarial thickening
6. Underdeveloped maxilla
7. Delayed union of the mandibular symphysis
8. Platybasia
9. Small cranial base
10. A large foramen magnum
11. Hypoplastic sinuses (paranasal, frontal, mastoid)

2. Clavicles
   1. Absent clavicles: rare
   2. Pseudarthrosis of one or both clavicles
   3. Hypoplasia of the acromial end: common
   4. Two separate fragments
   5. Absent sternal end with the presence of the acromial end
   6. Bilaterality is the rule but not always the case
3. The chest
   1. Small bell-shaped thoracic cage
   2. Short, oblique ribs
   3. The presence of cervical ribs
   4. The scapula often hypoplastic with deficient supraspinatus fossae and acromial facets
   5. Associated deficiency in musculature
4. The pelvis
   1. Widened pubis symphysis resulting from delay in ossification during adulthood
   2. Hypoplasia and anterior rotation of the iliac wings
   3. Wide sacroiliac joints
   4. Delayed ossification of the pubic bone
   5. Large femoral epiphyses
   6. Unusual shape of a femoral head reminiscent of a "chef's hat" (Aktas et al. 2000)
   7. Broad femoral necks
   8. Frequent coxa vara
5. The spine
   1. Hemivertebrae
   2. Posterior wedging
   3. Spondylolysis and spondylolisthesis
   4. Syringomyelia
   5. Spina bifida occulta of the cervical, thoracic, or lumbar region
6. Tubular bones
   1. The presence of both proximal and distal epiphyses in the second metacarpals and metatarsals leading to excessive growth and length
   2. Frequent cone-shaped epiphyses and premature closure of epiphyseal growth plates leading to shortening of bones
   3. Wide epiphyses
   4. Unusually short distal phalanges and the middle phalanges of the second and fifth fingers
   5. Poorly developed terminal phalanges giving a tapered appearance to the digit
   6. Occasional hypoplasia, dysplasia, and aplasia of nails
7. Dentition: impacted, supernumerary teeth

2. Panoramic radiology.
   1. Provide an overview of over-retained deciduous teeth
   2. Demonstrate multiple impacted permanent and supernumerary teeth
3. Cone-beam computed tomography can study the location, alignment, proximity of teeth to vital structures, as well as quality and quantity of basal bone available (Gupta et al. 2015).
4. Cytogenetic study: visible complex chromosome rearrangements occasionally seen (Purandare et al. 2008).
5. Molecular genetic studies of mutations involving *RUNX2* (Mendoza-Londono and Lee 2013).
   1. Sequence analysis
   2. Deletion/duplication analysis

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased unless a parent is affected with the disorder or has germline mosaicism
   2. Patient's offspring: 50%
2. Prenatal diagnosis
   1. Ultrasonography (Stewart et al. 2000; Hermann et al. 2009)

   1. Absent or hypoplastic clavicles (Hamner et al. 1994; Hassan et al. 1997)
   2. Less calcified cranium than expected for gestational age
   3. Other craniofacial and skeletal anomalies
2. Prenatal diagnosis and preimplantation genetic diagnosis: direct DNA testing possible for those families with a known mutation in the *RUNX2*

3. Management (Cooper et al. 2001)
   1. Hearing evaluation
   2. Evaluation of the presence of submucous cleft palate
   3. Evaluation of obstructive sleep apnea
   4. Medical and surgical therapy for upper airway obstruction, recurrent and chronic sinusitis, and otitis
   5. Monitoring of skeletal and orthopedic complications
   6. Early surgical and orthodontic intervention of unerupted permanent teeth to induce eruption (Farrar and Van Sickels 1983)
   7. Orthognathic surgery to correct midface hypoplasia to reduce or correct significant upper respiratory complications and malocclusions
   8. Surgical and orthodontic management of vertical maxillary deficiency (Dann et al. 1980)
   9. Women with cleidocranial dysplasia at risk for a cesarean section delivery

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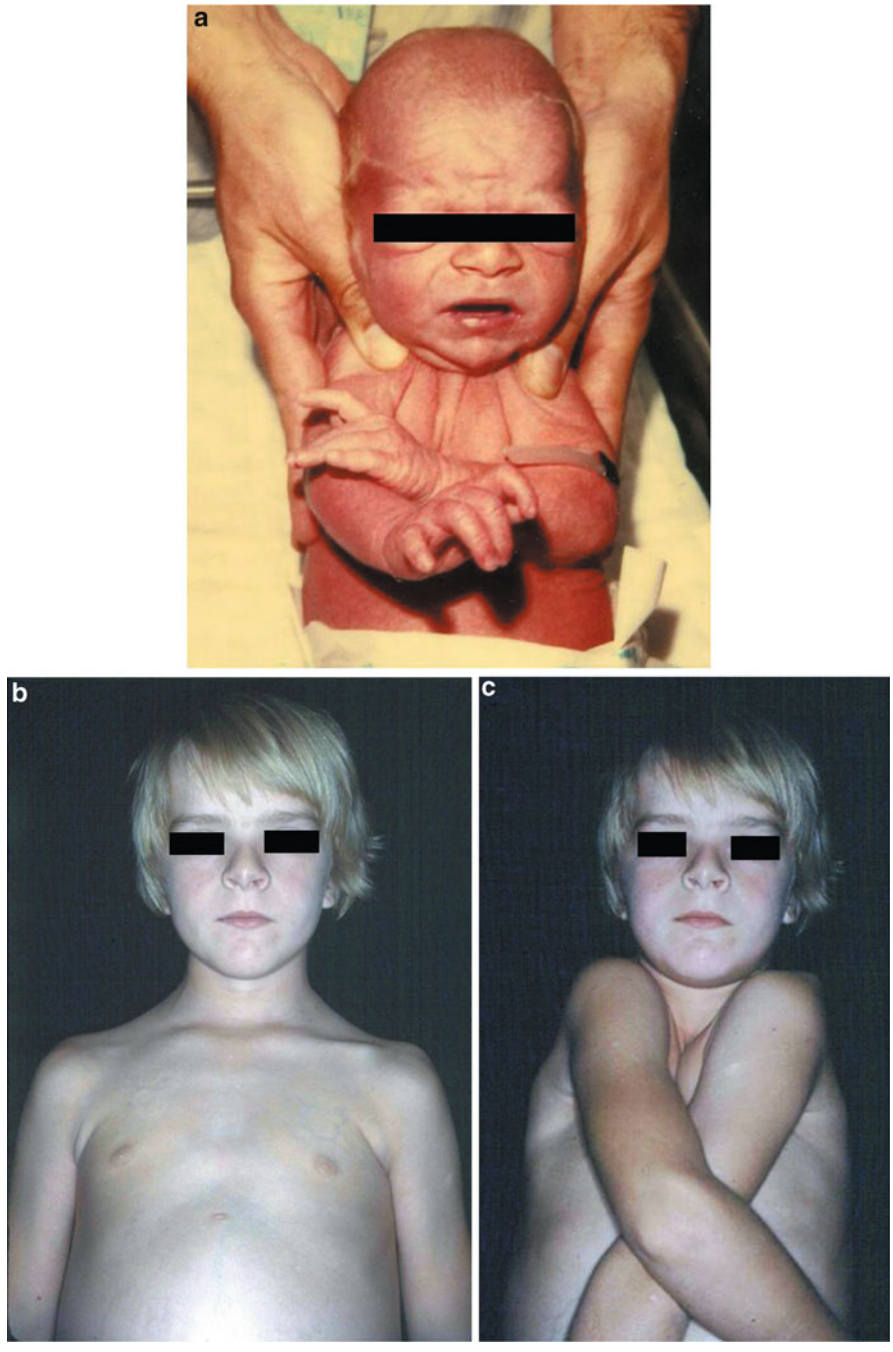

Fig. 1 (**a**–**c**) An infant and a child with cleidocranial dysplasia showing a large brachycephalic skull, frontal bossing, large anterior fontanel, widely spaced eyes, flat nasal bridge, and easily proximated shoulders

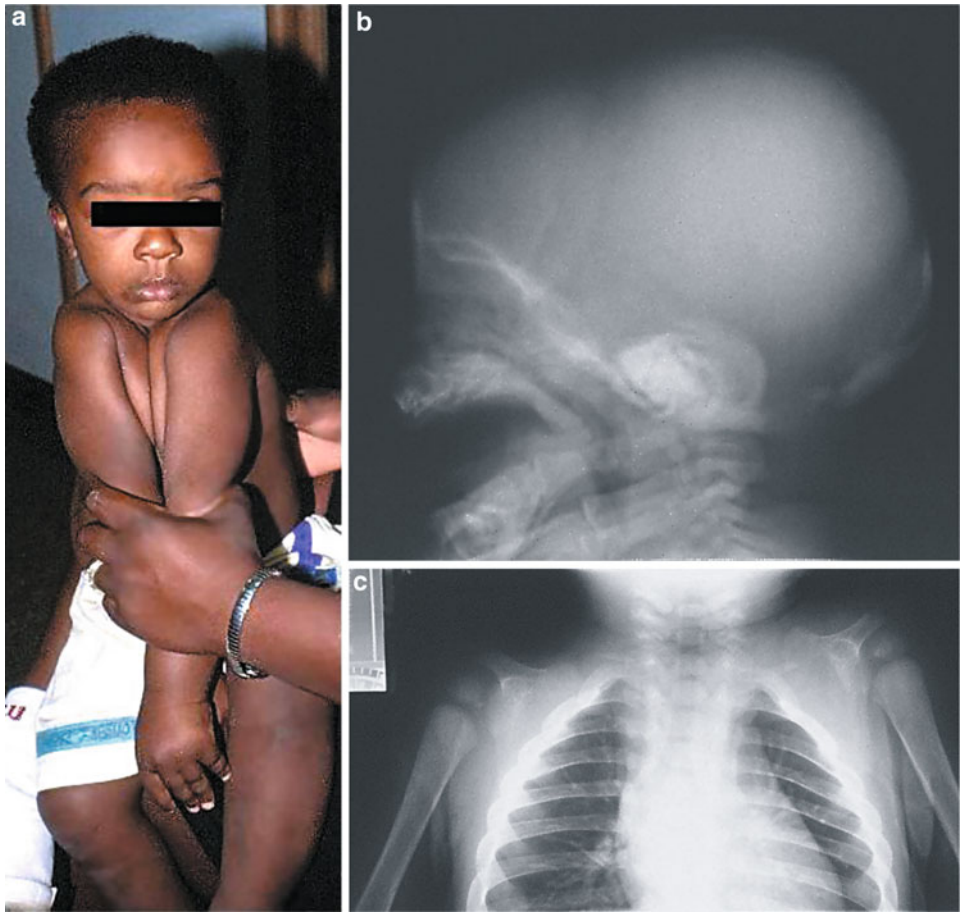

Fig. 2 (**a**–**c**) A child with cleidocranial dysplasia showing a prominent forehead, wide anterior fontanel and cranial sutures, wide eyes, depressed nasal bridge, and easily proximated shoulders. Radiographs show a poorly ossified skull, wide fontanels, cone-shaped thorax, and the absence of clavicles

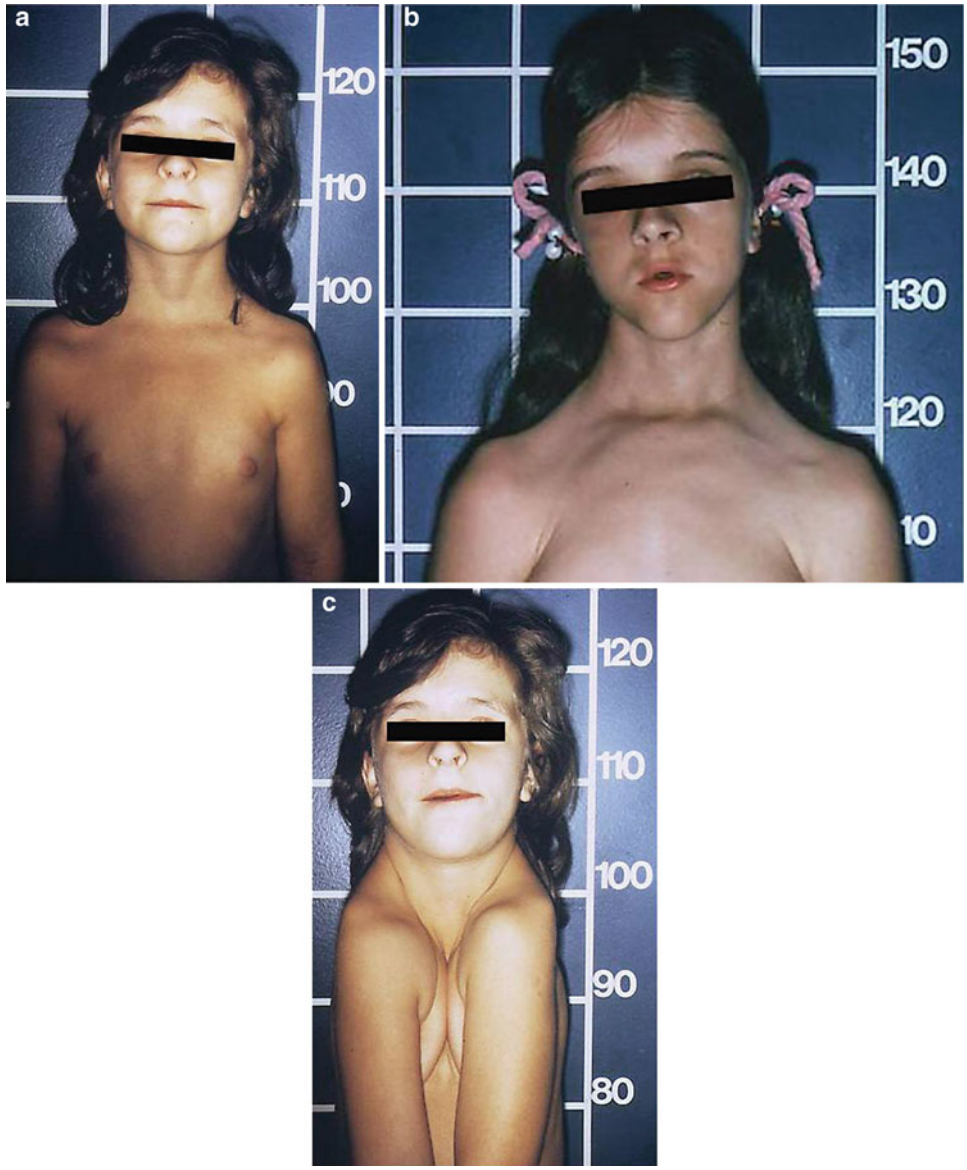

Fig. 3 (**a**–**c**) A girl with cleidocranial dysplasia at different ages showing short stature, frontal bossing, wide cranial sutures, wide set eyes, depressed nasal bridge, and sloping and easily proximated shoulders

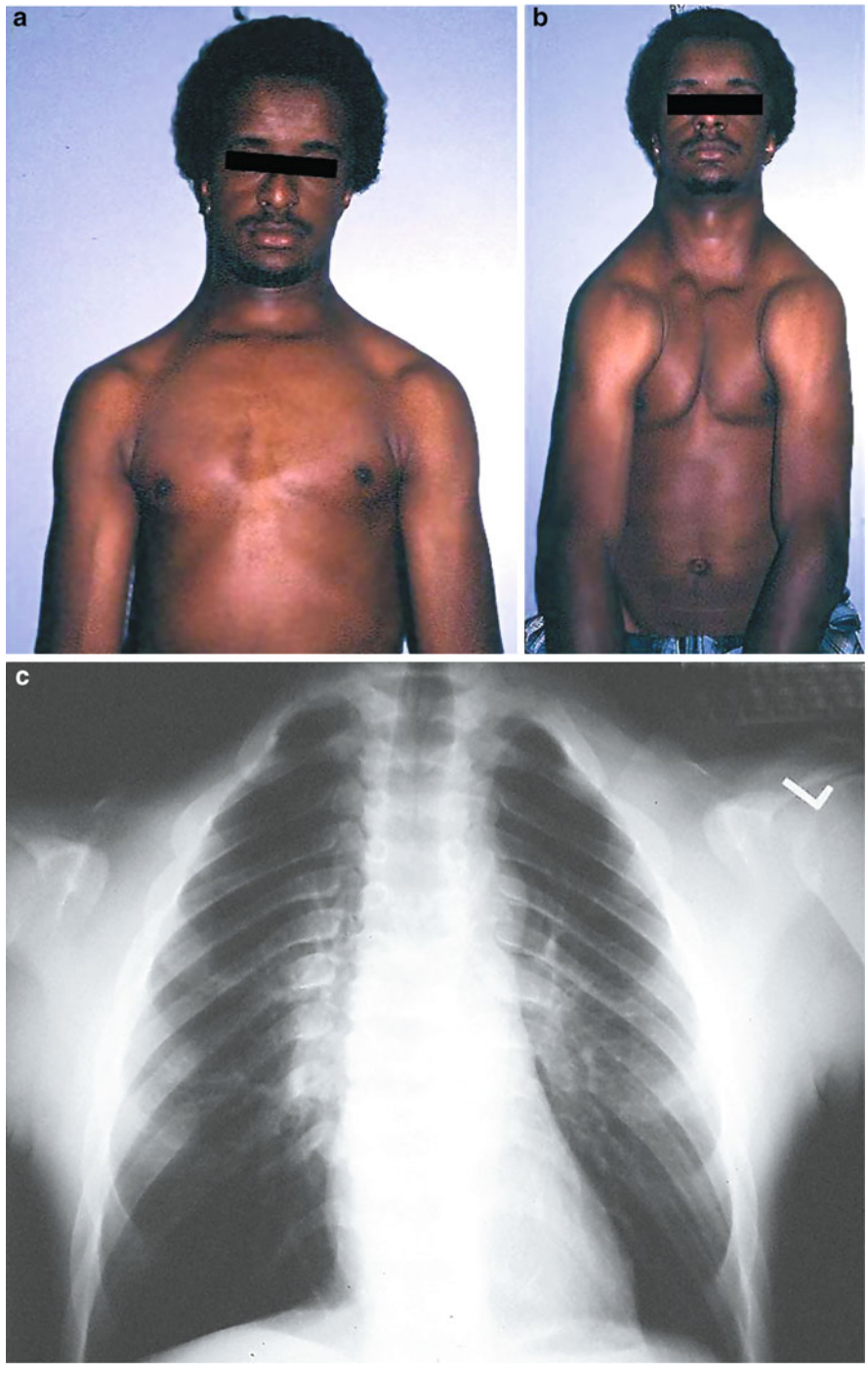

Fig. 4 (**a**–**c**) An adult with cleidocranial dysplasia showing widened cranial sutures, a characteristic face, and sloping and easily proximated shoulders. Radiograph showed a cone-shaped thorax with absent clavicles

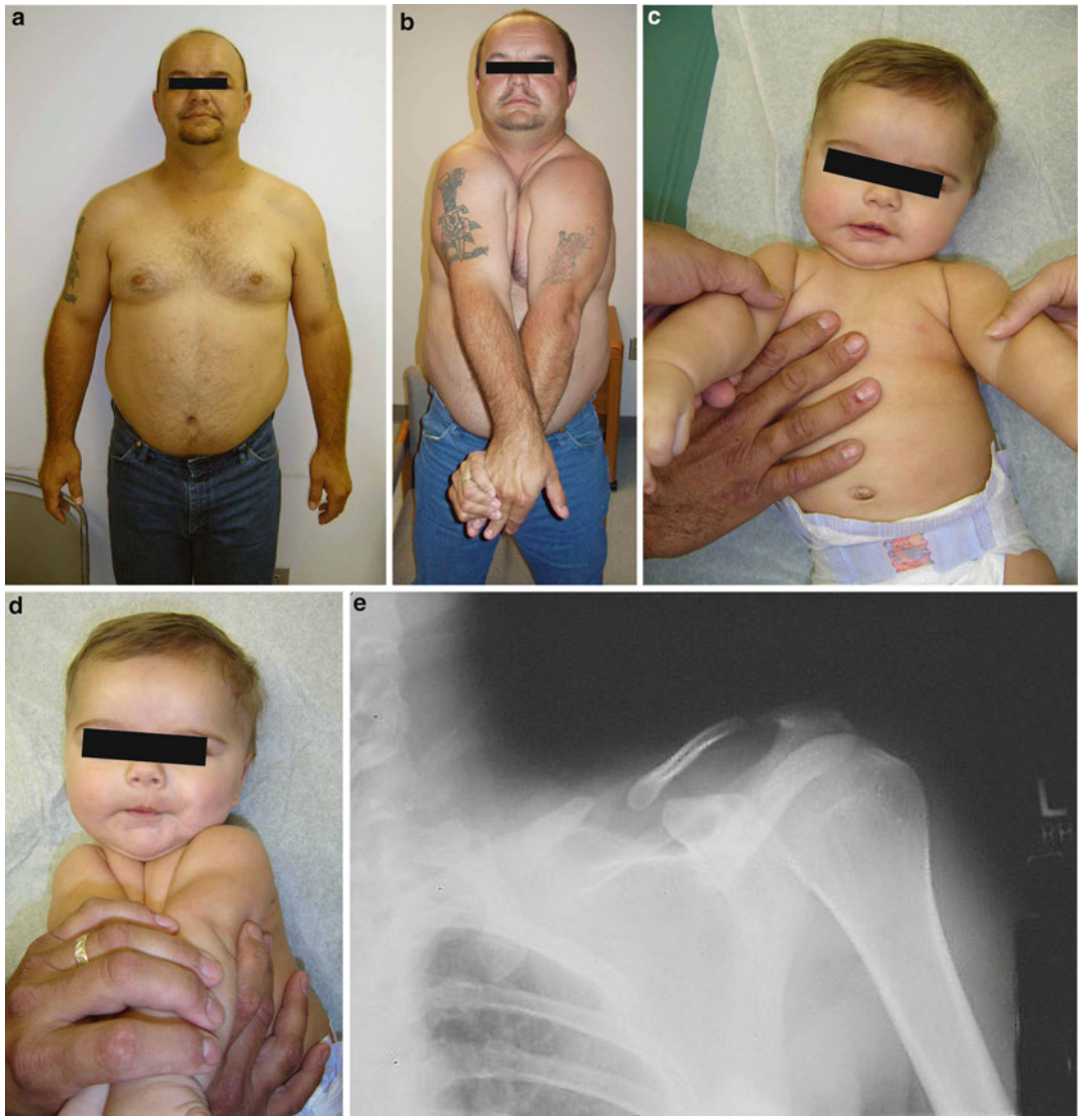

Fig. 5 (**a**–**e**) A father and a son with cleidocranial dysplasia showing characteristic clinical findings and a dysplastic left clavicle presenting as two separate fragments, illustrated by radiograph

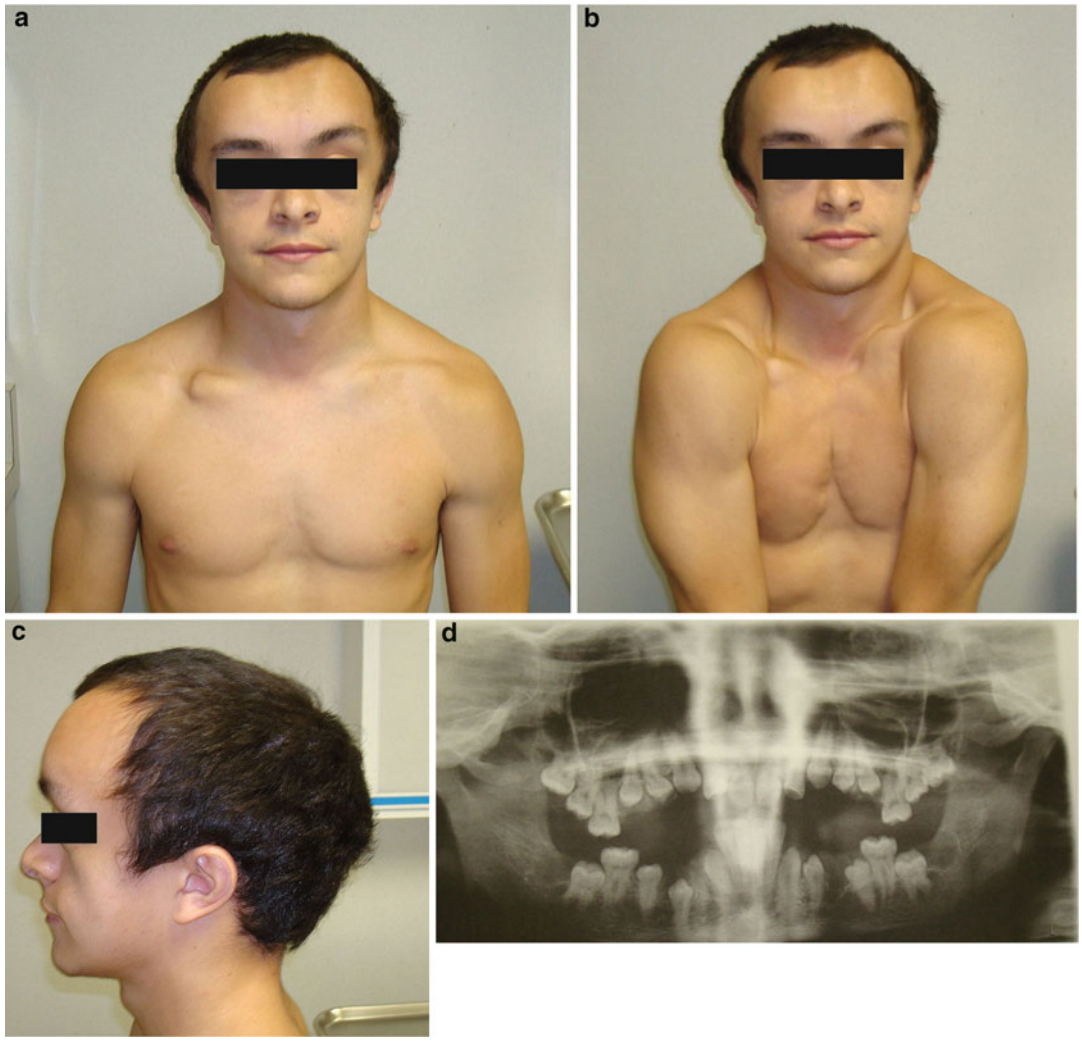

Fig. 6 (**a**–**d**) Another adult patient with cleidocranial dysplasia, showing typical clinical and dental features (radiograph)

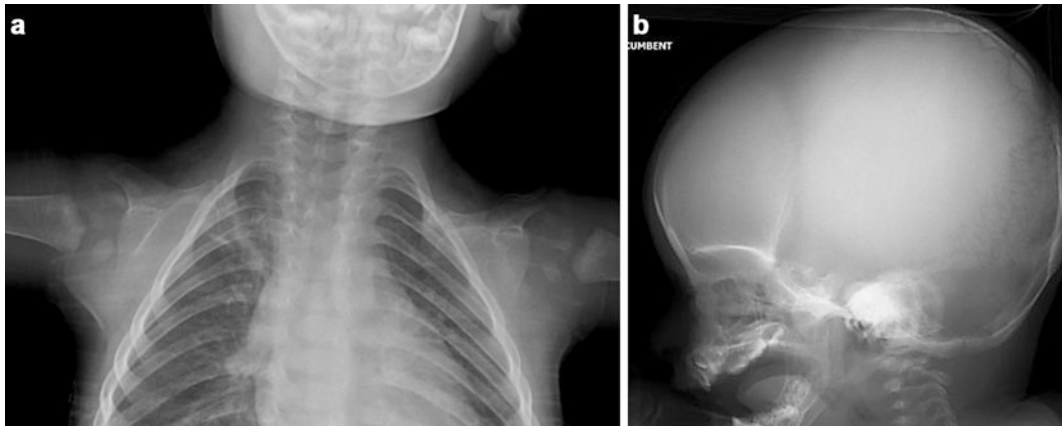

Fig. 7 (**a, b**) A 10-month-old female was seen with a large fontanel and absent clavicles. Her mother, maternal grandfather, and maternal uncle are known to have cleidocranial dysplasia. Chest X-ray showed absent bilateral clavicles (**a**). Skull radiograph (**b**) showed enlargement of the skull with Wormian bones in the lambdoidal sutures. There was widening of the sagittal and coronal sutures and prominent frontal bossing (Courtesy of Dr. Grace Guo)

Cloacal Exstrophy

Contents

Cloacal exstrophy is a rare congenital malformation resulting in exstrophy of the urinary, intestinal, and genital systems and is associated with anomalies of other organ systems. The term OEIS complex (*o*mphalocele, *e*xstrophy of the bladder, *i*mperforate anus, and *s*pinal defects) is used to describe the spectrum of malformations in cloacal exstrophy (Carey et al. 1978; Kaya et al. 2000). The incidence of cloacal exstrophy is estimated to be 1/200,000–1/400,000 live births (Carey et al. 1978; Hurwitz et al. 1987; Dick et al. 2001), although the true incidence may be as high as 1 in 10,000–50,000, taking into account the lack of diagnosis in stillborn infants (Keppler-Noreuil 2001).

Synonyms and Related Disorders

Covered cloacal exstrophy; OEIS complex (omphalocele-exstrophy of the bladder-imperforate anus-spinal defects)

Genetics/Basic Defects

1. Genetics
    1. Recurrence of OEIS complex in siblings (Smith et al. 1992) can be explained by the following mechanisms:
        1. Autosomal recessive inheritance
        2. Multifactorial determination
        3. Gonadal mosaicism for a dominant mutation
        4. Environmental factors
        5. Subclinical maternal disorder
        6. An unbalanced translocation between 9q and Y chromosome resulting in a 9q34.1-qter deletion, as a potential cause (Thauvin-Robinet et al. 2004)
        7. Mutations in a group of homeobox genes such as HLXB9 and HOX family which are involved in the development of embryonic mesoderm (Manner and Kluth 2005)
    2. Higher incidence of OEIS complex in monozygotic twins than in dizygotic twins suggests a possible genetic contribution to the occurrence of these defects
2. Basic defects of OEIS complex (Lee et al. 1999)
    1. Resulting from a single localized defect in the early caudal mesoderm at approximately 29 days of development
    2. Resulting in the following sequence of events:

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_45

1. Failure of cloacal septation leading to a persistence of the cloaca with a rudimentary mid-gut and imperforate anus
2. Failure of breakdown of the cloacal membrane leading to exstrophy of the cloaca, omphalocele, and lack of fusion of the pubic rami
3. The lumbosacral somites giving rise to abnormal vertebrae in which there is protrusion of the dilated spinal cord (hydromyelia) and a cystic, skin-covered mass in the lumbosacral region

3. Cloaca and cloacal exstrophy
   1. Cloaca
      1. A transient embryological structure
      2. The term "cloaca" literally means "sewer" in Latin
      3. The term used to represent the emptying of the gastrointestinal and urogenital tracts into a common sinus
      4. Defined as a common chamber (orifice) in the perineum into which the urinary, genital, and intestinal tract drain
   2. Cloacal exstrophy: The common orifice empties onto the anterior abdominal wall

Clinical Features

1. Classic exstrophy of the cloaca (Lee et al. 1999)
   1. Lower abdominal defect
   2. Exposure of intestinal and bladder mucosa
   3. Accompanied by the following anomalies
      1. Omphalocele
      2. Imperforate anus
      3. Urogenital anomalies
2. Gastrointestinal malformations (Woo et al. 2010)
   1. Omphalocele
   2. Imperforate anus, anal atresia/stenosis
   3. Rectovestibular/rectovesical fistula
   4. Small bowel anomalies (short gut syndrome)
      1. Foreshortened small bowel
      2. Rotational anomalies
      5. Intestinal duplication
      6. Meckel diverticulum
      7. Inguinal hernias
3. CNS malformations
   1. Spina bifida: the most common CNS malformation
      1. Leptomeningocele
      2. Myelomeningocele
      3. Meningocele
      4. Spina bifida occulta
      5. Cord tethering
   2. Craniosynostosis
4. Skeletal malformations
   1. Vertebral anomalies (Loder and Dayioglu 1990)
      1. Abnormal lumbosacral segmentation
      2. Congenital scoliosis and kyphosis
      3. Partial sacral agenesis
      4. Interpedicular lumbar widenings
   2. Pubic diastasis
   3. Lower extremity anomalies
      1. Clubfoot deformities
      2. Limb deficiencies
5. Genitourinary malformations
   1. Bladder anomaly
      1. Open
      2. Separated into two halves
      3. Flanking the exposed interior of the cecum
      4. Openings to the remainder of the hindgut
      5. Prolapse of the terminal ileum as a "trunk" of bowel onto the cecal plate
   2. Renal anomalies
      1. A single kidney
      2. Rudimentary kidney
      3. Pelvic ectopic kidney
      4. Ureteropelvic junction obstruction
      5. Malrotation
      6. Crossed renal ectopia
   3. Ureteral anomalies
      1. Duplication
      2. Ectopic insertion
      3. Distal stricture and megaureter
   4. Male genitalia anomalies
      1. Diminutive or absent penis (30% of males) (Schober et al. 2002)
      2. Bifid penis

3. Hemiglans located caudal to each hemibladder
5. Female genitalia anomalies
   1. Bifid clitoris
   2. Uterine duplication
   3. Vaginal duplication
   4. Vaginal agenesis
6. Prognosis (Lund and Hendren 2001)
   1. Used to be uniformly fatal malformation in its worst form
   2. Currently with an 80–100% survival rate due to early surgical repair but accompanied by lifelong severe morbidity
7. Covered cloacal exstrophy: frequently misdiagnosed condition (Bischoff et al. 2013)
   1. Low implantation of the umbilicus
   2. A single large perineal orifice
   3. Separation of the pubic bones
   4. Imperforate anus
   5. Intraabdominal anatomic abnormalities: resemble those observed in cases of cloacal exstrophies
   6. Considered as part of the cloacal exstrophy spectrum, even when the majority of the patients have an intact abdominal wall

Diagnostic Investigations

1. Evaluation of associated malformations
2. Karyotyping for genetic sex
3. Renal ultrasonography for renal and upper urinary tract anomalies
4. Voiding cystourethrography to assess bladder capacity in early childhood in preparation for continence reconstruction
5. Radiologic features (Meglin et al. 1990)
   1. Symphysis pubis diastasis: a prerequisite for diagnosis of cloacal exstrophy
   2. Hip subluxations/acetabular dysplasia
   3. Posterior element dysraphism with hemivertebrae, vertebral fusions, or absence of vertebral bodies
   4. Sacral dysplasia with posterior element dysraphism, widened neural foramina, axial torsion, and marked underdevelopment
   5. Scoliosis/gibbus deformity
   6. Hypoplasia of the thoracic cage
   7. Limb anomalies: clubfoot and hypoplastic lower extremity
   8. Bladder anomaly: classic cloacal exstrophy (bladder is separated into two hemi-bladders by a portion of interposed bowel)
   9. Renal anomalies: pelvic kidneys, renal ectopia, renal agenesis, renal atrophy, bifid collecting systems, and upper tract anomalies
   10. Genital anomalies: cryptorchidism (in genotypic males), duplication of internal genitalia with duplicated or bicornuate uterus, double cervix, duplicated vagina, and hypoplastic fallopian tube (in genotypic females)
   11. CNS anomalies: spinal dysraphism associated with lumbar lipomyelomeningocele, cord lipoma, meningocele, and myelomeningocele
   12. Gastrointestinal anomalies: bladder bisection by the ileocecal portion of the bowel, blind-ending colon with imperforate anus, malrotation or nonrotation, large-bowel duplication, appendiceal duplication, anatomically short small bowel, and hypoplastic superior half of the anterior abdominal wall
   13. Pelvic floor evaluated by MRI and 3D CT: hypoplasia of the levator musculature
6. Radiographic studies to demonstrate spinal dysraphism (Dick et al. 2001)
   1. Plain spinal radiographs
   2. Myelography
   3. CT
   4. CT myelography
   5. Spinal MRI to identify occult abnormalities that predispose to symptomatic spinal cord tethering (Lund and Hendren 1993)

Genetic Counseling

1. Recurrence risk (Mathews et al. 1998)
   1. Patient's sib: recurrence in subsequent pregnancies noted in one report

2. Patient's offspring: Lack of offspring from patients with cloacal exstrophy making the determination of inheritance difficult

2. Prenatal diagnosis by ultrasonography
   1. Elevated maternal serum α-fetoprotein (AFP) in OEIS complex. The open ventral wall defect likely results in AFP leakage (Gosden and Brock 1981; Kutzner et al. 1988).
   2. Ultrasonography (Chitrit et al. 1993; Austin et al. 1998; Keppler-Noreuil et al. 2007)
      1. Major ultrasound criteria
         1. Nonvisualization of the bladder (91%)
         2. A large midline infraumbilical anterior wall defect or cystic anterior wall structure (persistent cloacal membrane) (82%)
         3. Omphalocele (77%)
         4. Lumbosacral myelomeningocele (68%)
      2. Minor (less frequent) ultrasound criteria
         1. Lower limb defects (23%)
         2. Renal anomalies (23%)
         3. Ascites (14%)
         4. Widened pubic arches (18%)
         5. A narrow thorax (9%)
         6. Hydrocephalus (9%)
         7. A single umbilical artery (9%)
      3. Despite these criteria, often the full extent of anomalies cannot be identified prenatally
      4. The elephant trunk-like US finding as a new criterion for the prenatal diagnosis (Hamada et al. 1999; Clements et al. 2014)
      5. Prenatal ultrasound findings can be confused or difficult to differentiated with the following conditions:
         1. Limb–body wall complex
         2. Pentalogy of Cantrell
         3. Gastroschisis
         4. Amniotic band sequence
3. Fetal MRI (Gobbi et al. 2008; Bischoff et al. 2012; Calvo-Garcia et al. 2013)
   1. Absence of a normal bladder despite normal amniotic fluid volume (in the form of persistently absent bladder or thin-walled protruding anterior pelvic cyst)
   2. Protuberant anterior pelvic contour representing the exstrophy
   3. Lack of meconium in the rectum and colon supporting a primitive blind-ending hindgut
   4. Omphalocele (usually small and low)
   5. Additional findings: potential visualization of the prolapsed terminal ileum and the lateral bladder plates, distal ureters extending to the anterior abdominal wall, closed neural tube defects, and genitourinary abnormalities (hydronephrosis, hydroureter)
   6. Incompletely formed external genitalia
   7. Vaginal hydrocolpos (expanded fluid filled vaginal cavity)
   8. Infraumbilical anterior abdominal wall defect (omphalocele, bladder exstrophy)
   9. Midline structure corresponding to the "elephant trunk-like" (representing the intussuscepted ileum) image that is a characteristic feature of cloacal exstrophy
4. Management (Lund and Hendren 1993; Mathews et al. 1998)
   1. Appropriate parental counseling and referral to a center with significant expertise in the management of cloacal exstrophy when prenatal diagnosis is made (Bischoff et al. 2012)
   2. Medical stabilization of the infant
      1. Fluid and electrolyte replacement
      2. Parenteral nutrition
      3. Moisten the exstrophied bladder and bowel with saline and cover them with a protective plastic dressing
      4. Daily prophylactic antibiotics
   3. Gender assignment
      1. Evaluation of the genitalia
      2. Decision limited to the genetic male patients with cloacal exstrophy
         1. Male gender assignment appropriate for male patients with adequate bilateral or unilateral phallic structures
         2. Male neonates with minimal phallic structures: appropriate to raise as female subjects with early excision of the gonads

3. Appropriate hormonal manipulation to improve psychosexual dysfunction
4. Improvements in phallic reconstruction eventually allow most genetic male patients to be assigned male gender

3. Initial sexual reassignment to be done in conjunction with extensive family counseling as well as continued counseling for the parents and children

4. Management of gastrointestinal malformations
   1. Closure of omphalocele
   2. Combined with gastrointestinal diversion or reconstruction
      1. Ileostomy with resection of the hindgut remnant
      2. Colostomy
5. Management of genitourinary malformations
   1. Bladder closure (Diamond and Jeffs 1985)
   2. Initial bladder excision and urinary diversion (Smith et al. 1997)
   3. Further augmentation or urinary diversions to achieve continence
   4. Initial stages of surgery (Jeffs 1978)
      1. Should be undertaken at birth when the pelvic ring can be approximated without osteotomy and the bladder mucosa has not deteriorated from inflammatory changes
      2. Parental attitudes toward the child as well as successful reconstruction may both be best served by immediate surgery to begin reconstruction and reduce the visible defect
   5. Pelvic osteotomy: a well-established method of obtaining a successful cloacal exstrophy closure (Cervellione 2011)
6. Management of CNS malformations
   1. Closure of myelomeningocele
   2. Cord untethering
   3. Spinal fusion
   4. Cranial expansion for craniosynostosis
7. Management of orthopedic malformations
   1. Manage myelodysplasia
   2. Pelvic osteotomies
   3. Various orthopedic devices to assist with ambulation

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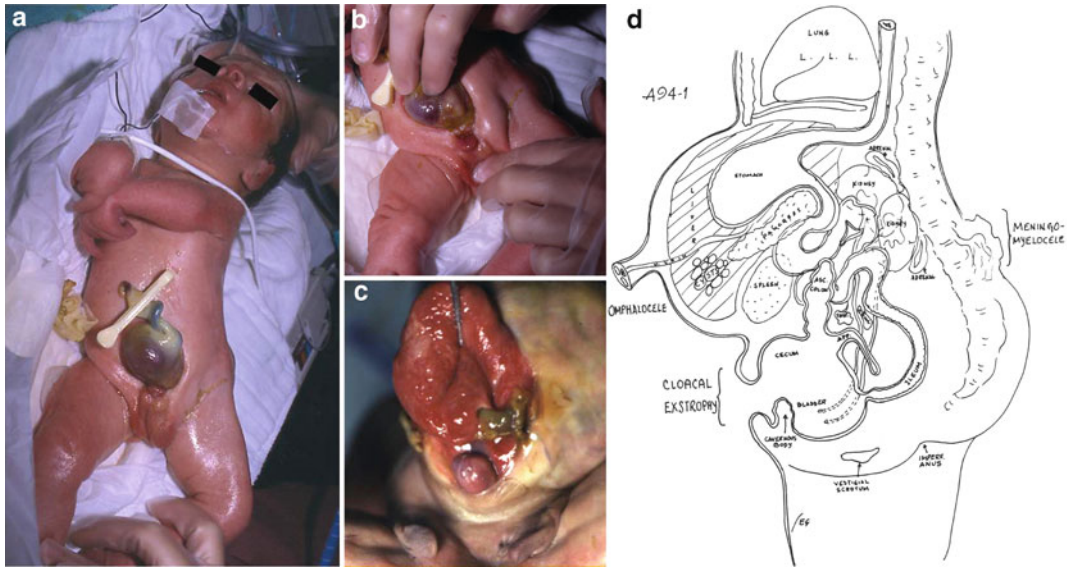

Fig. 1 Two infants (**a**, **b**, **c**) with cloacal exstrophy. The schematic diagram (**d**) illustrates the anatomy of Cloacal exstrophy, including omphalocele, exstrophy of the bladder, imperforate anus, and Meningomyelocele in the second infant (**c**)

Clubfoot

Contents

Clubfoot, or talipes equinovarus, is one of the most common congenital deformities affecting the lower limbs in approximately 1–2 in 1,000 live births. The incidence is higher in Hispanics and lower in Asians. Although clubfoot is recognizable at birth, the severity of the deformity can vary from mild to an extremely rigid foot that is resistant to manipulation (Dobbs and Gurnett 2009).

Synonyms and Related Disorders

Congenital talipes equinovarus; Syndromic clubfoot; TARP syndrome

Genetics/Basic Defects

1. Pathogenesis:
    1. Genetic cause: suggested because it tends to run in families (Lochmiller et al. 1998).
    2. Oligohydramnios: suggested as a cause from early amniocentesis data (CEMAT Group 1998).
    3. Osseous deformities (Shapiro and Glimcher 1979), muscle abnormalities (Herceg et al. 2006), and arrested fetal development (Fukuhara et al. 1994): hypothesized to play a role in pathogenesis.
    4. Beta-catenin mediates soft tissue contracture in clubfoot (Poon et al. 2009).
2. Etiology (Dobbs and Gurnett 2009):
    1. Most commonly as an isolated birth defect and considered idiopathic (Wynne-Davies 1964). Various theories on etiologies include:
        1. Vascular deficiencies (Hootnick et al. 1982)
        2. Environmental factors:
            1. Early amniocentesis (<13 weeks gestation): associated with an increased risk in talipes equinovarus (an uncommon risk factor), compared to midgestational amniocentesis or chorionic villus sampling (Philip et al. 2004)
            2. Partially associated with amniotic fluid leakage: suggesting that oligohydramnios occurring at a critical gestational period may be detrimental to foot development (Tredwell et al. 2001)
            3. Environmental exposure to cigarette smoke in utero: an independent risk factor (Honein et al. 2000)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_46

3. In utero positioning (Dunn 1972)
4. Abnormal muscle insertions (Bonnell and Cruess 1969)

2. Genetic factors suggested by:
   1. Thirty-three percent concordance of identical twins and the fact that nearly 25% of all cases are familial (Lochmiller et al. 1998)
   2. Differences in clubfoot prevalence across ethnic populations with the lowest prevalence in Chinese (0.39 cases per 1,000 live births) and the highest in Hawaiians and Maoris (seven per 1,000) (Beals 1978; Chung et al. 1969)
3. Prevalence of additional congenital anomalies (Gurnett et al. 2008b):
   1. Chromosomal abnormalities:
      1. Trisomy 18 syndrome in patients with clubfoot (24–50%) (Bakalis et al. 2002; Gurnett et al. 2008b).
      2. Other numerous cytogenetic abnormalities produce individuals with multiple congenital anomalies including clubfeet.
   2. Distal arthrogryposis
   3. Myelomeningocele
   4. Orthopedic abnormalities:
      1. Fibular hemimelia
      2. Polydactyly
      3. Hip dysplasia
      4. Ulnar longitudinal deficiency

3. Part of a genetic syndrome:
   1. An autosomal recessive inheritance of clubfoot, for example:
      1. Diastrophic dwarfism
      2. Larsen syndrome
      3. Smith-Lemli-Opitz syndrome
   2. An autosomal dominant inheritance of clubfoot, for example:
      1. Distal arthrogryposis type 2A (whistling face syndrome)
      2. Distal arthrogryposis type 1
      3. Freeman-Sheldon syndrome
   3. An X-linked recessive inheritance of clubfoot: for example, Pierre-Robin syndrome
   4. Other syndromic clubfoot, for example:
      1. Meningomyelocele/spina bifida
      2. Sacral agenesis
      3. Constriction band syndrome
      4. Congenital myopathy
4. Specific involvement of the foot also appears to exclude many of the skeletal muscle contractile genes that are responsible for distal arthrogryposis (Sung et al. 2003a, b; Toydemir et al. 2006; Veugelers et al. 2004) in the causation of idiopathic clubfoot, as mutations in these genes cause both upper and lower extremity involvement and were not identified in idiopathic clubfoot patients (Gurnett et al. 2009).
5. Genes and proteins involved in congenital talipes equinovarus (Bacino and Hecht 2014):
   1. Paired-like homeodomain 1 (*PITX1*):
      1. Recent identification of a rare mutation in the transcription factor PITX1 in a large family with idiopathic clubfoot: importance of genes involved in early limb development (Gurnett et al. 2008a)
      2. The first gene implicated in clubfoot that explains the specific involvement of the foot, since *PITX1* is expressed nearly exclusively in the hindlimb and is responsible for rapid evolutionary changes in pelvic morphology in lower vertebrates (Shapiro et al. 2004)
   2. Transcription factor (*TBX4*):
      1. Expressed in the hindlimb
      2. Involved in limb muscle and tendon patterning
      3. A 17q23.1q23.2 2.2 Mb microduplication (Alvarado et al. 2010; Lu et al. 2012):
         1. Segregated in three different families in an autosomal dominant fashion with reduced penetrance in 30% of individuals and variable expression
         2. A common cause for familial isolated clubfoot
         3. Deletion in the same region involving *TBX4* in one of the families with two siblings affected with clubfeet
         4. A small 350 kb 17q23.1q23.2 microduplication identified in one multiplex family: encompassed *TBX4*, *NACA2*, and part of *BRIP1*

3. RNA-binding motif protein 10 (*RBM10*) mutation:
    1. Associated with a syndromic form of congenital talipes equinovarus known as TARP syndrome (De Marco et al. 2012; Janda et al. 2012)
    2. Acronym for TARP:
        1. *T*alipes equinovarus
        2. *A*trial septal defect
        3. *R*obin sequence (micrognathia, glossoptosis, and cleft palate)
        4. *P*ersistence of left superior vena cava
4. Muscle contraction genes:
    1. Mutations in *TPM2*, *MYH3*, *TNNT3*, *TNNI2*, *MYH3*, *MYH3*, and *PIEZO2* gene cause distal arthrogryposis (DA1, DA2A, DA2B, DA7 (Bamshad et al., 1996), and DA5 (Coste et al., 2013)).
    2. *ZC4H2* gene mutation causes X-linked Wieacker-Wolff syndrome (pes equinovarus, hip dislocations, and scoliosis) (Wieacker et al. 1985; Hennekam et al. 1991; Hirata et al. 2013).
5. Homeobox A and D genes:
    1. Chromosomal abnormalities, deletions, and duplications in syndromic clubfoot (Brewer et al, 1998, 1999).
    2. 2q31-33 deletion region identified association with *CASP8*, *CASP10*, and *CFLAR*: these genes are involved in the mitochondria-mediated apoptotic pathway which is consistent with the key role that apoptosis plays in limb and muscle development (Ester et al. 2009; Heck et al. 2005).
6. Vascular and muscular abnormalities:
    1. Deficiency or absence of the anterior tibial artery, and of its derivative, the dorsalis pedis artery, has been reported in clubfeet and other lower limb malformations like fibular deficiency and tibial hypoplasia.
    2. Arterial dysgenesis may play a role in the etiology of clubfoot (Sodre et al. 1990; Kruse et al. 2009).
    3. MRI: showed abnormalities of the anterior tibial artery and dorsalis pedis artery in clubfoot and abnormalities of posterior tibial artery in vertical talus (Kruse et al. 2009).
    4. Vascular involvement can perhaps be secondary to environmental exposures like maternal smoking in pregnancy, use of misoprostol, and early amniocentesis.
    5. *PITX1* mutations may lead to decreased muscle volume development and vascular maldevelopment with narrowing of anterior peroneal and tibial arteries.
6. Multifactorial inheritance:
    1. Multifactorial and possibly polygenic causation suggested (Lochmiller et al. 1998; Wynne-Davies 1972).
    2. Most infants with clubfoot (idiopathic congenital clubfoot) have no identifiable genetic, cytogenetic, syndromal, or extrinsic cause. The idiopathic congenital clubfoot is primarily caused by a multifactorial inheritance.
    3. The observed percentages of talipes equinovarus in relatives of an affected child are consistent with a multifactorial mode of inheritance (Wynne-Davies 1965, 1972):
        1. Monozygotic twins with about 32.5% rate of concordance (both twins affected with clubfoot)
        2. First-degree relative (parents and siblings) occurrence rate:
            1. 2.14%
            2. About 17 times as high as the population rate
        3. Second-degree relative (aunts and uncles) occurrence rate:
            1. 0.61%
            2. About six times as high as the population rate
        4. Third-degree relative (cousins) occurrence rate:
            1. 0.2%
            2. Near the incidence in the general population
7. Extrinsic causes:
    1. Teratogenic agents:
        1. Sodium aminopterin

   2. Position in utero at the time of d-tubocurarine paralysis
2. Loss of amniotic fluid during gestation
3. Mechanical forces or positional influence (restriction of fetal foot movement by the uterus)
4. Drugs

Clinical Features

1. Bilateral in about 50% of cases
2. Three major components of talipes equinovarus:
   1. Equinus (limitation of extension) of the ankle and subtalar joint
   2. Hindfoot and midfoot varus
   3. Forefoot adduction
3. Evaluation of the foot, ankle, and leg:
   1. "Down and in" appearance
   2. Shorter and wider than the normal foot
   3. Flexible, softer heel due to hypoplastic calcaneus
   4. Concave medial border
   5. Transverse plantar creases or clefts at the midfoot and at the posterior part of the ankle
   6. Highly convex lateral border
   7. Internally rotated heel making the soles of the feet facing each other in cases of bilateral deformities
   8. Internal rotation of the leg
   9. Variable rigidity of the foot
   10. Calf and foot atrophy (more obvious in older child than in infant)
   11. Mild hypoplasia of the tibia, fibula, and bones of the foot
   12. Pronounced tightness of the Achilles tendon with very little dorsiflexion
   13. Range of motion of the joints
4. Idiopathic clubfoot:
   1. An isolated deformity of the foot and leg:
      1. Identifiable in utero
      2. Consists of four components:
         1. Equinus
         2. Hindfoot varus
         3. Forefoot adductus
         4. Cavus
   2. When untreated, children with clubfoot walk on the sides and/or tops of their feet, resulting in (Dobbs and Gurnett 2009):
      1. Callus formation
      2. Potential skin and bone infections
      3. Inability to wear standard shoes
      4. Substantial limitations in mobility and employment opportunities
   3. By far the most common form.
   4. Occurring more common in males than in females (2 ~ 2.5:1).
   5. Normal upper limbs.
   6. Associated features:
      1. Joint laxity
      2. Congenital dislocation of the hip
      3. Tibial torsion
      4. Ray anomalies of the foot (oligodactyly)
      5. Absence of some tarsal bones
      6. A history of other foot anomalies in the family
5. Various associated anomalies in syndromic talipes equinovarus

Diagnostic Investigations

1. Plain radiography (Chung 2015):
   1. Talocalcaneal parallelism: radiographic feature of clubfeet (Patel 2015)
   2. Limitations:
      1. Risk of ionizing radiation
      2. Proper positioning difficult
      3. Lack of ossification in some involved bones:
         1. Only talus, calcaneus, and metatarsals are ossified in neonates.
         2. Cuboid ossification at 6 months.
         3. Cuneiform ossification at 1 year.
         4. Navicular ossification after 3 years.
   3. Assessment:
      1. Hindfoot equinus (plantar flexion of the anterior calcaneus)
      2. Hindfoot varus (calcaneus rotated around the talus into a varus, i.e., toward midline, position)
      3. Forefoot varus (increased forefoot supination on dorsoplantar view)

4. Common measurements:
    1. Anteroposterior talocalcaneal angle (typically $<20^\circ$ in a clubfoot)
    2. Talar-first metatarsal angle:
        1. Up to about 30° of valgus in a normal foot
        2. Mild-to-severe varus in a clubfoot
    3. Medial displacement of the cuboid ossification center on the axis of the calcaneus representing either of the following:
        1. Angular deformity of the calcaneus
        2. Medial subluxation of the cuboid on the calcaneus
2. CT scan (Chung 2015):
    1. Limitations:
        1. Risk of ionizing radiation
        2. Lack of ossification of the tarsal bones
        3. Susceptible to motion artifact
    2. Advantage: better assessment of complex three-dimensional deformity by three-dimensional reconstructions
3. MRI (Chung 2015):
    1. Limitations:
        1. Need for patient sedation
        2. Loss of signal caused by ferromagnetic effects of fixation devices
    2. Advantages:
        1. Capability of multiplanar imaging
        2. Excellent depiction of following:
            1. Ossific nuclei
            2. Cartilaginous anlage
            3. Surrounding soft tissue structures
    3. Findings:
        1. Plantar flexion
        2. Varus angular deformity of the talus, calcaneus, and cuboid
4. Ultrasonography (Chung 2015):
    1. Limitation: inability of the beam to penetrate all of the bones, particularly if a post-operative scar is present
    2. Advantages:
        1. Lack of ionizing radiation
        2. No need for sedation
        3. Ability to depict non-ossified portions of bone
        4. Capacity for dynamic imaging
    3. Findings:
        1. Interosseous relationship in normal feet and clubfeet.
        2. Multiple views can be obtained through a dynamic range of motion.

Genetic Counseling

1. Recurrence risk depends on underlying etiology:
    1. Patient's sib:
        1. Multifactorial trait: approximately 2.1% (first-degree relatives)
        2. Autosomal recessive: 25%
        3. Autosomal dominant: not increased unless a parent is affected
        4. X-linked recessive: 50% of male sibs affected if the mother is a carrier
        5. Chromosomal: increased risk, especially a parent is a translocation carrier
    2. Patient's offspring:
        1. Multifactorial: approximately 2.1%.
        2. Autosomal recessive: not increased unless the spouse is also a carrier.
        3. Autosomal dominant: 50%.
        4. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
        5. Chromosomal: increased risk.
2. Prenatal diagnosis by ultrasonography: (Bar-On et al. 2005)
    1. Wide variation in the accuracy of ultrasonography:
        1. Isolated clubfoot:
            1. Better prognosis especially detected in the 3rd trimester of pregnancy
            2. Poor correlation between the prenatal appearance of the foot on ultrasound findings and the severity of the talipes at birth
        2. Complex clubfoot: associated with syndromic, neuromuscular, or chromosomal conditions.
        3. Overall prognosis is related to the presence of associated abnormalities (Treadwell et al. 1999).

2. The abnormalities detected at 20 weeks: present to some degree at birth (Tillett et al. 2000)

3. Management (Cummings and Davidson 2002):
   1. Traditional nonoperative approach: stretching and manipulations:
      1. Proper manipulation technique: the most important for treatment of clubfoot (Ippolito et al. 2003).
      2. Appropriate initial management for all children with clubfoot.
      3. Splintage begins at 2–3 days after birth.
      4. Order of correction:
         1. Forefoot adduction
         2. Forefoot supination
         3. Gentle correction of equinus
      5. Two methods most widely performed and with highest reported long-term success rates:
         1. Kite and Lovell method
         2. Ponseti method (Scher 2006)
      6. "Montpellier" method: remains popular in France.
   2. Ponseti method (Ponseti 1992): currently widely utilized with high success rate in treating clubfoot:
      1. Goal:
         1. To reduce or eliminate deformity (equinus, hindfoot varus, forefoot adductus, and cavus)
         2. To attain functional, pain-free, plantigrade foot with good mobility and without calluses and without need to wear modified shoes
      2. Techniques:
         1. Serial manipulation
         2. A specific technique of cast application
         3. Possible percutaneous Achilles tenotomy
      3. Significant risk factors for the recurrence of clubfoot deformity after correction with the Ponseti method (Dobbs et al. 2004):
         1. Noncompliance of the parents
         2. Lower educational level of the parents
      4. Outcome:
         1. A safe, effective, and low-cost treatment for neglected idiopathic club foot presenting after walking age (Lourenço and Morcuende 2007)
         2. Effective long-term clinical outcome (Hulme 2005)
         3. Requires only a reasonable amount of time out of the lives of the patient and his or her parents
         4. Frequently include some minimal invasive surgery without extensive correction surgery (Morcuende et al. 2004)
         5. Results of treatment: good in 71% of feet, slight residual deformity persisted in 28%, and one foot with a poor result (Ponseti and Smoley 2009)
         6. Anterior tibial tendon transfer to the third cuneiform: a useful operation for the treatment of cases of severe relapsing clubfoot (Ponseti and Campos 2009)
   3. Kite and Lovell method:
      1. Starting with stretching of the foot through longitudinal traction applied to the foot
      2. Less often requires minimally invasive surgery
      3. More time consuming
   4. "Montpellier" method:
      1. Requires fairly extensive physical therapy
      2. Demands substantial parental time and attention
      3. Long-term results yet to be confirmed
   5. Operative approach:
      1. Should be considered only after a suitable trial of manipulating the foot and holding it in a suitable cast or other device has failed
      2. Operative treatment:
         1. Incisions
         2. Medial plantar release
         3. Posterior release
         4. Lateral release

5. Reduction and fixation
6. Intraoperative assessment
7. Wound closure
8. Revision surgery
9. Postoperative evaluation

3. Treatment of residual deformity:
   1. Residual forefoot adduction
   2. Residual cavus
   3. Angulation of the heel for residual varus or valgus
   4. Dynamic forefoot supination
   5. Residual toeing-in
   6. Dorsal bunion (a painful swelling of the bursa of the first joint of the big toe)
   7. Overcorrected foot
   8. Skin problems

6. Complications of treatment:
   1. Failure to correct (undercorrection) resulting from:
      1. Selection of inappropriate procedure
      2. Inadequate performance of an appropriate procedure
   2. Overcorrection resulting from:
      1. Selection of an inappropriate procedure
      2. Overzealous release of appropriate structures
      3. Inappropriate release of normal structures
   3. Recurrence of deformity

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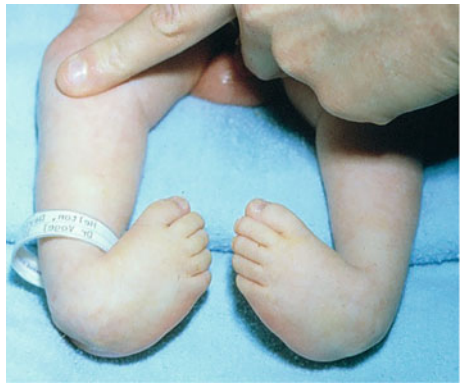

Fig. 1 Bilateral talipes equinovarus in an infant

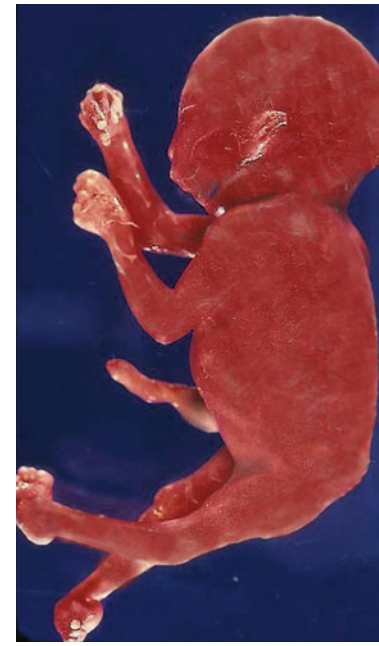

Fig. 3 Bilateral talipes equinovarus in a fetus with trisomy 18 syndrome

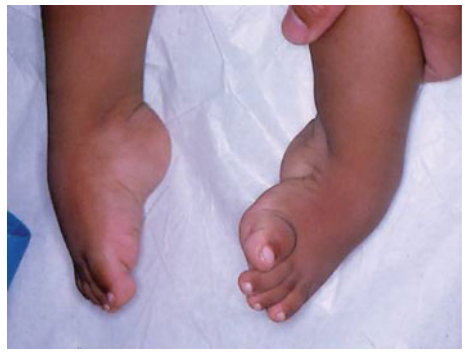

Fig. 2 Bilateral talipes equinovarus in an infant with Smith-Lemli-Opitz syndrome

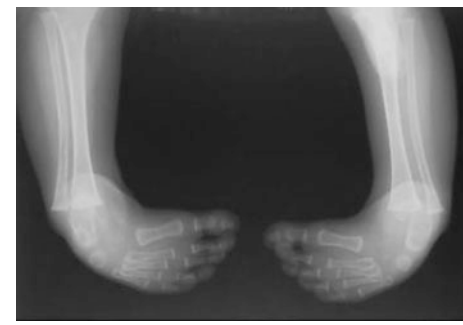

Fig. 4 Radiograph of talipes equinovarus in another infant

Collodion Baby

Contents

Collodion baby is a descriptive term for infants born encased in a membrane-like thick scale resembling oiled parchment or collodion. The presence of a collodion membrane at birth represents a defect in skin barrier function and is usually the initial presentation of a congenital ichthyosiform disorder, most often autosomal recessive congenital ichthyosis (ARCI). Thus, neonates born with the features of collodion baby subsequently develop lamellar ichthyosis (LI), nonbullous congenital ichthyosiform erythroderma (NCIE), or other forms of ichthyosis (Akiyama 2006). However, in 10% of neonates, spontaneous healing occurs (Raghunath et al. 2003). Collodion baby is a rare congenital condition accounting for 1 in 50,000 to 1 in 100,000 deliveries. Neonatal presentations of selected ichthyoses (Craiglow 2013) include collodion baby, "▶ Harlequin Ichthyosis" (please see the chapter of Harlequin Ichthyosis), "▶ X-Linked Ichthyosis" (please see the chapter of X-linked Ichthyosis), epidermolytic ichthyosis, and "▶ Netherton Syndrome" (please see the chapter of Netherton Syndrome (line 31)).

Synonyms and Related Disorders

Collodion fetus; congenital ichthyosis; epidermolytic ichthyosis; harlequin ichthyosis; lamellar exfoliation of newborn; lamellar ichthyosis; Netherton syndrome; X-linked ichthyosis

Genetics/Basic Defects

1. Etiology (Taïeb and Labrèze 2002)
    1. The presence of a collodion membrane at birth (Hackett et al. 2010)
        1. Represents a defect in skin barrier function.
        2. Usually the initial presentation of a congenital ichthyosiform disorder is most often autosomal recessive congenital ichthyosis.
    2. Major forms: common severe phenotype (severe congenital ichthyoses in the neonatal period) (Akiyama 1998; Rodríguez-Pazos et al. 2013)
        1. Autosomal recessive nonbullous congenital erythrodermic ichthyosis (50% of cases) including harlequin fetus. Harlequin ichthyosis represents the most severe end of the phenotypic spectrum.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Autosomal recessive lamellar ichthyosis (10%) with mutations in the gene for keratinocyte transglutaminase (*TGM1*) (Huber et al. 1995; Russell et al. 1995; Cserhalmi-Friedman et al. 2001) on chromosome 14q11 in many patients. Mapping of a second locus for lamellar ichthyosis to chromosome 2q33-q35 (Permentier et al. 1996). Rare reports of autosomal dominant lamellar ichthyosis.
3. Nonbullous congenital ichthyosiform erythroderma.
4. Bullous congenital ichthyosiform erythroderma.
5. Sjögren-Larsson syndrome.
6. Netherton syndrome.
7. Neural lipid storage disease.

3. Minor forms: common milder phenotypes (Rodríguez-Pazos et al. 2013)
   1. Mild form of ichthyosis vulgaris (10%)
   2. Recovery without sequelae: self-healing collodion babies, described in a minority of collodion babies (10%)
      1. Self-healing collodion baby: compound heterozygous transglutaminase 1 mutations G278R and D490G in two siblings (Raghunath et al. 2003); two cases of autosomal recessive congenital ichthyosis due to *CYP4F22* mutations (Noguera-Morel et al. 2015)
      2. An acral self-healing collodion baby caused by a new *TGM1* mutation (Mazereeuw-Hautier et al. 2009)
      3. Genotypic heterogeneity of *TGM1* mutations: can lead to nonbullous congenital ichthyosiform erythroderma, self-healing collodion baby (localized or generalized), lamellar ichthyosis, and bathing suit ichthyosis (Petit et al. 1997; Oji et al. 2006; Arita et al. 2007; Hackett et al. 2010)
4. Associated congenital ichthyosis
   1. Trichothiodystrophy
   2. Poorly documented true collodion membrane
      1. Sjögren-Larsson syndrome (ichthyosis, spastic paraplegia, mental retardation, and retinopathy with abnormal levels of fatty aldehyde dehydrogenase activity in cultured fibroblasts)
      2. Netherton syndrome
      3. Gaucher disease type II (Stone et al. 2000)
      4. Congenital hypothyroidism
      5. Conradi syndrome
      6. Dorfman-Chanarin syndrome
      7. Ketoadipic aciduria
      8. Koraxitrachitic syndrome
      9. Ichthyosis variegata
      10. Palmoplantar keratoderma with anogenital leukokeratosis

2. Genes known to be associated with autosomal recessive congenital ichthyosis (ARCI) (Bale and Richard 2009; Hackett et al. 2010)
   1. *TGM1*: Mutations in *TGM1* account for 50–60% of all ARCI and 90% or more of severe LI.
   2. *ALOXE3* and *ALOX12B* genes: Mutations in the two *ALOX* genes are present in an estimated 10% of individuals with NCIE or intermediate LI/NCIE phenotypes.
   3. *NIPAL4* (*ICHTHYIN*): *NIPAL4* mutations appear to be less common.
   4. *ABCA12*: The vast majority of individuals with harlequin ichthyosis and a few individuals with LI have mutations in *ABCA12*, including partial-gene deletions.
   5. *CYP4F22*.
3. Pathogenesis (Akiyama 1999)
   1. The term "collodion baby" is considered a descriptive term for infants born encased in membrane-like thick scale and includes several heterogeneous conditions.
   2. Several disorders of cornification showing this phenotype at birth.
   3. A mutation of keratinocyte transglutaminase may play a role in lamellar ichthyosis, although lamellar ichthyosis is still considered genetically heterogeneous.

4. Keratinocytes lacking specific transglutaminase will not cause cross-linked envelopes.

Clinical Features

1. Collodion babies are often the initial presentation of an autosomal recessive ichthyosis (Sandler and Hashimoto 1998).
2. Major clinical features (Sybert 1997)
    1. Newborn covered with a taut, shiny membrane resembling plastic wrap
    2. The membrane often fissured and cracked at birth.
    3. Lamellar exfoliation cracks and peels over the course of several weeks to reveal underlying normal skin or skin with mild scaling that goes on to resolve.
    4. Red-/ivory-colored (erythematous) underlying skin.
    5. Persistence of mild ichthyosis in some patients.
    6. Ectropion (eversion of the eyelids).
    7. Eclabium (eversion of the lips).
    8. Crumpled pinnae.
    9. Resolved tapered fingertips and partially flexed hands with shedding of the encasing membrane.
    10. Self-healing collodion baby in some cases (Frenk and de Techtermann 1992).
    11. The membrane eventually detaches in 3–4 weeks, usually revealing a permanent ichthyosis phenotype (Nguyen et al. 2015).
3. Minor clinical features
    1. Secondary skin infections in the cracks and fissures
    2. Scarring in the areas of deep fissuring
4. Complications
    1. Difficulties in temperature regulation (hypothermia)
    2. Increased insensible water loss predisposing to hypernatremic dehydration (Buyse et al. 1993)
    3. Secondary infections from gram-positive organisms and *Candida albicans*
    4. Septicemia
    5. Pneumonia secondary to aspiration of squamous material in the amniotic fluid
    6. Respiratory difficulty due to restricted chest wall movement
    7. Possible loss of vision caused by corneal damage
    8. Constrictive bands of the extremities resulting in vascular compromise and edema (Van Gysel et al. 2002; Roberts and Adelson 2010)
5. Prognosis
    1. Long-term prognosis is difficult to address at birth.
    2. Infrequently, a collodion baby may have normal skin after exfoliation of the membranes.

Diagnostic Investigations

1. Skin biopsy
    1. Reduced transglutaminase enzymatic activity in the epidermis (Akiyama et al. 2001)
    2. Conventional and electron microscopy (Akiyama et al. 1997)
        1. Hyperkeratosis with thick compact cornified layer (orthokeratotic stratum corneum).
        2. Aberrant keratinized/cornified cells.
        3. Irregularly convoluted horny cells and numerous intercellular Odland bodies (lamellar granules) and nuclear debris in distal layer of the stratum corneum.
        4. Presence of lipid inclusions within the cornified cells.
        5. Abnormal lamellar granules in the granular layer keratinocytes.
        6. Lack of extracellular lamellar structure between the first cornified cell and the granular cell.
        7. Cornified cell envelope appeared to be normally formed.
        8. Compact collodion membrane from a self-healing collodion baby showed a very compact keratin without the normal elimination of corneocytes, a thick horny

layer, and the structure of lower corneocytes with polygonal contour (De Almeida et al. 2015).

2. Molecular genetic analysis
    1. *TGM1* sequence analysis: identification of mutation of keratinocyte transglutaminase 1 gene for severe form of autosomal recessive lamellar ichthyosis and self-healing collodion baby.
    2. *TGM1* mutations include missense, nonsense, and splice site.
    3. Carrier testing available to at-risk family members on a clinical basis once the mutation in *TGM1* has been identified in the proband.
    4. Other gene mutations.
3. Studies for other associated conditions
    1. Polarized light examination of hair and eyebrows
        1. Trichothiodystrophy
        2. Netherton syndrome
    2. Leukocyte lipid inclusions
        1. Dorfman-Chanarin syndrome
        2. Neonatal Gaucher disease
    3. Thyroid hormone level: congenital hypothyroidism
    4. Skeletal study: Conradi syndrome
    5. Neurosensory evaluation

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive inheritance: 25% recurrence risk
        2. Autosomal dominant inheritance: not increased unless a parent is affected
    2. Patient's offspring
        1. Autosomal recessive inheritance: not increased unless the spouse is a carrier or affected
        2. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis: direct mutation analysis of the keratinocyte transglutaminase 1 gene on fetal DNA obtained from amniocentesis or CVS (Schorderet et al. 1997; Pigg et al. 2000) for severe form of autosomal recessive lamellar ichthyosis, provided the mutation in *TGM1* or other disease-causing mutations has been identified in the proband
3. Management: requiring intensive care (Shareef et al. 2000)
    1. Maintain skin integrity.
        1. Assess open skin lesions.
        2. Minimal handling with precaution.
        3. Prevent secondary infection and avoid prophylactic use of antibiotics.
    2. Maintain body temperature.
        1. Avoid radiant heat.
        2. Use humidified incubator for dehydration and hypothermia.
        3. Pre-warm all linen used to absorb weeping.
    3. Ophthalmological management of ectropion important for the prevention of conjunctivitis and keratitis.
    4. Sedation with opioids indicated for severe pain.
    5. Petrolatum-based creams/ointments to keep the skin soft, supple, and hydrated.
    6. Retinoids in case of delayed shedding of the collodion membrane beyond 3 weeks.
    7. Use keratolytic agents (e.g., alpha-hydroxy acid preparations) or urea preparations to promote peeling and thinning of the stratum corneum as the child becomes older.
    8. Release of collodion membrane on digits, when necessary, to maintain circulation and on the thorax for adequate respiration.

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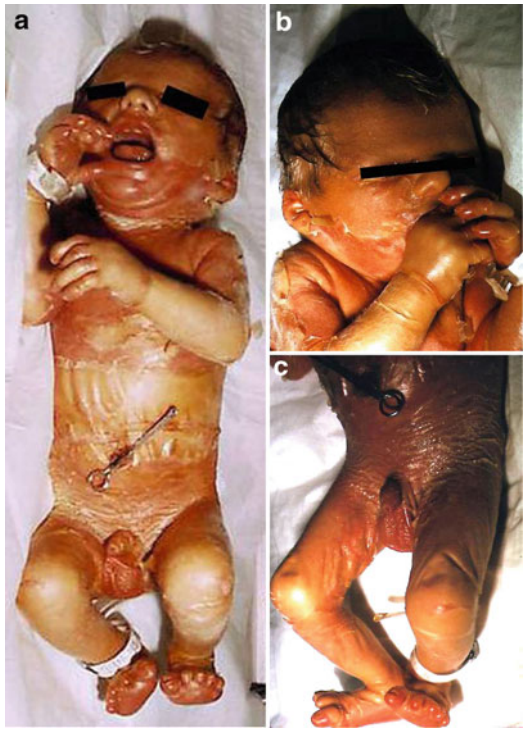

Fig. 1 (**a**–**c**) A collodion baby wrapped with a taut, shiny membrane over the whole body, red underlying skin, ectropion, crumpled pinnae, and partially flexed hands by encasing membrane

Congenital Adrenal Hyperplasia

Contents

Congenital adrenal hyperplasia (CAH) refers to a family of inherited disorders of adrenal steroidogenesis. The common functional defect in each disorder is impaired cortisol secretion, resulting in hypersecretion of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) and consequent hyperplasia of the adrenal glands (Antal and Zhou 2009).

More than 90% of cases of CAH are caused by a defect in the enzyme 21-hydroxylase (White and Speiser 2000). Four other enzyme deficiencies in the steroid biosynthesis pathway, along with one cholesterol transport protein defect, account for the remaining cases. Depending on the severity of the enzyme deficiency, 21-hydroxylase deficiency is defined as classic (severe form) or nonclassic (mild form). Approximately, 75% of patients who have the classic form also have salt wasting due to inadequate aldosterone production, further subdividing the classification into classic simple virilizing and classic salt-wasting forms. This chapter will discuss 21-hydroxylase deficiency in detail with a brief discussion of the other forms of CAH.

21-hydroxylase deficiency is the most common type of congenital adrenal hyperplasia (CAH). The incidence of classic 21-hydroxylase deficiency is estimated to be 1/12,000–1/15,000 births. The nonclassical form of the disease, also called "late-onset" CAH, occurs in approximately 1 in 1,000 of the general population depending on the ethnic group and in up to 6% of hirsute women (Deneux et al. 2001). Carrier frequencies for nonclassic disease range from 1:5 to 1:16, depending on the ethnic population sampled (Baumgartner-Parzer et al. 2005). Nonclassic CAH is especially common in Ashkenazi Jews, with a disease frequency as high as 1 in 27 individuals (Sherman et al. 1988).

Synonyms and Related Disorders

11-beta-hydroxylase deficiency; 17-alpha-hydroxylase deficiency; 21-hydroxylase deficiency; 3-beta-hydroxysteroid dehydrogenase deficiency; Lipoid congenital adrenal hyperplasia

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Molecular biology of steroid hormone synthesis: five groups of steroid hormones are

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generally recognized according to their physiological behavior (Miller 1988)
1. Mineralocorticoids: instruct the renal tubules to retain sodium
2. Glucocorticoids: named for their carbohydrate mobilizing properties but have many other effects as well
3. Estrogens: induce female secondary sexual characteristics
4. Progestins: essential for reproduction
5. Androgens: induce male secondary sexual characteristics

3. Biochemical and molecular basis
   1. Deficient 21-hydroxylase activity : the most common form (>90% of cases) of CAH
   2. Caused by mutations of *CYP21* (*CYP21A2*) gene, mapped on the short arm of chromosome 6 (6p21.3), present in duplicate
   3. A highly homologous pseudogene (*CYP21P*)
      1. Located in the same chromosomal region as the active gene
      2. Severe mutations of the pseudogene incompatible with coding for a functional enzyme
   4. About 95% of mutant alleles generated by recombination events between *CYP21* and *CYP21P* (Forest et al. 1998)
   5. Relatively common exchange of genetic material between these two homologous genes, the major reason for the high incidence of 21-hydroxylase deficiency compared to other forms of CAH
4. Pathophysiology (Cutler and Laue 1990; New 1995; New and Wilson 2002)
   1. Classic form of 21-hydroxylase deficiency
      1. Prenatal exposure to potent androgens (testosterone and delta4-androstenedione) at critical stages (8–12 weeks) of sexual differentiation resulting in virilization of the external genitalia in genetic females, resulting in varying degrees of genital ambiguity (female pseudohermaphroditism) at birth
      2. Subdivision of classic form
         1. Simple virilizing form (about 25%): sufficient aldosterone is produced, in response to elevated levels of renin and angiotensin, to prevent a salt-losing crisis
         2. Salt-wasting form (>75%) in which aldosterone production is inadequate and at risk of life-threatening salt-wasting crises
   2. Nonclassic "late-onset" form of 21-hydroxylase deficiency
      1. Has only moderate enzyme deficiency
      2. Present postnatally with signs of hyperandrogenism
      3. Females with the nonclassic form differing from the classic form: cortisol deficiency and virilization of newborn girls are absent (Turcu and Auchus 2015)
   3. Phenotype of congenital lipoid adrenal hyperplasia: result of the following two separate events (Bose et al. 1996):
      1. An initial genetic loss of steroidogenesis that is dependent on steroidogenic acute regulatory protein
      2. A subsequent loss of steroidogenesis that is independent of the protein due to cellular damage from accumulated cholesterol esters
5. CAH due to 21- hydroxylase deficiency
   1. 21-hydroxylase
      1. A microsomal cytochrome P450 enzyme
      2. Required to convert:
         1. 17-hydroxy-progesterone to 11-deoxycortisol
         2. Progesterone to deoxycorticosterone
   2. 21-hydroxylase deficiency
      1. Impairs the metabolism of cholesterol to cortisol, generating excessive level of 17-hydroxyprogesterone
      2. Produces androstenedione and other androgens from the precursor (17-hydroxyprogesterone) via an alternative metabolic pathway
      3. Aldosterone deficiency
         1. Inability to synthesize adequate amounts of aldosterone due to severely impaired 21-hydroxylation of progesterone in about 75% of patients

2. Resulting in sodium loss via the kidney, colon, and sweat glands and excrete potassium from the renal tubules
3. Cortisol deficiency
   1. Glucocorticoids
      1. Increase cardiac contractility
      2. Increase cardiac output
      3. Increase cardiac and vasculature sensitivity to the pressor effects of catecholamines and other pressor hormones
   2. Absence of glucocorticoids
      1. Decrease in cardiac output
      2. Decrease in glomerular filtration leading to an inability to excrete free water and consequently to hyponatremia
4. Shock and severe hyponatremia much more likely in 21-hydroxylase deficiency in which both cortisol and aldosterone biosynthesis are affected

6. Phenotype-genotype correlations (Wedell 1996, 1998; White 2001; Hughes 2002b)
   1. Mutations in CYP21, such as deletions, frameshifts, or nonsense mutations
      1. Totally ablate enzyme activity
      2. Most often associated with salt wasting
   2. Mutations mainly consisting of the missense mutation Ile172Asn (Il72N)
      1. Yielding enzymes with 1–2% normal activity
      2. Carried predominantly by patients with simple virilizing disease
   3. Mutations such as Val281Leu (V281L) and Pro30Leu (P30L)
      1. Producing enzymes with 20–60% of normal activity
      2. Most often associated with the nonclassical disorder
   4. Two different CYP21 mutations
      1. Producing compound heterozygotes
      2. Most often with a phenotype compatible with that of the less severe gene defects
   5. All patients homozygous or compound heterozygous for large deletions or gene conversions have a salt-wasting classic form
   6. A strong correlation exists between genotype and phenotype: mutational analysis can be used to predict disease severity in affected individuals
7. Characteristics of other forms of CAH (Speiser 2001; Antal and Zhou 2009)
   1. 11-beta-hydroxylase deficiency
      1. Incidence: 1:100,000
      2. Gene involved: *CYP11B1*
      3. Chromosome location: 8q24.3
   2. 17-alpha-hydroxylase deficiency
      1. Incidence: rare
      2. Gene involved: *CYP17*
      3. Chromosome location: 10q24.3
   3. 3-beta-Hydroxysteroid dehydrogenase deficiency
      1. Incidence: rare
      2. Gene involved: *HSD3B2*
      3. Chromosome location: 1p13.1
   4. Lipoid CAH
      1. Incidence: rare
      2. Gene involved: steroidogenic acute regulatory protein (*STAR*)
      3. Chromosome location: 8p11.2
8. Affect of CAH (steroidogenic disorders) on female fertility (Reichman et al. 2014)
   1. Classic CAH due to 21-hydroxsylase deficiency: virilization
      1. Anatomic distortion leading to impaired sexual functioning
      2. Delayed gender assignment
      3. Elevated, noncyclic progesterone (P4) impacting endometrium and hypothalamic-pituitary-ovarian (HPO) axis
      4. Alter psychosocial development
      5. Elevated androgens disturbing HPO axis, leading to anovulation
   2. Classic CAH due to 11β-hydroxylase deficiency: as above, with exception of significant P4 elevation
   3. Nonclassic CAH due to 21-hydroxylase deficiency: hyperandrogenemia affecting HPO axis, leading to anovulation and polycystic ovary syndrome-like phenotype
9. Simple classification of intersex: type, cause, and result (Hughes 2002c)
   1. Masculinized female

1. Fetal androgens resulting in:
   1. CAH
   2. Placental aromatase deficiency
2. Maternal androgens resulting in:
   1. Adrenal tumors
   2. Ovarian tumors

2. Undermasulinized male
   1. Abnormal testis determination resulting in:
      1. Gonadal dysgenesis
      2. X/XY mosaicism
   2. Defects in androgen biosynthesis and metabolism resulting in:
      1. 17β-OH-dehydrogenase deficiency
      2. 5α-reductase deficiency
   3. Resistance to androgen resulting in partial androgen insensitivity syndrome
3. True hermaphroditism: presence of both testicular and ovarian (with follicles) tissues resulting in XX, XY, or XX/XY

Clinical Features

1. Neonatal presentation of CAH (Hughes 1986)
   1. Either virilization of females or
   2. Salt loss in both sexes
2. Typical signs and symptoms of acute adrenal crisis (Antal and Zhou 2009)
   1. Decreased activity/fatigue
   2. Altered sensorium/unresponsiveness
   3. Poor feeding/weak suck
   4. Dry mucous membranes
   5. Hyperpigmentation
   6. Abdominal pain
   7. Vomiting
   8. Hyponatremia
   9. Hyperkalemia
   10. Hypoglycemia
   11. Metabolic acidosis
   12. Hypothermia
   13. Hypotension
   14. Dehydration
   15. Lack of weight gain
3. Clinical manifestations of 21-hydroxylase deficiency (Hughes 1988; New 2001b)
   1. Newborn
      1. Ambiguous genitalia
      2. Cryptorchid/hypospadic "male"
      3. Salt wasting
   2. Later in life
      1. Pseudoprecocious puberty
      2. Isolated pubarche
      3. Isolated clitoromegaly
      4. Rapid growth
      5. Hirsutism (Kuttenn et al. 1985)
      6. Menstrual disorders
      7. Infertility
      8. Cryptic cases
4. Classic CAH phenotype (Levine 2000; White 2001; New and Wilson 2002; Speiser and White 2003)
   1. Simple (complete) virilizing form (about 25% of patients): can present later in life with abnormalities of somatic or sexual development (Woelfle et al. 2002)
   2. Salt-wasting form (>75% of patients)
      1. Adrenal crises present at 1–4 weeks of age in severely affected patients
         1. Severe dehydration
         2. Hypotension
         3. Severe hyponatremia, hyperkalemia, and hyperreninemia
         4. Progression to adrenal crisis (azotemia, vascular collapse, hypovolemic shock, and death) if adequate medical care is not provided
         5. Affected infant boys who are not detected in a newborn screening program are at high risk of a salt-wasting crisis since their normal genitalia fail to alert physicians to the diagnosis of congenital adrenal hyperplasia
      2. Nonspecific symptoms
         1. Poor appetite/feeding
         2. Vomiting
         3. Hypotension
         4. Lethargy
         5. Failure to gain weight (weight loss)
      3. Improved sodium balance and more efficient aldosterone synthesis with age in patients known to have severe salt-wasting episodes in infancy and early childhood

4. Siblings may be discordant for salt wasting
5. The degree of salt wasting may vary in individuals carrying identical mutations
6. Patients with 3β-hydroxysteroid hydrogenase deficiency, aldosterone synthase deficiency, or lipoid hyperplasia
    1. Unable to synthesize aldosterone
    2. May present with salt-wasting crises

3. Children with classic CAH
    1. Lack of sufficient amounts of cortisol to mount a stress response and frequently succumb to minor illnesses
    2. Premature closure of the epiphyses resulting in short stature even though these children grow at an accelerated rate when young
4. Growth disturbances
    1. Accelerated skeletal maturation in untreated patients due to high levels of androgen
    2. Growth retardation in patients treated with excessive doses of gluco-corticoids
    3. Final height, despite careful monitoring and good patient compliance, usually averaging one to two standard deviations below the population mean or the target height based on parental heights
5. Behavioral and physical masculinization in girls with CAH (Hall et al. 2004)
    1. Related to each other and to genotype
    2. A consequence of prenatal androgen exposure
6. Reproductive problems in affected females (White 2001)
    1. Ambiguous genitalia typically present in the neonatal period
        1. Clitoromegaly (mild)
        2. With or without partial fusion of the labioscrotal folds (intermediate)
        3. Complete fusion of the labioscrotal folds with the appearance of a penile urethra (severe)
    2. Internal genitalia
        1. Normal ovaries, fallopian tubes, and uteri
        2. Normal upper third of the vagina but urogenital sinus may be present distally with one opening on the perineum
    3. Signs of androgen excess in affected females without glucocorticoid replacement therapy (New and Wilson 2002)
        1. Clitoral enlargement
        2. Excessive linear growth
        3. Advanced bone age
        4. Acne
        5. Early onset of pubic and axillary hair
        6. Hirsutism
        7. Male pattern baldness
        8. Menstrual abnormalities
        9. Reduced fertility
    4. Adolescence (White 2001)
        1. Late menarche in inadequately treated girls
        2. Sonographic finding of multiple ovarian cysts similar to patients with polycystic ovarian syndrome
        3. Anovulation/oligo-ovulation (Garner 1998)
        4. Irregular bleeding
        5. Hyperandrogenic symptoms
    5. Pregnancy and live-birth rates
        1. Severely reduced in salt-wasting patients
        2. Mildly reduced in simple virilizing patients
        3. Normal in nonclassical patients
    6. Factors suggested responsible for the impaired fertility (Stikkelbroeck et al. 2003)
        1. Adrenal overproduction of androgens and progestins (17-hydroxyprogesterone, progesterone, and androstenedione)
        2. Ovarian hyperandrogenism
        3. Polycystic ovary syndrome
        4. Ovarian adrenal rest tumors
        5. Neuroendocrine factors
        6. Genital surgery
        7. Psychosocial factors (delayed psychosexual development, reduced sexual activity, low maternal feelings)
    7. No evidence of an excess of congenital malformations in offspring of women

with 21-hydroxylase deficiency (White 2001)

8. Other types of congenital adrenal hyperplasia (White 2001)
    1. 11β-hydroxylase deficiency: similar to 21-hydroxylase deficiency
    2. 17α-hydroxylase deficiency: remains sexually infantile due to inability to synthesize sex hormones unless supplemented with estrogen
    3. 3β-hydroxysteroid hydrogenase deficiency: slightly virilized due to high levels of dehydroepiandrosterone

7. Reproductive function and problems in affected males (New and Wilson 2002; White 2001)
    1. Signs of androgen excess in affected males without glucocorticoid replacement therapy
        1. Penile enlargement
        2. Small testes
        3. Excessive linear growth
        4. Advanced bone age
        5. Acne
        6. Early onset of pubic and axillary hair
    2. Ability to father children
    3. Testicular adrenal rests
        1. Most often benign
        2. Manifest as testicular enlargement
        3. Seen most often in inadequately treated patients, particularly those with the salt-wasting form of 21-hydroxylase deficiency
    4. Other types of congenital adrenal hyperplasia
        1. Men with 11β-hydroxylase deficiency: similar to those with 21-hydroxylase deficiency
        2. Genetic males with 3-β-hydroxysteroid hydrogenase deficiency, 17α-hydroxylase deficiency, or lipoid hyperplasia: usually raised as females and castrated during or before adolescence to prevent malignant transformation of abdominal testes

8. Effects on gender role, sexual orientation, and identity (Meyer-Bahlburg 2001; White 2001)
    1. Gender role
        1. Referring to gender-stereotyped behaviors such as choice of play toys by young children
        2. Girls with 21-hydroxylase deficiency may show low interest in maternal behavior, extending from lack of doll play in early childhood to lack of interest in childrearing in women.
    2. Sexual orientation
        1. Referring to homosexual versus heterosexual preferences
        2. Heterosexuality in most adult women with 21-hydroxylase deficiency
        3. Homosexuality or bisexuality or increased tendency to homo-erotic fantasies in a small but significant proportion in women with 21-hydroxylase deficiency
    3. Gender identity
        1. Referring to self-identification as male or female
        2. Self-reassignment to the male sex is unusual in women with 21-hydroxylase deficiency
        3. Severely virilized females are more likely to be raised as males in cultures that value boys more highly and/or in third world countries in which the diagnosis is likely to be delayed

5. Nonclassic (late-onset) CAH phenotype (White 2001; Wichel 2013)
    1. Nonambiguous external genitalia, with normal or mild clitoromegaly, in females affected with mild, nonclassical form of 21-hydroxylase deficiency
    2. Signs of androgen excess
        1. Wide spectrum of symptoms and signs
        2. Asymptomatic in many affected individuals
        3. Children: premature pubarche

4. Young women
    1. Severe cystic acne
    2. Hirsutism
    3. Oligomenorrhea
3. Signs and symptoms suggesting mild CAH (Deaton et al. 1999; Miller 1999)
    1. Children
        1. Moderate to severe recurrent sinus or pulmonary infections
        2. Severe acne
        3. Hyperpigmentation, especially of the genitalia
        4. Tall for age
        5. Early onset of puberty
    2. Adults
        1. Childhood history as described above
        2. Syncope or near-syncope
        3. Shortened stature compared with either parent
        4. Hypotension (21-hydroxylase deficiency)
        5. Hypertension (11β-hydroxylase deficiency)
    3. Women
        1. Clitoromegaly
        2. Poorly developed labia
        3. Premature adrenarche
        4. Hirsutism
        5. Menstrual disturbances
        6. Infertility
        7. Polycystic ovary syndrome
6. Clinical characteristics of other forms of CAH (Antal and Zhou 2009)
    1. 11-beta-Hydroxylase deficiency
        1. Ambiguous genitalia in females
        2. Rare adrenal crisis
    2. 17-alpha-ydroxylase deficiency
        1. Ambiguous genitalia in males
        2. No adrenal crisis
    3. 3-beta-hydroxysteroid dehydrogenase deficiency
        1. Ambiguous genitalia in males
        2. Adrenal crisis present
    4. Lipoid CAH
        1. Ambiguous genitalia in males
        2. Severe adrenal crisis

Diagnostic Investigations

1. Newborn screening (Pang 1997; Pang and Shook 1997; Therrell 2001; Joint LWPES/ESPE CAH Working Group 2002; New and Wilson 2002; White 2001, 2009)
    1. Objectives
        1. Detect a common and potentially fatal childhood disease (classic form of CAH)
        2. Prevent serious morbidity and mortality by early recognition and treatment
        3. Prevent incorrect male sex assignment of affected female infants with ambiguous genitalia
        4. Detect most, but not all, cases of the nonclassic form of 21-hydroxylase deficiency
    2. Filter paper blood spot sample (White 2001)
        1. Markedly elevated 17- hydroxyprogesterone by radioimmunoassay
        2. False positives
            1. Samples taken in the first 24 h of life (elevated in all infants)
            2. Variation of weight-adjusted cutoff values among newborn screening programs
            3. Infants with low birth weight or prematurity
    3. Early diagnosis is based on elevated levels of 17-hydroxyprogesterone (Hughes 1986), the preferred substrate for steroid 21-hydroxylase
    4. Initial testing usually involves dissociation-enhanced lanthanide fluorescence immunoassay that has a low positive predictive value (about 1%), leading to many follow-up evaluations that have negative results
    5. Second level of screening based on detection of actual mutations on DNA extracted from the same dried blood spots or liquid chromatography followed by tandem mass spectrometry

6. Main benefits of newborn screening
    1. Reduced morbidity and mortality
    2. Reduced time to diagnosis of infants with 21-hydroxylase deficiency
    3. Infants ascertained through screening
        1. Less severe hyponatremia
        2. Tend to be hospitalized for shorter periods of time

2. Intersex: initial investigation (Hughes 2002c)
    1. Chromosomes
        1. Fluorescent in situ hybridization on interphase spreads with X, Y specific probes
        2. Full karyotype
    2. Hormones
        1. Serum 17OH-progesterone at 24–48 h after birth
        2. Serum testosterone
        3. Plasma renin
        4. Save serum, DNA, urine
    3. Biochemistry
        1. Serum electrolytes
        2. Plasma glucose
    4. Imaging
        1. Pelvic ultrasonography for uterus/cervix
        2. Renal ultrasonography
3. Diagnosis of CAH
    1. Female neonates
        1. With genital ambiguity
            1. Genital ambiguity highly distressing to the family
            2. Require urgent expert medical attention
            3. Need immediate comprehensive evaluation by a multidisciplinary team including specialists from pediatric endocrinology, psychosocial services, pediatric surgery/urology, and genetics
        2. With or without salt loss
        3. Presence of elevated concentration of serum 17-hydroxyprogesterone
            1. Only diagnostic of CAH when measured after the 3rd day of life
            2. Presence of relatively high concentrations in the immediate neonatal period in normal infants
        4. Normal internal female genitalia on pelvic ultrasonography
        5. Normal female karyotype (46,XX)
    2. Male neonates
        1. Salt-losing crises
        2. Presence of elevated 17-hydroxyprogesterone concentration
4. Clinical chemistry
    1. Important initial laboratory evaluation for patients suspected of experiencing adrenal crisis due to 21-hydroxylase deficiency (Antal and Zhou 2009)
        1. Glucose/dextrose stick at bedside
        2. Chem-20 (including electrolytes and liver function panel): critical to assure that the potassium concentration is obtained from a nonhemolyzed sample to minimize the likelihood of a falsely elevated potassium value
        3. Arterial blood gas/serum pH
        4. Cortisol
        5. ACTH
        6. 17-OHP
        7. Pelvic ultrasonography
        8. Karyotype
    2. ACTH stimulation test: necessary to evaluate adrenal function and differentiate among the various potential enzymatic defects (Antal and Zhou 2009)
    3. Comparison of baseline and cortrosyn-stimulated serum concentrations of the steroid precursor 17-hydroxyprogesterone (nonclassical)
    4. Increased serum levels of progesterone, 17-hydroxyprogesterone, and androstenedione in affected males and females with classic 21-hydroxylase deficiency
    5. Elevated serum levels of testosterone and adrenal androgen precursors in affected girls
    6. Salt losers
        1. Low serum bicarbonates, sodium, and chloride levels
        2. Elevated levels of serum potassium and serum urea nitrogen
        3. Hyponatremia and hyperkalemia usually not present before 7 days of age

4. Inappropriately increased urine sodium levels
5. Elevated plasma rennin levels
6. Serum aldosterone level inappropriately low for the rennin level

5. Karyotyping or fluorescence in situ hybridization for sex chromosome material
   1. 46,XX in females with 21-hydroxylase deficiency
   2. 46,XY in males with 21-hydroxylase deficiency
6. Careful monitoring of linear growth
7. Imaging studies (Wilson 2015)
   1. Transabdominal pelvic sonography (Chertin et al. 2000)
      1. Perform in patients with CAH undergoing vaginal reconstruction
      2. Provide adequate information about the anatomy of the vagina and urogenital sinus
      3. Demonstrate presence or absence of a uterus or associated renal anomalies
   2. Urogenitogram helpful to define the anatomy of the internal genitalia
   3. Adrenal ultrasonography to detect enlarged, lobulated adrenals with stippled echogenicity invariably associated with CAH (Al-Alwan et al. 1999)
   4. CT scanning of adrenal gland: helps exclude bilateral adrenal hemorrhage in patients with signs of acute adrenal failure without ambiguous genitalia or other clued to adrenal hyperplasia (Purandare et al. 2001)
   5. Sonography or MRI for testicular adrenal rest tumors
   6. Bone age radiography: useful in evaluating for advanced skeletal maturation in a child who develops precocious public hair, clitoromegaly, or accelerated linear growth
8. Carrier detection (New and Wilson 2002)
   1. Carriers: asymptomatic individuals who have one normal allele and one mutant allele
   2. ACTH stimulation test
      1. Resulting in slightly elevated serum concentrations of deoxycortisol and 17-hydroxyprogesterone
      2. Overlap in serum concentration of 17-hydroxyprogesterone between carriers and noncarriers
      3. No longer the preferred method of carrier detection
   3. Molecular genetic testing
      1. Molecular genetic testing of the *CYP21A2* gene available to at-risk relatives, given that the disease-causing mutation(s) have been identified in the proband
      2. The preferred method of carrier detection
9. Molecular genetic testing (New and Wilson 2002)
   1. Molecular genetic analysis for *CYP21A2* gene for a panel of 9 common mutations and gene deletions detect about 90–95% of disease-causing alleles in affected individuals and carriers
   2. Complete gene sequencing detects more rare alleles in affected individuals in whom the panel of nine mutations and deletions reveals only one or neither disease-causing allele
   3. Applications
      1. Primarily used in genetic counseling for carrier detection of at-risk relatives and for prenatal diagnosis
      2. Can be used for diagnosis in newborns with slight to moderate elevations of 17-hydroxyprogesterone
10. Laboratory characteristics of other forms of CAH (Antal and Zhou 2009)
    1. 11-beta-Hydroxylase deficiency
       1. Glucocorticoid values: decreased
       2. Mineralocorticoid values: elevated
       3. Androgens: elevated
       4. Sodium concentrations: elevated
       5. Potassium concentrations: decreased
       6. Elevated metabolites
          1. Deoxycorticosterone (DOC)
          2. 11-deoxycortisol
    2. 17-alpha-hydroxylase deficiency
       1. Glucocorticoid values: decreased
       2. Mineralocorticoid values: elevated
       3. Androgens: decreased
       4. Sodium concentrations: increased

5. Potassium concentrations: decreased
6. Elevated metabolites
    1. Deoxycorticosterone
    2. Corticosterone

3. 3-beta-Hydroxysteroid dehydrogenase deficiency
    1. Glucocorticoid values: decreased
    2. Mineralocorticoid values: decreased
    3. Androgens
        1. Elevated in females
        2. Decreased in males
    4. Sodium concentrations: decreased
    5. Potassium concentrations: elevated
    6. Elevated metabolites
        1. Dehydroepiandrosterone (DHEA)
        2. 17-hydroxypregnenolone
4. Lipoid CAH
    1. Glucocorticoid values: decreased
    2. Mineralocorticoid values: decreased
    3. Androgens: decreased
    4. Sodium concentrations: decreased
    5. Potassium concentrations: elevated
    6. Elevated metabolites: none

Genetic Counseling

1. Recurrence risk (Nimkarn and New 2013)
    1. Genetic counseling according to autosomal recessive inheritance
        1. Most parents: heterozygotes with one normal allele and one mutated allele
        2. One percentage of probands having only one parent who is heterozygous since 1% of mutations occur de novo
        3. In some instances, a parent, who was previously not known to be affected, was found to have the nonclassic form of 21-hydroxylase deficiency
        4. For individuals with CAH, the risk of having a child with CAH depends on the probability that the partner is a carrier; this is typically about 1 in 60. Thus, the risk of having a CAH fetus is 1:120 and the risk of having a female infant with CAH is 1:240 (Wichel 2013)
        5. Prevalence of CAH among children of women with nonclassic adrenal hyperplasia is higher than predicted, presumably because affected individuals tend to marry within their own ethnic background (Moran et al. 2006)
    1. Patient's sib
        1. When the parents of a proband are both obligate heterozygotes
            1. Twenty-five percent risk of inheriting both altered alleles and being affected
            2. Fifty percent risk of inheriting one altered allele and being an unaffected carrier
            3. Twenty-five percent risk of inheriting both normal allele and being unaffected
            4. Two-third chance of unaffected sibs of a proband being a carrier
        2. When a parent of a proband has 21-hydroxylase deficiency and the other is heterozygous
            1. Fifty percent risk of inheriting both mutant alleles and being affected
            2. Fifty percent risk of inheriting one mutant allele and being a carrier
    2. Patient's offspring for a woman with classic 21-hydroxylase deficiency
        1. When the spouse status is unknown (Lo and Grumbach 2001)
            1. Risk of having an infant with the same disorder: approximately 1 in 120 births
            2. Risk of having an affected female infant: approximately 1 in 240 births
            3. Risk figures are based on an estimated 1 in 60 incidence of heterozygous individuals with a *CYP21* mutation, derived from newborn screening data
        2. When the spouse is not a carrier or not affected: risk is not increased
        3. Appropriate to offer molecular genetic testing of the *CYP21A2* gene to the spouse given the high carrier rate for 21-hydroxylase deficiency
    3. Patient's offspring for a woman with nonclassic CAH and are compound

heterozygotes with one severe *CYP21A2* mutation: risk of having an affected infant with classic CAH is 1 in 4 pregnancies (or 1 in 8 pregnancies for an affected female infant) when the spouse is a known carrier of the severe form of *CYP21A2* deficiency

2. Prenatal diagnosis and preimplantation genetic diagnosis for pregnancies require prior identification of the disease-causing mutations in the family (New 2001b; Nimkarn and New 2013)
    1. Noninvasive prenatal diagnosis (Khattab et al. 2016)
        1. Utilization of cell-free fetal DNA in mothers carrying at-risk fetuses as early as 6 gestational weeks by targeted massively parallel sequencing of the genomic region including and flanking the CYP21A2 gene
        2. Should permit the diagnosis of CAH before genital development begins, therefore restricting the purposeful administration of dexamethasone to mothers carrying affected females
    2. Determination of amniotic fluid (AF) hormone levels
        1. Elevated 17α-hydroxyprogesterone
        2. Elevated Δ^4-androstenedione
    3. Human leukocyte antigen (HLA) typing on cultured chorionic villus cells and cultured AF cells
        1. Basis for prenatal diagnosis: the gene for 21-hydroxylase has been linked to the HLA system on chromosome 6
        2. HLA type
            1. Fetus with an HLA type identical to that of the proband with 21-hydroxylase deficiency predicted to be affected
            2. Fetus sharing 1 parental haplotype with the proband predicted to be a heterozygous carrier
            3. Fetus with both haplotypes different from the index case predicted to be homozygous normal
    4. Molecular DNA diagnosis
        1. Molecular genetic testing of the proband and both parents should be undertaken prior to conception:
            1. To identify the two disease-causing mutations
            2. To confirm both parents are carriers
        2. Analysis of both parents
            1. To determine the phase of different mutations (whether they lie on the same or opposite alleles)
            2. To distinguish homozygotes and hemizygotes (individuals who have a mutation on one chromosome and a deletion on the other)
        3. De novo mutations, found in patients with CAH but not in parents, observed in 1% of disease-causing CYP21B mutations
        4. Before 10 weeks of gestation and prior to any prenatal testing, administer dexamethasone to the pregnant mother to suppress excess fetal adrenal androgen secretion and to prevent virilization of an affected female
        5. Obtain fetal cells to determine fetal sex by chromosome analysis or FISH using Y-chromosome specific probes
            1. Chorionic villus sampling in the 10th–12th week of gestation (preferable because of early result)
            2. Amniocentesis at 16–18 weeks of gestation
        6. If the fetus is a female and if the two *CYP21A2* disease-causing mutations have been identified in the proband:
            1. Perform molecular genetic testing to determine whether the fetus has inherited both disease-causing alleles
            2. Female fetus known to have 21-hydroxylase deficiency by DNA analysis or having an indeterminant status: continue dexamethasone treatment to term
        7. If the fetus is a male or unaffected female by DNA analysis: discontinue dexamethasone treatment

3. Management (White 2001; Turcu and Auchus 2015)
    1. Replacement with glucocorticoids (hydrocortisone, prednisone, dexamethasone)
        1. Indicated in all patients with classic and symptomatic nonclassical patients with 21-hydroxylase deficiency
        2. To suppress the excessive secretion of CRH and ACTH by the hypothalamus and pituitary
        3. To reduce the abnormal blood levels of adrenal sex steroids
        4. Situations in which increased hydrocortisone dose is needed in patients with classic 21-hydroxylase deficiency
            1. Febrile illness
            2. Surgery under general anesthesia
        5. Increase dose of hydrocortisone or prednisone in pregnancy due to pregnancy-induced alterations in steroid metabolism and clearance
        6. Glucocorticoid replacement also required in patients with CAH caused by other enzymatic deficiencies
    2. Mineralocorticoid replacement
        1. Mineralocorticoid (fludrohydrocortisone) and sodium chloride supplements required in infants with the salt-wasting form of 21-hydroxylase deficiency
        2. Treat patients with simple virilizing form of the disease by fludrohydrocortisone to aid in adrenocortical suppression and reduce the dose of glucocorticoid required to maintain acceptable 17-hydroxyprogesterone levels
        3. Signs of overtreatment with mineralocorticoid and sodium replacement
            1. Hypertension
            2. Tachycardia
            3. Suppressed plasma rennin activity
        4. Other indications of fludrohydrocortisone replacement
            1. 3β-hydroxysteroid hydrogenase deficiency
            2. Aldosterone synthase deficiency
            3. Lipoid hyperplasia
    3. Other pharmacological approaches
        1. A novel 4-drug regimen for 21-hydroxylase deficiency
            1. Flutamide (an androgen receptor blocking drug), testolactone (an aromatase inhibitor), and low dose of hydrocortisone and fludrocortisone can achieve short-term normalization of growth rate, weight gain, and bone maturation (Merke and Cutler 1997)
            2. Benefit: produces less bone age advancement and attain more appropriate linear growth velocity than standard treatment
            3. Side effect: occurrence of central precocious puberty requiring treatment with gonadotrophin-releasing hormone analog
        2. Experimental treatment with carbenoxolone, an inhibitor of 11β-hydroxysteroid dehydrogenase
    4. Corrective surgery
        1. Decision about surgery
            1. Made by the parents, together with the clinical team
            2. After disclosure of all relevant clinical information and all available options
            3. Obtain informed consent
        2. Objectives
            1. Genital appearance compatible with gender
            2. Unobstructed urinary emptying without incontinence or infections
            3. Good adult sexual and reproductive function
        3. Clitoroplasty, rather than clitoridectomy, done in infancy
        4. Vaginal reconstruction
            1. Often postponed until the age of expected sexual activity
            2. Single-stage corrective surgery in children
    5. Adrenalectomy
        1. Questionable therapeutic alternative
        2. Likely to be used, if at all, in patients with severe 21-hydroxylase deficiency refractory to standard medical management

6. Management of testicular adrenal rests
    1. Effective adrenal suppression with dexamethasone since many of these tumors are ACTH-responsive
    2. Testis-sparing surgery for cases unresponsive to dexamethasone after imaging the tumor by sonography and/or MRI
7. Management of adolescence with classical and nonclassical CAH (Clayton et al. 2002)
    1. Psychological assessment and support of the patient
    2. Counseling
        1. Sexual function
        2. Future surgeries
        3. Gender role
        4. Issues related to living with a chronic disorder
        5. Low risk of women with CAH or nonclassic CAH having an affected fetus
8. Management of pregnancy in women with classic 21-hydroxylase deficiency (Lo and Grumbach 2001)
    1. Factors contributing to lower fertility rates
        1. Masculinization of the external genitalia
        2. An inadequate introitus
        3. Factors relating to genital reconstructive surgery (poor surgical repair, vaginal stenosis, and clitoral dysfunction)
        4. Hormonal factors (increased levels of adrenal androgens and progestational steroid, and ovarian hyperandrogenism)
    2. Recent improvement of fertility prognosis
        1. Earlier detection and treatment of 21-hydroxylase deficiency
        2. Surgical advances in genital reconstruction (Schnitzer and Donahoe 2001)
        3. Higher patient compliance rates
    3. Preconception issues for all women with classic 21-hydroxylase deficiency who desire pregnancy
        1. Need for glucocorticoid treatment
        2. Careful endocrine monitoring throughout gestation
        3. Ovulation induction with clomiphene citrate or gonadotropin therapy or in vitro fertilization for patients who do not achieve normal ovulatory cycles and fertility despite effective glucocorticoid therapy
        4. Most pregnancies are successful in carrying to term with a healthy outcome
        5. Preconceptional counseling about the risk of having a child affected with 21-hydroxylase deficiency
    4. Gestational management (Lo and Grumbach 2001)
        1. Regular assessment of maternal clinical status, serum electrolytes, and circulating adrenal androgen levels during gestation to determine the need for increased glucocorticoid or mineralocorticoid therapy
        2. Signs of adrenal steroid insufficiency (excessive nausea, salt craving, and poor weight gain)
        3. Monitor hypertension and fluid retention in patients receiving mineralocorticoid therapy, particularly in the third trimester
    5. Labor and delivery (Lo and Grumbach 2001)
        1. Require stress doses of glucocorticoid therapy during labor and delivery
        2. Elective cesarean section considered for pregnant women with virilizing CAH, for cephalopelvic disproportion due to android pelvic characteristics and especially for those who have had reconstructive surgery of the external genitalia
    6. Evaluation of the infant (Lo and Grumbach 2001)
        1. Clinical signs of adrenal suppression (hypotension, hypoglycemia), particularly in cases in which dexamethasone was administered during pregnancy

2. Sign of ambiguous external genitalia
3. Female pseudohermaphroditism secondary to either maternal hyperandrogenism or fetal 21-hydroxylase deficiency (if the father is a carrier)

9. Prenatal therapy (Speiser and New 1994; Pang 1997; Ritzén 2001; Turcu and Auchus 2015)
   1. Encouraging results from prenatally treating congenital adrenal hyperplasia due to 21-hydroxylase deficiency (David and Forest 1984)
      1. Hydrocortisone treatment: fetal adrenal suppression was only partial with slightly abnormal external genitalia
      2. Dexamethasone treatment: fetal adrenal suppression was achieved with normal external genitalia at birth (New 2001a)
   2. Prenatal treatment significantly reduces or eliminates virilization in the newborn female (New et al. 2001) and spares the newborn female the consequences of genital ambiguity, genital surgery, sex misassignment, and gender confusion (New 2001b)
   3. Inclusion criteria (Clayton et al. 2002)
      1. A previously affected sibling or first-degree relative with known mutations causing classic CAH, proven by DNA analysis
      2. Reasonable expectation that the father is the same as the father of the proband
      3. Availability of rapid, high-quality genetic analysis
      4. Therapy started less than 9 weeks after the last menstrual period
      5. No plans for therapeutic abortion
      6. Reasonable expectation of patient compliance
   4. Dexamethasone
      1. No salt-retaining activity
      2. Not significantly metabolized by placental 11β-hydroxysteroid dehydrogenase
      3. Able to cross the placenta
   5. Administer oral dexamethasone to the mother in pregnancies at risk for a female child affected with virilizing adrenal hyperplasia
      1. To suppress fetal adrenal androgen production, beginning after conception and before the 7–8th week of gestation, to prevent ambiguity of the external genitalia in the female fetus with classic CAH
      2. To prevent progression of virilization on therapy after 7–8th week of gestation
      3. Short-term outcomes of children exposed to dexamethasone in utero indicate no significant adverse effects (Hughes 2002a)
      4. Chromosome analysis from fetal cells obtained from either CVS at 10–12 weeks of gestation or amniocentesis at 14–18 weeks of gestation
      5. If the fetus is a female, additional molecular genetic testing is performed on the sample to determine if she has 21-hydroxylase deficiency (Antal and Zhou 2009)
      6. If the fetus is affected, maternal dexamethasone administration is continued to term; if not, it can be discontinued
   6. Outcome of prenatally treated females (American Academy of Pediatrics 2000)
      1. Approximately 70% born with normal or only slightly virilized genitalia with clitoromegaly, partial labial fusion, or both
      2. Approximately 30% born with marked genital virilization
   7. Disadvantage: 7 out of 8 fetuses unnecessarily treated since CAH is inherited as an autosomal recessive disease and only affected girls benefit from the treatment
   8. Prompt discontinuation of dexamethasone therapy to minimize potential risks of glucocorticoid toxicity if (White 2001):
      1. Male sex determination by prenatal genetic diagnosis

2. *CYP21* genotype indicating that the fetus is unaffected
9. Refer patient to centers with expertise in the prenatal management of pregnancies at risk for CAH
10. Long-term follow-up studies still needed for prenatally treated children
11. Side effects of women treated to term (10%)
    1. Features of Cushing syndrome (excessive weight gain, severe striae, hypertension, hyperglycemia)
    2. Resolved when the treatment is discontinued
12. Side effects of women treated for a shorter time (10–20%)
    1. Edema
    2. Gastrointestinal upset
    3. Mood fluctuations
    4. Acne
    5. Hirsutism
13. Similar therapeutic approaches: effective in families at risk for 11-β-hydroxylase deficiency, in which affected female fetuses may also suffer severe prenatal virilization
14. Prenatal therapy not appropriate for nonclassic CAH
15. Parents of affected girls
    1. Many opting for prenatal medical treatment because of severe psychological impact of ambiguous genitalia on the child and on the family
    2. Obtain informed consent as to the potential fetal and maternal risks, some of which may yet to be recognized

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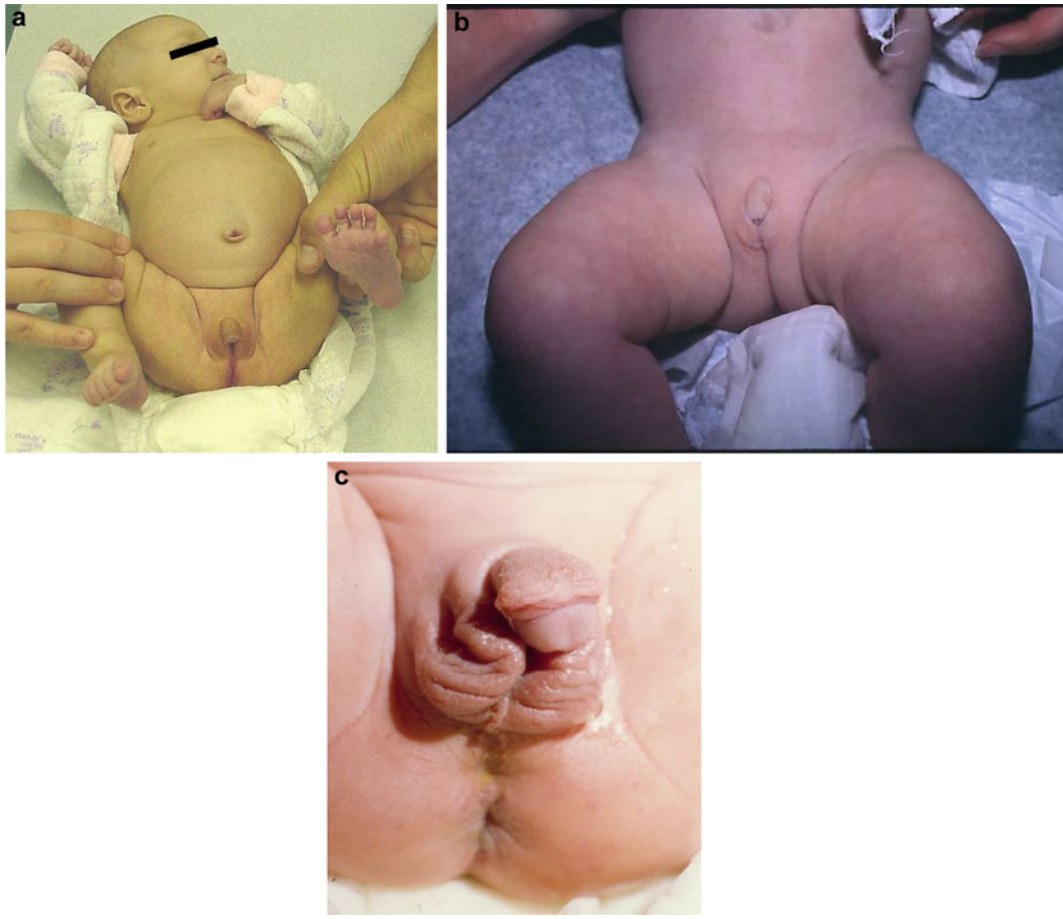

Fig. 1 (**a**–**c**) Female infants (46,XX) with classic form of CAH showing varying degree of virilization

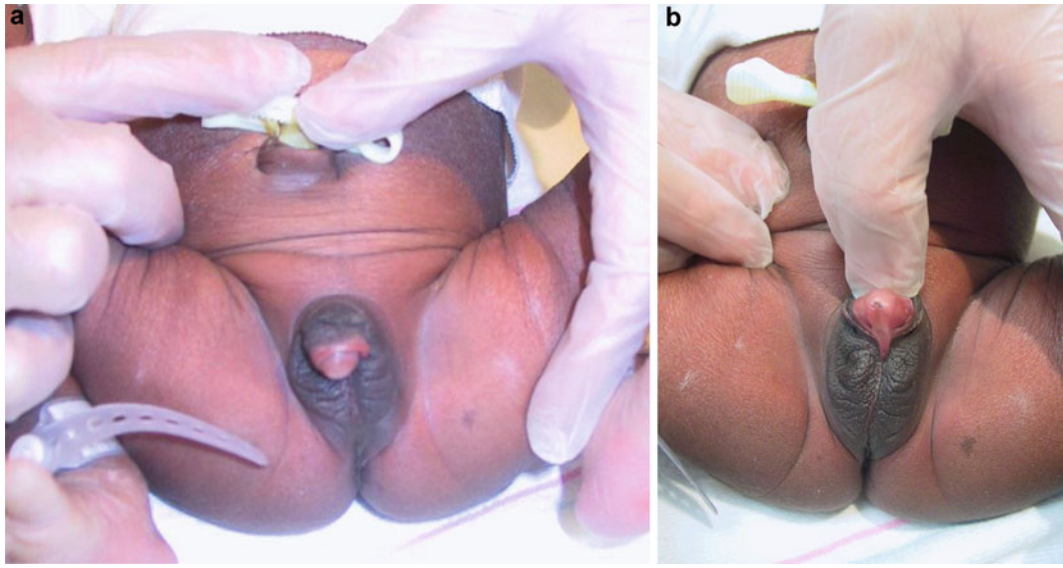

Fig. 2 (**a**, **b**) A newborn with congenital adrenal hyperplasia showing ambiguous genitalia. Newborn screening from filter paper showed total 17OHP of >240 ng/mL (normal <33). A pair of intron 2 mutations were detected by PCR

Congenital Cutis Laxa

Contents

Congenital cutis laxa is a rare inherited connective tissue disorder manifested by inelastic, loose, pendulous skin, giving the appearance of premature aging (Andiran et al. 2002).

Synonyms and Related Disorders

Arterial tortuosity syndrome; Cutis laxa with or without congenital disorder of glycosylation; Cutis laxa, Debre type (cutis laxa with growth and developmental delay); Macrocephaly, alopecia, cutis laxa, and scoliosis syndrome; Occipital horn syndrome/Menkes syndrome; Progeroid syndrome of De Barsy (cutis laxa-corneal clouding-mental retardation syndrome; Urban-Rifkin-Davis syndrome (cutis laxa with severe pulmonary, gastrointestinal, and urinary abnormalities)

Genetics/Basic Defects

1. Genetic heterogeneity of congenital cutis laxa (Beighton 1972, 1974; Berk et al. 2012)
    1. Autosomal recessive cutis laxa (ARCL), a genetically heterogeneous condition: the most common type
        1. Type I (ARCL-I): less frequent than type II
        2. Type IIA (ARCL-IIA) (cutis laxa, Debre type; cutis laxa with growth and developmental delay (Patton et al. 1987); cutis laxa with or without congenital disorder of glycosylation)
        3. Type IIB (ARCL-IIB): cutis laxa with progeroid features
        4. Type III (ARCL-III) (also known as De Barsy syndrome)
        5. Urban-Rifkin-Davis syndrome
        6. Macrocephaly, alopecia, cutis laxa, and scoliosis syndrome
        7. Arterial tortuosity syndrome
    2. Autosomal dominant cutis laxa (ADCL) (Damkier et al. 1991; Fischer-Zimsak et al. 2015)
    3. X-linked recessive cutis laxa (XLCL)
        1. Previously called occipital horn syndrome
        2. At present, best termed as Ehlers-Danlos syndrome type IX
        3. XLCL and Menkes syndrome are allelic, existing along a spectrum, with XLCL,

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representing the mildest form (Tumer and Moller 2009)

2. Biochemical and molecular defects of congenital cutis laxa (Loeys et al. 2002; Berk et al. 2012)
    1. ARCL-I: Molecular studies in a large consanguineous Turkish family demonstrated the presence of a homozygous missense mutation (T998C) in the fibulin-5 (*FBLN5*) gene, resulting in a serine-to-proline (S227P) substitution in the fourth calcium-binding epidermal growth factor-like domain of fibulin-5 protein
    2. ARCL-IIA
        1. Caused by mutation in the ATPase, H + transporting, lysosomal, V0 subunit A2 gene (*ATP6V0A2*)
        2. A combined disorder of N- and O-linked glycosylation has been described in children with congenital cutis laxa in association with severe central nervous system involvement, brain migration defects, seizures, and hearing loss (Morava et al. 2008).
    3. ARCL-IIB: caused by mutation in the *PYCR1* gene (Dimopoulou et al. 2013)
    4. ARCL-III (Fischer et al. 2014)
        1. ARCL-IIIA: caused by mutations in *ALDH18A1*
        2. ARCL-IIIB: caused by mutations in *PYCR1*
    5. URDS: caused by *LTBP4* mutations (Urban et al. 2009)
    6. MACS syndrome: caused by homozygous mutation in the *RIN2* gene (Basel-Vanagaite et al. 2009)
    7. ATS: caused by inactivating mutations in SLC2A10, which encodes GLUT10, a member of the glucose transporter family (Coucke et al. 2006; Callewaert et al. 2008)
    8. Autosomal dominant cutis laxa (Fischer-Zimsak et al. 2015)
        1. Can be caused by mutations in the elastin gene (*ELN*) (Graul-Neumann et al. 2008)
        2. Due to deficiency of lysyl oxidase (Byers et al. 1976, 1980)
        3. Autosomal dominant cutis laxa with progeroid features (ADCL): proposed by Fischer-Zimsak et al. (2015) to distinguish it from *ELN*-ADCL (ADCL2) (Urban et al. 2005; Callewaert et al. 2011) and *FBLN5*-ADCL (ADCL2) (Markova et al. 2003)
    9. X-linked recessive cutis laxa (Byers et al. 1980; Gorlin and Cohen 1990)
        1. Caused by mutations in the *ATP7A* gene
        2. Characterized by diminished activity of lysyl oxidase in the skin from affected males
        3. Reduced serum copper and ceruloplasmin in affected males, suggesting that the lysyl oxidase deficiency may be secondary to a defect in copper metabolism
3. Acquired cutis laxa (Banks et al. 2003)
    1. Drug ingestion: generalized skin involvement associated with the following:
        1. Penicillamine
        2. Penicillin
        3. Isoniazid
        4. Melphalan
        5. Phenacetin
    2. Paraneoplastica: skin manifestation of paraneoplastic syndromes associated with solid or hematogenous neoplasias
        1. Chronic neutrophilic leukemia
        2. Chronic myelogenous leukemia
    3. Postinflammatory: hyperextensible skin lesions with inflammatory infiltrates
        1. Sweet syndrome
        2. Bowel bypass syndrome
        3. Postinflammatory elastolysis and cutis laxa
        4. Marshall syndrome

Clinical Features

1. Autosomal recessive cutis laxa (Gorlin and Cohen 1990; Berk et al. 2012)
    1. More common than the autosomal dominant form
    2. ARCL-I
        1. Abundant facies
        2. Redundant folds around the face and neck

3. An aged appearance
4. Associated with severe systemic complications
    1. Pulmonary emphysema
    2. Diaphragmatic defects
    3. Arterial tortuosity
    4. Aneurysms
    5. Poorest prognosis: Many patients die from pulmonary or cardiac complications in early childhood
5. Muscular hypotonia
6. Joint laxity
7. Umbilical and inguinal hernias
8. Gastrointestinal and vesicourinary tract diverticuli
9. Normal mental and motor development

3. ARCL-II: also called cutis laxa with joint laxity and developmental delay
    1. ARCL-IIA (Van Maldergem et al. 2015)
        1. Furrowing of the skin of the whole body, particularly obvious in neck, axillae, and groin
        2. Droopy skin on the cheeks of the face and marked nasolabial folds, giving rise to distinctive facial features that also include prominent large nasal root, downslanted palpebral fissures, and delayed closure of the fontanelles
        3. Skin when extended does not display marked hyperelasticity but rather maintains its consistency and pretibial pseudo-ecchymotic skin lesions (as is observed in the Ehlers-Danlos syndromes) (Greally et al. 2014)
        4. Frequent motor nervous system abnormalities
        5. Cardiovascular abnormalities
        6. Patent anterior fontanel
        7. Congenital hip dislocation
        8. Inguinal hernias
        9. High myopia
        10. Bruch's membrane rupture
        11. Female predominance
    2. ARCL-IIB (Dimopoulou et al. 2013)
        1. Wrinkled inelastic skin, especially on the dorsal acral surfaces and abdomen
        2. Thin/translucent skin
        3. Triangular dysmorphic facies with progeroid appearance, bulbous nose, prognathism, hypotelorism, epicanthal folds, blue sclera, large ears, and microcephaly
        4. Intrauterine and postnatal growth retardation and developmental delay
        5. Hypotonia
        6. Microcephaly
        7. Blue sclera
        8. Cataract/corneal clouding
        9. Joint hyperlaxity
        10. Hip dislocation
        11. Osteoporosis/osteopenia
        12. Finger contractures
        13. Athetoid movements
4. ARCL-III (De Barsy syndrome) (de Barsy et al. 1968; Gorlin and Cohen 1990; Andiran et al. 2002; Morava et al. 2009; Fischer et al. 2014)
    1. The most severe disease of the autosomal recessive cutis laxa spectrum
    2. Thin and translucent skin, visibility of the veins
    3. A specific facial gestalt with triangular face and prognathism resulting in a progeroid appearance. Additionally, affected individuals show skeletal abnormalities
    4. Ophthalmological abnormalities
        1. Corneal clouding due to degeneration of the tunica elastica of the cornea
        2. Bilateral corneal opacification
    5. Intrauterine growth retardation
    6. Considerable intellectual disability in the majority of cases [9,10].
    7. Muscular hypotonia
    8. Reduced subcutaneous fat
    9. Athetoid movements early in life
    10. Hypermobility of small joints
5. Urban-Rifkin-Davis syndrome (Urban et al. 2009)
    1. Cutis laxa
    2. Severe respiratory complications: often fatal during infancy including emphysema, atelectasis, tracheomalacia, and diaphragmatic hernia

3. Gastrointestinal distension, diverticulosis, stenoses, and tortuosities
6. Macrocephaly, alopecia, cutis laxa, and scoliosis (MACS) syndrome (Basel-Vanagaite et al. 2009; Albrecht et al. 2010; Syx et al. 2010)
   1. Caused by mutations in the *RIN2* gene
   2. Very characteristic, discriminatory facial features with sagging chin and severe developmental delay.
   3. Described in an Israeli-Arab family with age-dependent redundant skin, macrocephaly, down-slanting palpebral fissures, droopy eyelids, everted lips, gingival hypertrophy, dental anomalies, sparse hair, joint hypermobility, scoliosis, and high-pitched voice
   4. There were no ocular, neurologic, or respiratory abnormalities.
7. Arterial tortuosity syndrome
   1. Characterized by elongation and tortuosity of major arteries and variable skin laxity. (Beuren et al. 1969; Gardella et al. 2004)
   2. Distinctive complications include vascular aneurysms, dissections, and stenoses (Zaidi et al. 2005; Callewaert et al. 2008)
   3. Death may occur in early childhood (Wessels et al. 2004) although milder phenotypes have been described (Callewaert et al. 2008)

2. Autosomal dominant cutis laxa (Hadj-Rabia et al. 2013)
   1. Less common than the autosomal recessive form
   2. Skin laxity (100%)
   3. Clinical features presenting in infancy (Andiran et al. 2002)
      1. Intrauterine growth retardation
      2. Delayed fontanelle closure
      3. Ligamental laxity
      4. Episodes of edema may precede the skin changes, usually within the first 2 months of life.
      5. Aging appearance by the end of the second year
      6. Pulmonary emphysema common (37%) due to a loss of elastic tissue in the lungs
      7. Aortic root dilatation (55%)
      8. Inguinal hernias (51%)
   4. Skin changes presenting in adulthood
      1. Usually no internal defects
      2. Having a normal life expectancy
   5. Aging appearance
      1. Drooping of eyelids
      2. Sagging facial skin
      3. Accentuation of the nasolabial and other facial folds
      4. Often hooked nose with everted nostrils
      5. Long philtrum
   6. Few complications
      1. Hoarseness
      2. Pulmonary artery stenosis
      3. Mitral valve prolapse
      4. Bronchiectasis
      5. Joint dislocations
      6. Tortuosity and dilatation of carotid arteries and aorta
      7. Dilatation of sinuses of Valsalva
      8. Coarctation of the aorta
   7. Normal life span
3. X-linked recessive cutis laxa (Brown et al. 1982; Berk et al. 2012)
   1. Known as occipital horn syndrome, formerly classified as Ehlers-Danlos syndrome type IX (Please see the chapter on "► Ehlers-Danlos Syndrome"), and allelic to Menkes syndrome (Please see the chapter on "► Menkes Disease")
   2. Hyperextensible wrinkled skin with droopy facies at birth
   3. Mainly with connective tissue problems
      1. Long and thin face, neck, and trunk
      2. Mild hyperelastic (but not lax) and bruisable skin with resultant atrophic scars
      3. Inferior cranial spurs (occipital horns)
         1. A constant feature
         2. May be palpated or found on radiographs
         3. May become larger with age
         4. May represent ectopic bone formation within the trapezius and sternocleidomastoid aponeuroses
      4. Skeletal dysplasia most prominent at the wrists and elbows

5. Limitation of extension of the elbows, shoulders, knees
6. Hypermobility of the finger joints
7. Pes planus
8. Genu valga
9. Pectus excavatum or carinatum (40%)

4. Obstructive uropathy secondary to bladder diverticula with bladder neck obstruction (60–70%)
5. Various hernias (hiatal, femoral, and inguinal) (35%)
6. Chronic diarrhea (40%)
7. Coarse, kinky hair with pili torti can be observed

4. Clinical and biochemical features guiding the diagnostics in neurometabolic cutis laxa (Gardeitchik et al. 2014)
   1. Abnormal glycosylation and gyration abnormalities: mostly, but not always associated with *ATP6V0A2* mutations
   2. Epilepsy: most common in *ATP6V0A2* defects
   3. Corpus callosum dysgenesis: associated with *PYCR1* and *ALDH18A1* mutation
   4. Dystonic posturing: discriminatory for *PYCR1* and *ALDH18A1* defects
   5. Metabolic markers of mitochondrial dysfunction: found in one patient with *PYCR1* mutations
   6. White matter abnormalities: associated with *GORAB* and *RIN2* mutations
   7. Migration defects and corpus callosum hypoplasia: not always diagnostic for a specific genetic defect in cutis laxa
   8. All patients with *ATP6V0A2* defects had abnormal glycosylation
   9. Central nervous system and metabolic abnormalities in cutis laxa: discriminatory in this genetically heterogeneous group, although not always diagnostic for a certain genetic defect
5. Differential diagnosis: syndromes featuring lax or wrinkled skin (Berk et al. 2012)
   1. Wrinkling skin syndrome
      1. A rare autosomal recessive disorder of the connective tissue: *ATPV0A2* mutations
      2. Cutaneous findings
         1. Wrinkled skin over abdomen and on the dorsum of the hands and feet
         2. Poor skin elasticity in affected areas
         3. Increased palmar and plantar creases
         4. A prominent venous pattern on the chest
      3. Other predominant findings
         1. Mental retardation
         2. Microcephaly
         3. Hypotonia
         4. Musculoskeletal abnormalities
   2. Geroderma osteodysplasticum
      1. An autosomal recessive disorder: caused by mutations in *SCYL1BP1*
      2. Also caused by *GORAB* mutations involving Golgi apparatus function
      3. Cutaneous findings
         1. Lax, nonhyperelastic skin, most prominent over extremities
         2. Premature aging
      4. Other predominant findings
         1. Frequent bone fractures
         2. Joint luxations
   3. Cantu syndrome
      1. An autosomal dominant disorder
      2. Cutaneous findings
         1. Hypertrichosis
         2. Wrinkled palms and soles
      3. Other predominant findings
         1. Delayed psychomotor development
         2. Short stature
         3. Large head
         4. Peculiar facies
         5. Cardiac abnormalities
         6. Mild mental retardation
         7. Osteochondrodysplasia
   4. Costello syndrome (Davies and Hughes 1994)
      1. An autosomal recessive disorder: caused by *HRAS* mutations
      2. Cutaneous findings
         1. Cutis laxa most prominent over palms, soles, and neck
         2. Coarse craniofacial appearance

3. Papillomata around mouth, nares, and anus
3. Other predominant findings
1. Postnatal growth retardation
2. Cardiovascular abnormalities
3. Mental retardation

5. SCARF syndrome (Koppe et al. 1989)
1. An X-linked recessive disorder
2. Cutaneous findings
1. Cutis laxa
2. Webbed neck
3. Other predominant findings
1. Facial abnormalities: multiple hair whorls, epicanthal folds, ptosis, high and broad nasal root, low-set and posteriorly rotated ears, and small chin
2. Mild to moderate psychomotor retardation
3. Wide-spaced nipples
4. Diastasis recti
5. Umbilical and inguinal herniae
6. Craniostenosis
7. Enamel hypoplasia and hypocalcification of the teeth
8. Short sternum
9. Pectus carinatum
10. Abnormally shaped vertebrae
11. Abnormal modeling of long tubular bones
12. Ambiguous genitalia: micropenis, perineal hypospadias

6. Williams syndrome (Please see the chapter of "► Williams Syndrome")

7. Patterson syndrome (pseudoleprechaunism)
1. Cutaneous findings
1. Cutis gyrata of hands and feet
2. Bronze hyperpigmentation
2. Other predominant findings
3. Hyperadrenocorticism
4. Diabetes mellitus
5. Bladder diverticuli
6. Severe mental retardation
7. Major bony deformities

8. Hutchinson-Gilford syndrome
1. An autosomal dominant disorder: caused by *LMNA* mutations
2. Cutaneous findings
1. Wrinkled aged-looking skin
2. Loss of subcutaneous fat
3. Alopecia
3. Other predominant findings
1. Progeria
2. Short stature
3. Micrognathia
4. Craniofacial disproportion
5. Joint stiffness

9. Kabuki syndrome (Please see the chapter of "► Kabuki Syndrome")

10. Barber-Say syndrome
1. Cutaneous findings
1. Redundant, lax skin
2. Generalized hypertrichosis
3. Ectopion of eyelids
2. Other predominant findings
1. Ambiguous genitalia
2. Macrostomia

11. Congenital hemolytic anemia with emphysema and cutis laxa
1. An autosomal recessive disorder
2. Cutaneous finding: cutis laxa
3. Other predominant findings
1. Hemolytic anemia
2. Emphysema
3. Hemorrhagic necrosis of adrenals

12. Hereditary gelsolin amyloidosis (amyloidosis V)
1. An autosomal dominant disorder
2. Cutaneous finding: skin laxity
3. Other predominant findings
1. Corneal lattice dystrophy
2. Cranial and peripheral polyneuropathy

13. Ablepharon macrostomia syndrome
1. An autosomal recessive disorder
2. Cutaneous findings
1. Redundant, lax skin
2. Absence or hypoplasia of eyelids
3. Other predominant findings
1. Ambiguous genitalia
2. Abnormal ears
3. Rudimentary nipples
4. Macrostomia

14. Lenz-Majewski hyperostotic dwarfism
1. An autosomal dominant disorder

2. Cutaneous findings
    1. Thin, wrinkled, and atrophic skin
    2. Prominent cutaneous veins
3. Other predominant findings
    1. Delayed closure of fontanelle
    2. Mental retardation
    3. Progressive skeletal sclerosis with severe growth retardation

15. GAPO (growth retardation, alopecia, pseudoanodontia (failure of tooth eruption), and progressive optic atrophy) syndrome (Tipton and Gorlin 1984)
    1. An autosomal recessive disorder
    2. Cutaneous finding: redundant skin
    3. Other predominant findings
        1. Growth retardation
        2. Alopecia
        3. Pseudoanodontia
        4. Optic atrophy
        5. Facial dysmorphism
        6. Short stature
        7. Glaucoma
16. Ehlers-Danlos syndrome (classic type) (Please see the chapter of "▶ Ehlers-Danlos Syndrome")
17. Pseudoxanthoma elasticum
    1. An autosomal recessive disorder: caused by *ABCC6* mutations
    2. Cutaneous findings
        1. Lax skin with redundant folds in affected areas
        2. Yellowish papules coalescing to plaques on neck and flexural areas
    3. Other predominant findings
        1. Angioid streaks
        2. Cardiovascular disease

Diagnostic Investigations

1. Radiography
    1. Autosomal recessive cutis laxa
        1. Presence of a variety of hernias
            1. Femoral
            2. Inguinal
            3. Obturator
            4. Hiatal
        2. Eventrations of the diaphragm
        3. Rectal and uterine prolapse
        4. Common intrathoracic abnormalities
            1. Hyperexpansion of the lungs
            2. Emphysema which may lead to cor pulmonale and death in childhood
            3. Upper airway obstruction caused by excessively lax vocal cords, leading to congestive heart failure
            4. Frequent peripheral pulmonary artery stenosis and aortic dilatation
        5. Diverticula involving the entire bowel but no functional significance
        6. Diverticula of the urinary tract predisposing to infection or causing obstruction
        7. Arteriographic changes
            1. Peripheral pulmonary stenosis
            2. Dilatation and tortuosity of the aorta
            3. A peculiar corkscrew appearance of the peripheral systemic arteries, similar to the arterial changes seen in Menkes syndrome
    2. X-linked recessive cutis laxa (Gorlin and Cohen 1990)
        1. Occipital exostosis (horns) symmetrically located on each side of the foramen magnum
        2. Short clavicles with a widened medullary cavity
        3. Hammer-shaped distal extremities
        4. Focal hyperostosis of the femora at sites of tendon and ligament insertion
        5. Carpal fusion involving capitate-hamate and trapezium-trapezoid coalescence (over 50%)
        6. Deformation of humerus, radius, ulna, tibia, and fibula (90%)
        7. Osteoporosis (70%)
        8. Narrowing of rib cage (65%)
        9. Dislocation of radial head (40%)
        10. Mild platyspondyly
        11. Coxa valga
        12. Flattening of acetabular roofs
    2. Histopathological abnormality: fragmentation and paucity of elastic fibers in the skin

3. X-linked cutis laxa
    1. Nonmolecular testing
        1. Low serum copper concentration
        2. Low serum ceruloplasmin concentration
        3. Copper transport studies in cultured fibroblasts: impaired cellular copper exodus demonstrated by increased cellular copper retention in pulse-chase experiments with radiolabeled copper
        4. Plasma and CSF catecholamine analysis: abnormal levels reflecting partial deficiency of dopamine-beta-hydroxylase, a copper-dependent enzyme critical for catecholamine biosynthesis
        5. Low activity of a copper-dependent enzyme, lysyl oxidase
    2. Molecular genetic testing
        1. Mutation analysis: multiplex PCR analysis, available on a clinical basis, to detect large *ATP7A* deletions
        2. Sequence analysis: direct sequence analysis of the *ATP7A* coding region and flanking intron sequences, available on a clinical basis
        3. Mutation scanning: heteroduplex analysis, available on a clinical basis, to detect small mutations

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive cutis laxa: 25%
        2. Autosomal dominant cutis laxa: not increased unless a parent is affected
        3. X-linked recessive cutis laxa:
            1. When the mother is a carrier: 50% risk of brother will be affected and 50% of sisters carriers
            2. When mother is not a carrier: the recurrence risk is low but greater than that for the general population because the risk of germline mosaicism in mother is not known.
    2. Patient's offspring
        1. Autosomal recessive cutis laxa: not increased unless the spouse is a carrier or affected
        2. Autosomal dominant cutis laxa: 50%
        3. X-linked recessive cutis laxa: Males with occipital horn syndrome will pass the disease-causing gene to all of their daughters and none of their sons.
2. Prenatal diagnosis
    1. DNA-based analysis on fetal DNA obtained from amniocentesis or CVS for the previously characterized disease-causing mutation
    2. Fetal sex determination for X-linked recessive cutis laxa (occipital horn syndrome)
    3. Preimplantation genetic diagnosis may be an option for some families in which the pathogenic variants have been identified (Van Maldergem et al. 2015)
3. Management (Nahas et al. 1999; Strohecker 1995)
    1. Supportive therapy: antibiotic prophylaxis for bladder infection
    2. Surgery for bladder diverticula
    3. Plastic surgery (Beighton et al. 1970) to improve aging appearance
        1. Serial excisions of the skin
        2. Blepharoplasty
        3. Rhytidectomy
        4. Rhinoplasty
        5. Shortening of the upper lip
        6. Earlobe reduction
        7. Neck lift
        8. Correction of lower eyelid laxity, epiphora, and upper eyelid ptosis

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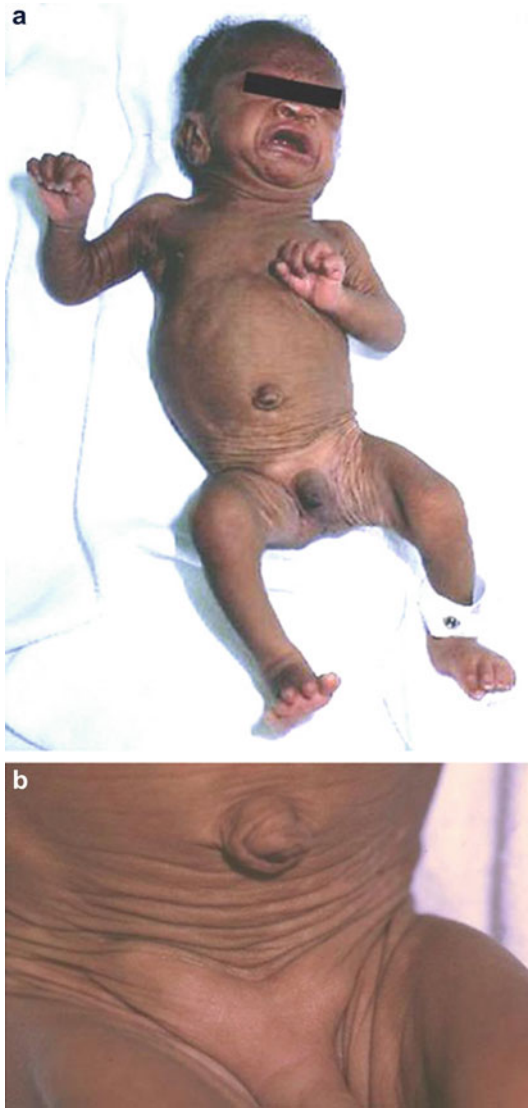

Fig. 1 (**a**, **b**) An infant with cutis laxa showing redundancy of skin folds and bilateral hernias

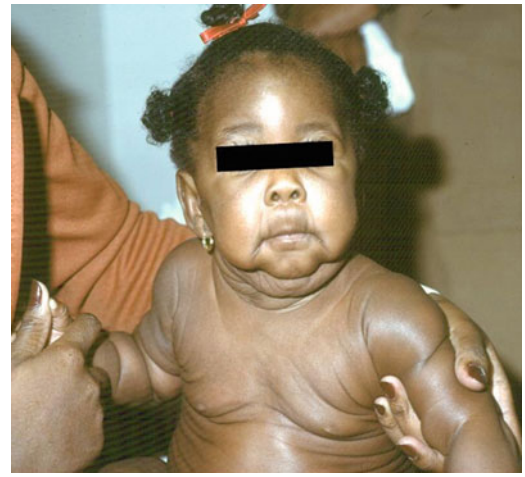

Fig. 2 A young girl with cutis laxa showing redundancy of the skin folds, short columella, long philtrum, and sagging of the lower chin and prominent loose skin folds of the trunk

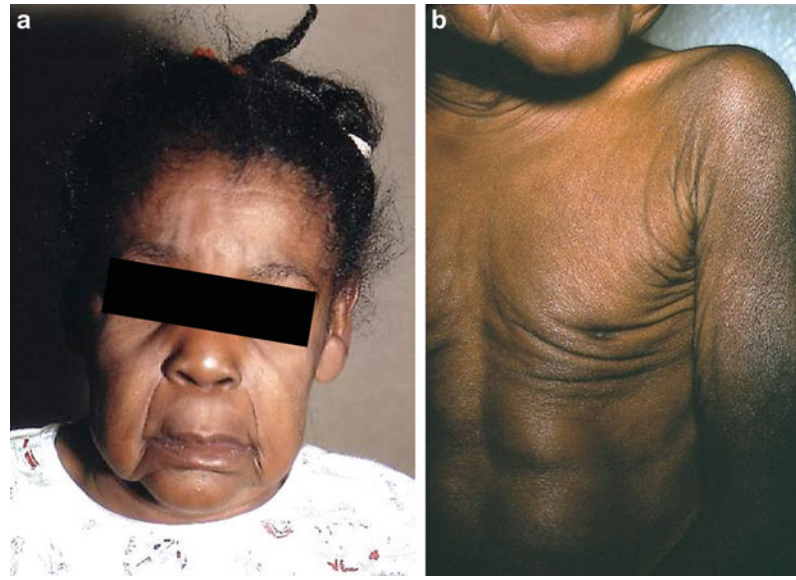

Fig. 3 (**a**, **b**) A 10-year-old girl with cutis laxa showing redundancy of the skin, sagging of the upper lids, short columella, long philtrum, and sagging skin folds over trunk

Congenital Cytomegalovirus Infection

Contents

Congenital cytomegalovirus infection is the most common congenital infection in neonates in the USA, affecting approximately 0.5–1.5% of all live births and 30,000–40,000 newborns annually. Congenital infections result from transplacental transmission of cytomegalovirus (CMV).

Synonyms and Related Disorders

Intrauterine cytomegalovirus infection of fetus

Genetics/Basic Defects

1. Human cytomegalovirus (HCMV) (Griffiths et al. 2015)
    1. A DNA virus belonging to the herpesvirus group (herpes simplex, varicella zoster, Epstein-Barr) (Brown and Abernathy 1998).
    2. Ability of the virus (Pass 2002).
        1. To destroy host cells (lytic infection)
        2. To infect a wide range of cells and tissues
        3. To evade and interfere with host defense mechanisms
        4. To persist indefinitely in the host
        5. To infect and destroy cells during productive infection (with release of progeny virus)
    3. HCMV: a recognized cause of disease in the fetus, the allograft recipient, and AIDS patients.
    4. More recently, it has been recognized as a pathogen for those admitted to intensive care units, for the elderly, and for the general population.
2. Transmission of CMV (Del Pizzo 2011)
    1. Horizontal transmission: close intimate contact with another person shedding the virus in body fluids (saliva, blood, cervical secretions, semen, urine, or respiratory droplets)
    2. Vertical transmission: from mother to infant
        1. In utero by transplacental passage of maternal blood-borne virus.
        2. At birth by passage through an infected maternal genital tract.
        3. Postnatally by ingestion of CMV-positive human milk from seropositive mothers.
        4. Mothers who have been exposed to CMV before pregnancy are still at risk for transmitting the infection to the fetus by way of reactivation or infection with a

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new strain. However, maternal infection before pregnancy and subsequent development of immunity significantly decrease the risk of congenital CMV.
   3. Infected organ or bone marrow transplantation
   4. Infected blood transfusion from CMV-seropositive donors
3. Primary sources of CMV infection for women of childbearing age
   1. Young children
   2. Sexual contacts
4. Classifications of CMV (Mestas 2016)
   1. Primary CMV (first experience): primary maternal CMV infection during pregnancy presents the greatest danger to the fetus.
   2. Secondary CMV (recurrent or reactivated CMV infection): In secondary maternal CMV infection during pregnancy the presence of maternal anti-CMV antibodies offers substantial protection against congenital infection and presents much less danger to the fetus with much lower transmission rates (Guerra et al. 2000).
   3. Congenital CMV: CMV that has been transmitted from the mother to the fetus during pregnancy.
   4. Perinatal CMV: CMV acquired during the intrapartum period such as during delivery, via cervical secretions or maternal blood exposure.
   5. Postnatal CMV: CMV acquired after delivery, such as that acquired via maternal breast milk.
5. The most common vertically transmitted viral infection from mother to fetus in pregnancy
   1. Recurrent infection: 1% risk of vertical transmission
   2. Primary infection
      1. Pose a 30–40% risk of vertical transmission, and adverse outcome is more likely when infection occurs within the first half of gestation (Stagno et al. 1986).
      2. Congenital CMV infection resulting from primary maternal infection: more likely to be serious than that resulting from recurrent infection (Stagno et al. 1982).
      3. Congenital CMV infection acquired from primary maternal infection with normal fetal imaging: associated with a high rate of subtle signs and symptoms after birth (Amir et al. 2016).
6. Greatest risk occurring with infection during the first 22 weeks of gestation
7. Congenitally infected newborns: may shed the virus for many years
8. Perinatal CMV infection acquired during birth or from mother's milk: not associated with newborn illness or CNS sequelae, except perhaps in very preterm newborns who have very low levels of passively acquired CMV antibody at the time of infection

Clinical Features

1. Symptomatic at birth in 5–10% of congenital CMV infections (Enders et al. 2001).
   1. Approximately 20% of these will die.
   2. Ninety percent of survivors will develop major neurological sequelae.
2. Asymptomatic or "silent" congenital infections at birth in vast majority (85–90%) of cases. Ten to fifteen percent of the asymptomatic newborns will be afflicted by late sequelae such as mental retardation, deafness, or hearing defects, usually during the first 2 years of life (Enders et al. 2001).
3. Non-neurologic symptoms at birth.
   1. Prematurity
   2. Small size for gestation
   3. Petechiae (most common non-neurologic symptom)
   4. Blueberry muffin rash
   5. Thrombocytopenia
   6. Purpura
   7. Ecchymoses
   8. Hepatosplenomegaly
   9. Jaundice
   10. Intrauterine growth retardation
   11. Chorioretinitis
   12. Pneumonitis
   13. Anemia
   14. Nonimmune hydrops

4. Neurologic symptoms at birth.
    1. Hypotonia
    2. Lethargy
    3. Jitteriness
    4. Split sutures
    5. Immature primitive reflexes
    6. Feeding difficulties
    7. Microcephaly: the most specific predictor of mental retardation and major motor disability
    8. Seizures
5. Eye manifestations (Coats et al. 2000; Metz 2001).
    1. Chorioretinitis resulting in a chorioretinal scar
    2. Corneal opacities
    3. Bilateral anterior polar cataracts
    4. Optic nerve hypoplasia and optic nerve coloboma
    5. Strabismus
    6. Visual impairment
    7. Cyclopia (Byrne et al. 1987) and anophthalmia
6. Later neurologic symptoms.
    1. Sensorineural hearing loss
        1. Likely caused by asymptomatic congenital CMV infection (Fowler et al. 1997)
        2. Underscores the importance of congenital cytomegalovirus as a cause of sensorineural hearing loss in childhood (Goderis et al. 2014)
    2. Learning disability
    3. Mental retardation
    4. Cerebral palsy
7. Atypical findings in preterm infants rarely reported in term infants (Perlman and Argyle 1992).
    1. Hypotonia
    2. Multiple contractures
    3. Periventricular leukomalacia
    4. Optic atrophy
8. Prognosis.
    1. Neonatal clinical abnormalities expected to resolve spontaneously within weeks, except for those involving the CNS and hearing.
    2. Neonates with symptomatic congenital CMV infection have a multisystem disease with significant morbidity and mortality (Boppana et al. 1992).
    3. A leading cause of mental retardation and sensory impairment (50–90% of symptomatic newborns) and sensorineural hearing loss (7–15% of asymptomatic infants).
    4. An important cause of cerebral palsy and retinal damage.
    5. Children with postnatal microcephaly, postnatal seizures, and an abnormal central nervous system imaging study: more likely to have severe developmental sequelae (Bale et al. 1990).
9. Long-term sequelae of congenital cytomegalovirus infection in children with and without symptoms at birth (Sharon and Schleiss 2007; Schleiss 2008).
    1. Overall incidence
        1. Symptomatic: 50–90%
        2. Asymptomatic: 10–15%
    2. Hearing loss
        1. Symptomatic: 50–60%
        2. Asymptomatic: 7–15%
    3. Cognitive deficits
        1. Symptomatic: 50–70%
        2. Asymptomatic: ~4%
    4. Microcephaly
        1. Symptomatic: 35–40%
        2. Asymptomatic: ~2%
    5. Ocular abnormalities
        1. Symptomatic: 25–50%
        2. Asymptomatic: ~3%
    6. Seizures
        1. Symptomatic: 15–20%
        2. Asymptomatic: ~1%
    7. Mild to moderate motor deficits
        1. Symptomatic: 25–30%
        2. Asymptomatic: <1%
    8. Severe motor deficits
        1. Symptomatic: 15–25%
        2. Asymptomatic: <1%
10. Maternal primary CMV infection.
    1. Asymptomatic: vast majority of pregnant women
    2. Symptomatic (mononucleosis-like syndrome) in approximately 10% of infected pregnant patients
        1. Fever
        2. Fatigue/malaise
        3. Myalgia

4. Pharyngitis
5. Cough
6. Nausea
7. Headache

Diagnostic Investigations

1. Children with symptomatic congenital CMV infection (Istas et al. 1995; Pass 2002; Bonalumi et al. 2011)
    1. Virus detection by PCR amplification in the urine or saliva samples (Joseph et al. 2013)
    2. Elevated alanine aminotransferase (ALT >80 IU/mL)
    3. Thrombocytopenia (<100,000 cells/mcL)
    4. Conjugated hyperbilirubinemia (direct bilirubin >2 mg/dL)
    5. Anemia
    6. Elevated CSF protein (>120 mg/dL)
2. Diagnostic tests for identification of CMV infection in mother, fetus, and newborn infants (Naing et al. 2016)
    1. Prenatal
        1. Maternal CMV: IgM positivity
        2. IgM/IgG serology: IgG seroconversion, low IgG avidity
        3. Qualitative CMV-PCR (amniotic fluid): CMV-DNA positive
        4. Real-time PCR (amniotic fluid): CMV-DNA positive, with high viral load ($>10^4$ copies/mL)
        5. Fetal ultrasound: fetal abnormalities (cerebral ventriculomegaly, echogenic bowel, intrauterine growth restriction)
    2. At birth
        1. Maternal CMV-IgM/IgG serology: IgM detection, IgG seroconversion, and low IgG avidity
        2. Qualitative CMV-PCR (cord blood, infant urine, placenta/infant saliva): CMV-DNA positive
        3. Real-time PCR (cord blood, infant urine, placenta/infant saliva): CMV-DNA positive, with high viral load ($>10^4$ copies/mL)
3. Ultrasonography (Crino 1999; Lipitz et al. 2002; Malinger et al. 2003, 2011; Bonalumi et al. 2011)
    1. Fetal growth restriction
    2. Cerebral ventriculomegaly
    3. Increased periventricular echogenicity
    4. Periventricular pseudocysts and intraventricular synechiae
    5. Ascites
    6. Intracranial calcifications
    7. Abnormality of amniotic fluid volume (usually oligohydramnios)
    8. Microcephaly
    9. Hyperechogenic bowel
    10. Hydrops fetalis
    11. Pleural effusion
    12. Liver calcifications
4. Radiography
    1. Intracranial calcification: usually periventricular (Roach et al. 1983)
    2. Microcephaly
5. CT scan
    1. Intracerebral calcification: the most frequent finding (Boppana et al. 1997)
    2. Microcephaly: the most specific predictor of poor cognitive outcome in children with symptomatic congenital CMV infection (Noyola et al. 2001)
    3. White matter lucencies
    4. Ventriculomegaly
    5. Destructive encephalopathy
    6. Brain atrophy
    7. Neuronal migration disorders
6. Fetal MRI (Doneda et al. 2010; Averill et al. 2015)
    1. Anterior temporal cysts and occipital horn septations, as dilation of these areas may decrease later in development.
    2. Cortical migration abnormalities.
    3. White matter abnormalities.
    4. Cerebellar dysplasia.
    5. Periventricular calcifications.
    6. Fetal MR imaging can show abnormalities in the fetal brain after CMV infection, even when US results are normal. The early detection of some brain

abnormalities, such as microencephaly and cortical anomalies, may substantially influence the prognosis of fetal infection.

7. Neonatal auditory screening (Hicks et al. 1993)
8. Evidence of infection with CMV
    1. Fourfold rise in anti-CMV IgG titers.
    2. Seroconversion from negative to positive.
    3. Sensitivity of the CMV-IgM assays (50–90%). The IgM titers may not become positive during acute infection.
9. Viral isolation
    1. The most sensitive method to diagnose CMV infection
    2. Culture of CMV from virtually all body fluids, including saliva and urine of the newborn, semen, and cervicovaginal secretions
    3. Detection of CMV within the first 3 weeks of life: considered proof of congenital CMV infection
10. Identification of CMV-DNA through PCR on amniotic fluid (best sensitivity and 100% specificity) (Lazzarotto et al. 2000; Liesnard et al. 2000)
11. Newborn screening for congenital cytomegalovirus infection (Bale 2010)
    1. Universal screening methods by using polymerase chain reaction (PCR) analysis of newborn dried blood spots (Boppana et al. 2010).
    2. Cytomegalovirus infection.
        1. Accounts for as much or more disability over the past 50 years than was associated with congenital rubella syndrome
        2. Represents the most common nongenetic cause of permanent hearing loss among children in the USA
    3. The most effective strategy for reducing CMV-induced sensorineural hearing loss, as well as for eliminating CMV-associated neurodevelopmental disability, will not be universal screening but prevention of congenital CMV infection (Pass et al. 2009).

Genetic Counseling

1. Recurrence risk
    1. Preconceptional immunity to CMV provides substantial protection against intrauterine transmission and severe fetal infection.
    2. Presence of maternal humoral antibody: conferring no fetal protection in subsequent reinfection or reactivation.
2. Prenatal diagnosis
    1. Prenatal ultrasonography.
        1. Intrauterine growth retardation
        2. Microcephaly
        3. Ventriculomegaly
        4. Periventricular calcifications
        5. Intrahepatic calcifications
        6. Nonimmune hydrops
        7. Fetal ascites
        8. Pericardial effusion
        9. Hepatosplenomegaly
        10. Echogenic bowel
        11. Cardiomegaly
        12. Oligohydramnios
        13. Placentomegaly
    2. Prenatal diagnosis of congenital CMV infection by combined detection of CMV-DNA and CMV-IgM in fetal blood or by combined testing of AF and fetal blood for CMV-DNA and IgM antibodies (sensitivity of 100%) (Enders et al. 2001) or isolating the virus from amniotic fluid (Plosa et al. 2012).
    3. Prenatal diagnosis: established by serological tests in umbilical cord blood and confirmed by detection of viral DNA in fetal blood and tissues from the postmortem specimen after termination of pregnancy (Beksaç et al. 2001).
    4. Negative results of CMV culture or PCR in the amniotic fluid cannot formally exclude intrauterine infection (Bodéus et al. 1999).
    5. Prenatal diagnosis of CMV infection remains a "long-standing problem still seeking a solution" as long as no assistance (treatment or prevention) can be offered to the pregnant women.

6. Amniotic fluid peptidome analysis: effectively predict the severity of congenital CMV infection (Desveaux et al. 2016).

3. Management
   1. Prevention.
      1. Complicated because both primary and secondary maternal infections give rise to disease in the offspring and absence of characteristic symptoms in CMV-infected mothers excludes clinical recognition of at-risk pregnancies
      2. Routine screening of pregnant patients for CMV status: not currently recommended because no effective antiviral therapy is available during gestation and also there is no means to predict the outcome in an infected fetus
      3. Risk to CMV infection for women in high-risk environments (day-care centers, nurseries, elementary schools, or health-care facilities)
      4. Strict hygiene practices for seronegative women to reduce the risk for the infection
   2. Prospects of intervention (Cheeran et al. 2009).
      1. Antiviral drugs (Ganciclovir, Valganciclovir, Foscarnet, Cidofovir, CMV immune globulin) are available for treatment of congenital CMV infection (Plosa et al. 2012), and there is evidence that therapy ameliorates the severity of one of the CNS complications of infection, sensorineural hearing loss. Long-term neurodevelopmental follow-up studies should further clarify the value of antiviral therapy in congenitally infected infants.
      2. Uncontrolled studies of therapy in utero with CMV immune globulin have suggested an impact on neuropathogenesis, and controlled trials should be conducted with pregnant women.
      3. CMV vaccines (Pass et al. 2009; Bale 2010) may hold the greatest promise in reducing the neurodevelopmental consequences of congenital infection, although the immune correlates of protection of the fetus remain incompletely defined.
      3. Recent progress in developing novel antiviral drugs and vaccines suggests the possibility that the diverse effects of HCMV may soon become controllable at the individual and population level, respectively (Griffiths et al. 2015).

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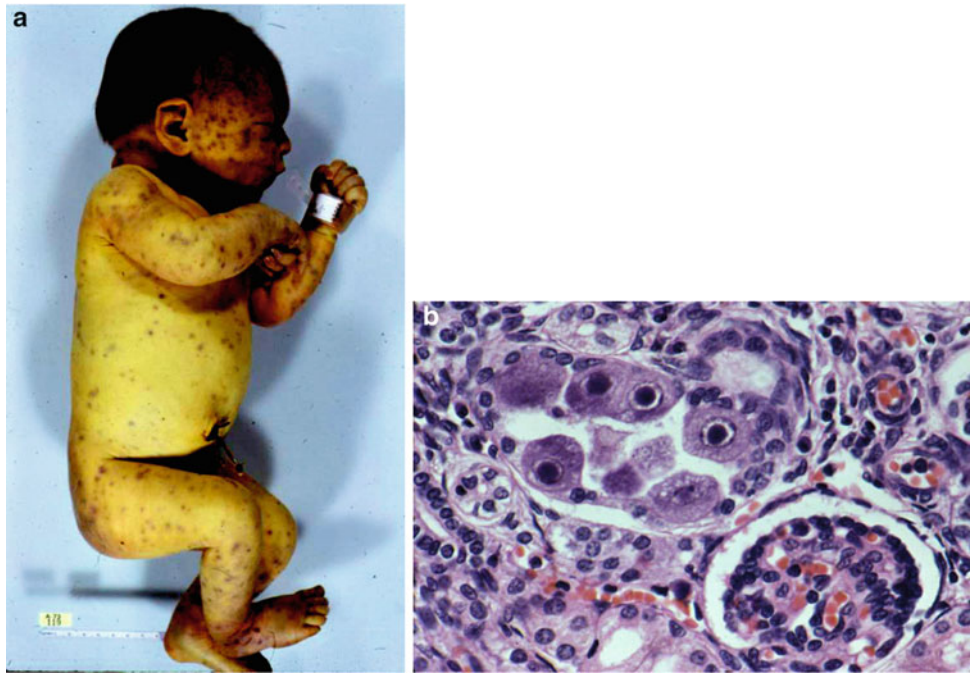

Fig. 1 (**a**, **b**) A neonate with blue berry muffin skin lesions (generalized purpura) due to cytomegalovirus infection. He died 20 h after birth. CMV inclusions were noted in the kidneys, lungs, liver, pancreas, thyroid, brain, and eyes and also in the urine. Photomicrograph of the kidney shows many tubular epithelial cells containing large cytomegalic inclusion bodies (Courtesy of Dr. Samuel Yang)

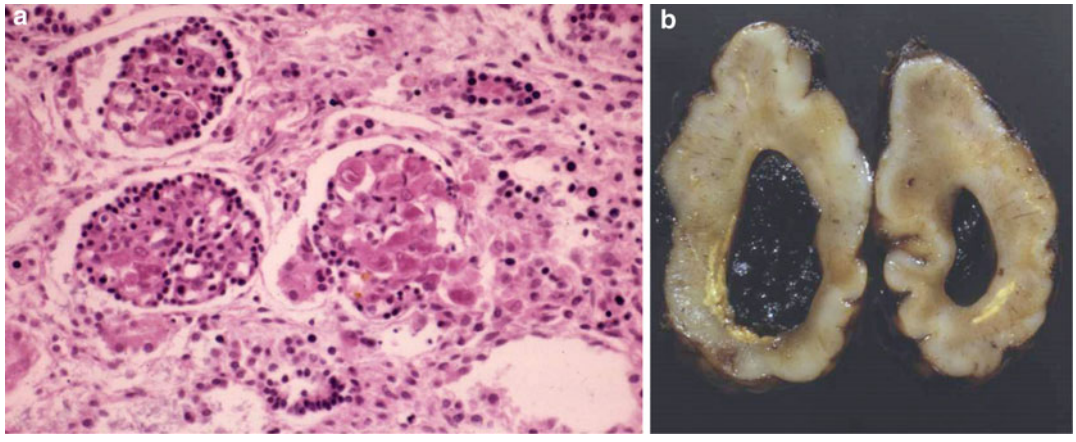

Fig. 2 (**a**, **b**) Photomicrograph of the kidney (macerated fetus, 16-week gestation). Even though the tissue is macerated, many cytomegalic inclusion bodies are demonstrable. Coronal section of the brain (frontal lobe) showing ventricular hemorrhage and focal encephalomalacia (chalky white discoloration) due to cytomegalovirus infection

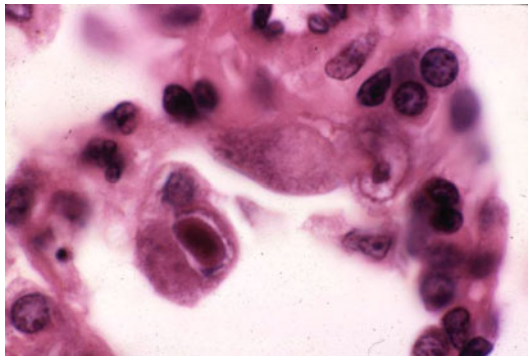

Fig. 3 Photomicrograph of premature lung of a different patient showing a single large cytomegalic inclusion body

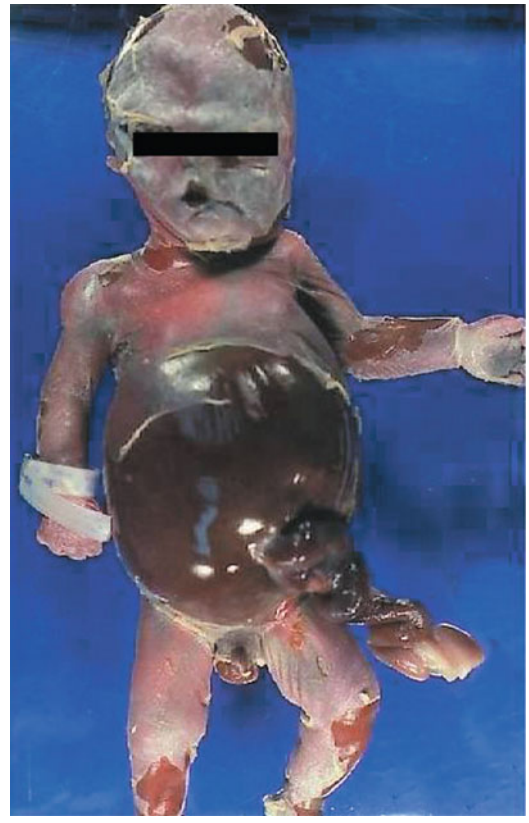

Fig. 5 A macerated stillborn with hydrops fetalis from congenital CMV infection

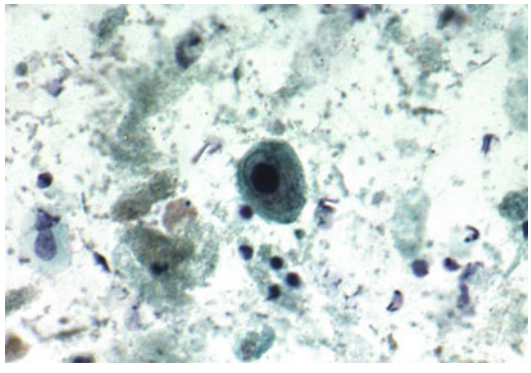

Fig. 4 One cytomegalic inclusion body in the urine sediment in another patient

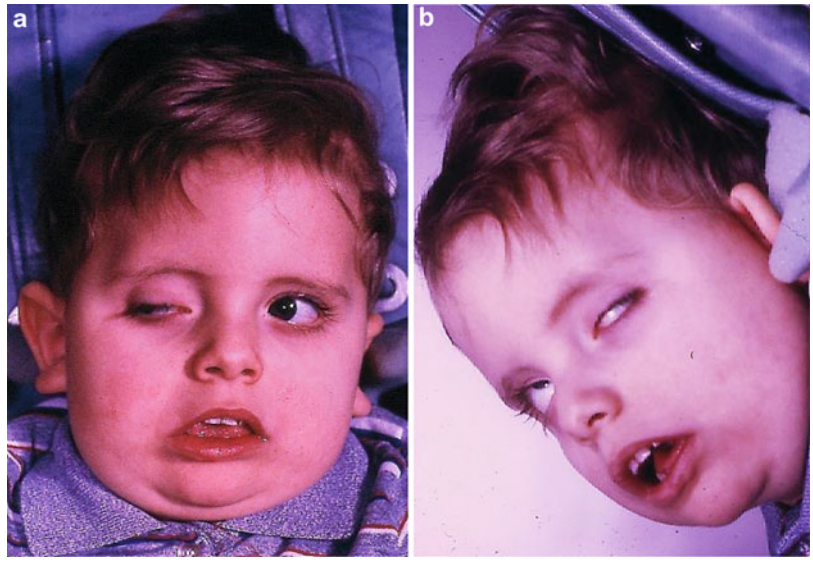

Fig. 6 (**a**, **b**) An infant with CNS involvement and chorioretinitis from congenital CMV infection

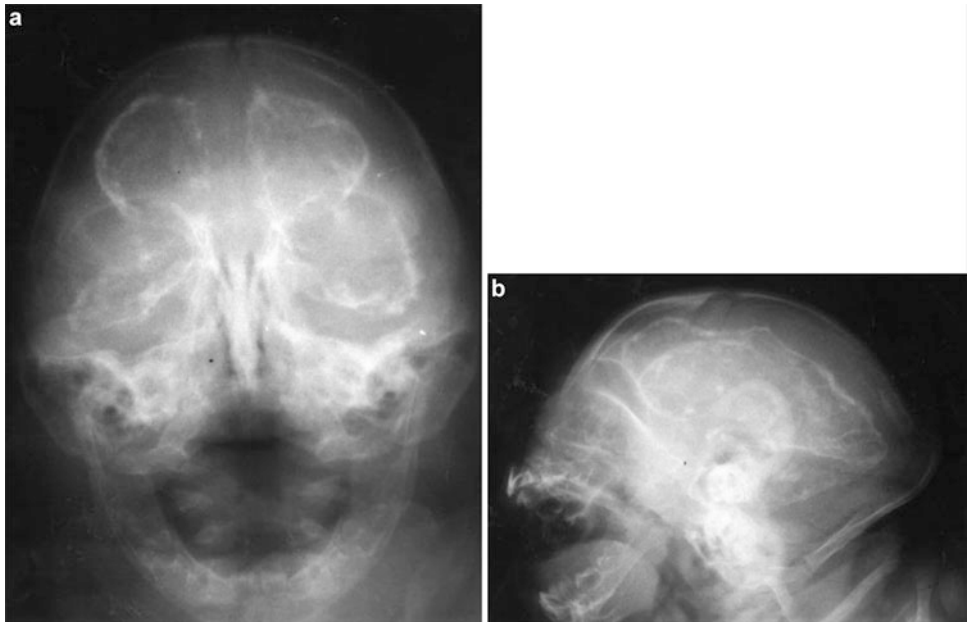

Fig. 7 (**a**, **b**) Skull radiographs of another patient with congenital CMV infection showing microcephaly and typical intracranial ventricular subependymal calcifications

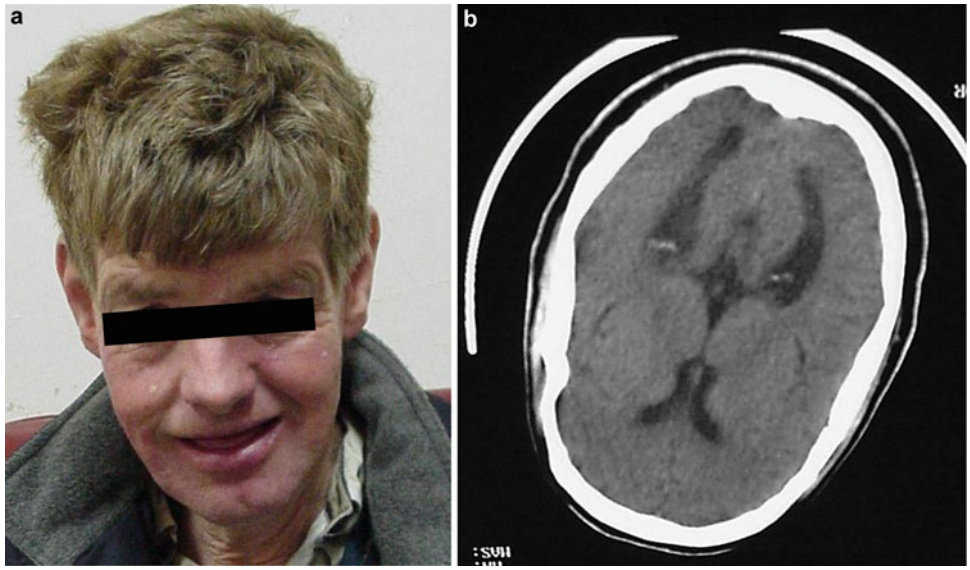

Fig. 8 (**a**, **b**) An adult with congenital CMV infection showing mental retardation and intracranial calcifications by CT scan

Congenital Generalized Lipodystrophy

Contents

Congenital generalized lipodystrophy (CGL), also called Berardinelli-Seip syndrome (BSCL) (Berardinelli 1954; Seip 1959; Seip and Tryqstad 1963, 1996), is an extremely rare genetic disorder characterized by extreme paucity of adipose tissue from birth, extreme insulin resistance, hypertriglyceridemia, hepatic steatosis, and early onset of diabetes (Agarwal et al. 2002). Its prevalence is estimated to be 1 in 200,000 (Portugal) to 1 in 12 million people (USA) (Mandal et al. 2006).

Synonyms and Related Disorders

Barraquer-Simons syndrome; Berardinelli-Seip congenital lipodystrophy; Dunnigan syndrome; Köbberling syndrome; Lawrence syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Garg 2004)
2. Existence of two loci in a gene for congenital generalized lipodystrophy (CGL) (Berardinelli-Seip congenital lipodystrophy) (Heathcote et al. 2002; Magré et al. 2003)
    1. Berardinelli-Seip congenital lipodystrophy 1 (BSCL1)
        1. Identification of the aberrant gene, 1-acylglycerol-3-phosphate *O*-acyltransferase 2 (*AGPAT*2), in patients from several pedigrees in which the lipodystrophy was linked to chromosome 9q34
        2. Several homozygous or compound heterozygous mutations in the *AGPAT*2 gene identified in affected patients
        3. *AGPAT*2 (1-acylglycerol-3-phosphate *O*-acyltransferase 2) (Agarwal et al. 2004)
            1. Encodes the enzyme AGPAT2 that is responsible for the production of an important intermediate in the synthesis of triglycerides or fat (Agarwal and Garg 2003)
            2. Mutations of *AGPAT*2: which may cause CGL by inhibiting the fat synthesis and storage in adipocytes (fat cells)
    2. Berardinelli-Seip congenital lipodystrophy 2 (BSCL2)
        1. Identification of another disease locus (*BSCL*2) which is mapped to chromosome 11q13 (Magré et al. 2001)
        2. Identification of mutations of *BSCL*2 gene in all families linked to 11q13
        3. *BSCL*2 (*Seipin*) gene

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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    1. Highly expressive in the brain and testis
    2. Encodes a protein whose function remains unknown
  3. Berardinelli-Seip congenital lipodystrophy X (BSCLX): specific genetic locus that has not been identified (Van Maldergem et al. 2002)
3. Causes of CGL (Garg 2011; Cortés and Fernández-Galilea 2015)
  1. CGL-1: caused by mutations in *AGPAT*2
  2. CGL-2: caused by mutations in *BSCL*2
  3. CGL-3: caused by mutations in *CAV*1, encoding Caveolin 1, which is the main protein component of plasma membrane caveolae and a fatty acid (FA)-binding protein relevant for FA uptake
  4. CGL-4: caused by mutations in *PTRF*, encoding RNA polymerase I and transcript release factor, which enables the dissociation of paused ternary polymerase I transcription complexes from the 3′ end of pre-rRNA transcripts
4. Several other genes that are responsible for different types of inherited lipodystrophies
  1. Lamin A/C (*LMNA*) gene in familial partial lipodystrophy Dunnigan variety (autosomal dominant familial partial lipodystrophy) mapped to 1q21-22
  2. *PPAR-γ* (peroxisome proliferator-activated receptor-γ) gene in autosomal dominant familial partial lipodystrophy
5. The genetic heterogeneity (Rajab et al. 2002) also accompanied by phenotypic heterogeneity (Agarwal et al. 2003; Simha and Garg 2003)
6. Proposed pathogenesis: genetic defect resulting in poor growth and development of metabolically active adipose tissue with preservation of mechanical disposition of the adipose tissue (Garg et al. 1999; Premkumar et al. 2002)

Clinical Features

1. Classification of primary lipodystrophies (Cortés and Fernández-Galilea 2015)
  1. Genetic lipodystrophy
    1. Generalized (Berardinelli-Seip syndrome)
      1. Severe generalized lipoatrophy
      2. Acanthosis nigricans
      3. Hyperphagia
      4. Hyperlipidemia
      5. Hyperinsulinemia
      6. Diabetes mellitus
      7. Hypoleptinemia
    2. Familial partial lipodystrophy
      1. Type 1 (Köbberling syndrome): deficiency of subcutaneous fat in limbs and gluteal regions
      2. Type 2 (Dunnigan syndrome): reduced AT in extremities; lipohypertrophy in trunk, neck, supraclavicular fossa, and face; diabetes mellitus; and hypertriglyceridemia
      3. Types 3, 4, and 5: diabetes mellitus and dyslipidemia
  2. Acquired lipodystrophy
    1. Generalized (Lawrence syndrome)
      1. General lack of adipose tissue
      2. Insulin resistance
      3. Diabetes mellitus
      4. Dyslipidemia
      5. Hepatic steatosis
    2. Partial (Barraquer-Simons syndrome)
      1. Asymmetrical loss of subcutaneous adipose tissue
      2. Mild metabolic disorders
2. BSCL1 (Garg 2000, 2004; Kobashi et al. 2007)
  1. Prevalent in African-Americans
  2. Less severe
  3. Usually comes to clinical attention in the second or third decade of life
  4. Demonstrates marked lack of metabolically active adipose tissue in subcutaneous tissues, muscles, bone marrow, and intra-abdominal and intrathoracic regions
  5. Normal intelligence
3. BSCL2
  1. Slightly more common than BSCL1 worldwide
  2. More severe
  3. Onset in the neonatal period or early

4. Demonstrates marked lack of metabolically active adipose tissue in subcutaneous tissues, muscles, bone marrow, and intra-abdominal and intrathoracic regions
5. In addition, characterized by a paucity of adipose tissue from anatomical areas in which it serves a mechanical function such as the palms, soles, orbits, scalp, and periarticular regions (Simha and Garg 2003)

4. BSCLX (Van Maldergem et al. 2002)
   1. A very rare type
   2. Tends to be severely affected
   3. Comes to clinical attention in early infancy
5. Extreme paucity (near complete absence) of adipose tissue from birth, resulting in a generalized muscular appearance (an essential diagnostic criterion)
6. Characteristic features during early childhood
   1. Accelerated linear growth
   2. Voracious appetite
   3. Increased basal metabolic rate (hypermetabolism)
   4. Advanced bone age
7. Acanthosis nigricans (dark velvety pigmentation of the skin)
   1. Common occurrence
   2. Usually appears by age 8
   3. May be widespread, involving the neck, axillae, groin, and trunk
   4. Can eventually cause skin tag formation
   5. Associated with diabetes (Reed et al. 1965)
8. Umbilical hernia: common
9. Hepatosplenomegaly
   1. Almost universal presence of hepatomegaly from fatty liver, ultimately leading to cirrhosis
   2. Splenomegaly common
10. Acromegaloid appearance
    1. Enlarged hands and feet
    2. Prominent mandible
11. Premature thelarche and adrenarche
12. Affected women (Garg et al. 1999)
    1. Virilization (clitoromegaly and hirsutism)
    2. Oligo-amenorrhea
    3. Polycystic ovaries (Huseman et al. 1979) in postpubertal female patients
    4. Successful pregnancy rare
13. Affected males with normal reproductive potential.
14. Multiple focal lytic lesions in the appendicular bones in postpubertal patients.
15. Severe fasting and postprandial hyperinsulinemia and marked hypertriglyceridemia resulting in chylomicronemia, eruptive xanthomas, acute pancreatitis, and predisposing to premature atherosclerosis
16. Abnormal glucose intolerance and diabetes mellitus that develop during puberty or early adolescence. Diabetic nephropathy and nephropathy that may develop during adulthood
17. Rare hypertrophic cardiomyopathy (Rheuban et al. 1986)
18. Mental retardation in a few patients
19. Clinical diagnosis criteria (Van Maldergem 2012): three major criteria or two major criteria plus two or more minor criteria that make a diagnosis of BSCL very likely
    1. Major criteria
       1. Lipoatrophy affecting the trunk, limbs, and face
          1. Generalized lipodystrophy: apparent at birth
          2. In some individuals, the face which may be normal at birth with lipoatrophy becoming apparent during the first months of life
          3. Lipoatrophy that gives an athletic appearance, especially because skeletal muscle hypertrophy is also present
       2. Acromegaloid features
          1. Gigantism
          2. Muscular hypertrophy
          3. Advanced bone age
          4. Prognathism
          5. Prominent orbital ridges
          6. Enlarged hands and feet
          7. Clitoromegaly
          8. Enlarged external genitalia in the male

3. Hepatomegaly
    1. Secondary to fatty liver early on
    2. Progresses to cirrhosis late in the disease course
4. Elevated serum concentration of triglycerides
    1. Serum concentration of triglycerides that can be elevated up to 80 g/L
    2. Sometimes associated with hypercholesterolemia
5. Insulin resistance
    1. Elevated serum concentrations of insulin and C-peptide that may occur starting in the first years of life
    2. Overt clinical diabetes mellitus that usually develops during the second decade
    3. Its early clinical expression that is acanthosis nigricans of the groin, neck, and axillae, which may have, in some cases, a verrucous appearance

2. Minor criteria
    1. Hypertrophic cardiomyopathy: may be present in infancy or develop later in life
    2. Psychomotor retardation: mild (IQ: 50–70) and moderate (IQ: 35–50)
        1. Mild-to-moderate intellectual impairment observed in approximately 80 % of individuals with mutations in *BSCL*2
        2. Intellectual impairment observed in only 10 % of individuals with mutations in *AGPAT*2
    3. Hirsutism
        1. Manifests with low frontal and posterior hairline
        2. Apparently independent of hormonal stimulation
    4. Precocious puberty in females: in a series of 75 individuals with BSCL, three females that underwent puberty before age 7 years (Van Maldergem et al. 2002)
    5. Bone cysts
        1. Occur in 8–20 % of affected individuals and have a polycystic appearance in X-rays
        2. Located in the epiphyseal and metaphyseal regions of the long bones: often diagnosed during the second decade
        3. Are mostly observed in individuals with mutations in *AGPAT*2
    6. Phlebomegaly: prominence of the veins of the lower and upper limbs observed, in part because of the lack of subcutaneous fat

20. Differential diagnosis with other genetic lipodystrophies (Agarwal and Garg 2006; Garg 2011)
    1. Other autosomal recessive lipodystrophies
        1. Lipodystrophy associated with mandibuloacral dysplasia: characterized by hypoplasia of the mandible and clavicles and by acro-osteolysis (resorption of terminal phalanges) and other features (Simha and Garg 2002)
            1. Partial lipodystrophy (type A pattern): *LMNA* (lamin A/C) mutations (Shackleton et al. 2000)
            2. Generalized lipodystrophy (type B pattern): *ZMPSTE*24 (zinc metalloproteinase) mutations
            3. Other varieties
        2. Lipodystrophy associated with SHORT (*s*hort stature, *h*yperextensibility of joints and/or inguinal hernia, *o*cular depression, *R*ieger anomaly, and teething delay) syndrome: characterized by defects in multiple organs and loss of adipose tissue
        3. Lipodystrophy associated with neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome) (Pivnick et al. 2000)
    2. Autosomal dominant lipodystrophies
        1. Familial partial lipodystrophy (FPL): characterized by variable symmetrical loss of body fat with or without disappearance of fat from the arms, chest, abdomen, and hips, but with retention

of distal adipose depots (Senior and Gellis 1964). The diagnosis made easily in women but difficult in men because even many normal men appear muscular. The diagnosis that can be suspected in nonobese patients with early onset of diabetes and hypertriglyceridemia, particularly if they have marked loss of fat from the extremities and hips
    1. Dunnigan variety (FPLD): LMNA (lamin A/C) mutations (Cao and Hegele 2000)
    2. FPL associated with *PPARG* (peroxisome proliferator-activated receptor-γ) mutations
    3. FPL associated with AKT2 (v-AKT murine thymoma oncogene homolog 2) mutations
    4. Other varieties
2. Lipodystrophy associated with SHORT syndrome
3. Lipodystrophy associated with Hutchinson-Gilford progeria syndrome
    1. Progressive and generalized loss of body fat during childhood resulting in severe lipodystrophy with increasing age
    2. Most patients having a de novo synonymous heterozygous Gly608Gly mutation in the *LMNA* gene of paternal origin (Eriksson et al. 2003; De Sandre-Giovannoli et al. 2003)
4. Puberty-onset generalized lipodystrophy due to *LMNA* mutations
    1. Puberty-onset of generalized lipodystrophy
    2. Diabetes
    3. Progeroid features
    4. Reported to have novel missense mutations in *LMNA* (Caux et al. 2003)

Diagnostic Investigations

1. Clinical laboratory workup
    1. Marked insulin resistance
    2. Severe hyperinsulinemia
    3. Nonketotic insulin-resistant diabetes mellitus
    4. Hypertriglyceridemia with low serum high-density lipoprotein (HDL) and cholesterol concentration
    5. Chylomicronemia
    6. Markedly low plasma leptin levels
2. Skeletal imaging (Fleckenstein et al. 1992; Westvik 1996)
    1. Radiographs
        1. Show numerous focal lesions within the long bones
        2. Advanced skeletal age
        3. A sclerotic skeleton: a major feature in childhood, later turning into osteolytic lesions or more distinct sclerotic patches in adolescence or early adulthood
    2. MRI
        1. Abnormal entire marrow space of the long bones
        2. Characterized, at least in part, by the absence of marrow fat
        3. Prolonged T1 and T2 times and marked gadolinium enhancement: observed in radiographically normal-appearing long one
        4. Radiographically lytic lesions: occasionally demonstrated fluid-fluid levels on MRI and enhanced peripherally after gadolinium infusion
    3. Appendicular skeleton of patients with CGL that is diffusely abnormal and predisposed to focal osteolysis and cyst formation
3. Ultrasonography and computerized tomography (Westvik 1996)
    1. Hepatosplenomegaly with fatty infiltration
    2. Lack of subcutaneous and intra-abdominal fat: easily confirmed with computerized tomography
    3. Pneumoencephalography: dilated brain ventricles and basal cisterns
4. MRI (confirmatory) and necropsy (Garg 1992; Garg et al. 1999)

1. An extreme paucity of subcutaneous and intermuscular fat
    1. Intra-abdominal sites (omental, mesenteric, and retroperitoneal areas)
    2. Thoracic cavity (retrosternal, epicardial, and superior mediastinal areas)
    3. Bone marrow
    4. Parathyroid glands
2. In contrast, a peculiar distribution of normal amounts of adipose tissue over whole body
    1. Orbits
    2. Crista galli
    3. Palms
    4. Soles
    5. Scalp
    6. Perineum
    7. Vulva
    8. Epidural area
    9. Pericalyceal regions of the kidney
    10. Periarticular regions (knee, hip, shoulder, elbow, wrist, and ankle joints)
    11. Some fat localizing in breasts, tongue, and buccal region
5. Skeletal radiography: multiple focal lytic lesions appearing in appendicular skeletons after puberty
6. Echocardiography to detect hypertrophic cardiomyopathy
7. Light and electron microscopy (Afifi et al. 1976)
    1. Variation in fiber size
    2. Ringbenden (circular myofibrils wrapped around the longitudinal myofibrils)
    3. Various degrees of fiber degeneration and fragmentation
    4. Accumulation of glycogen and aggregation of mitochondria
    5. Streaming of Z line
    6. Myofilamentous inclusions and dilatation of sarcoplasmic reticulum profiles
8. Molecular genetic analysis of mutations in *BSCL2* (*Seipin*) gene and *AGPAT2* gene
9. Exome sequencing: as a powerful diagnostic tool in Mendelian disorders that may complement missing clinical information and accelerate clinical diagnosis, such as CGL (Schuster et al. 2014)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25 %
    2. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis (Van Maldergem 2012)
    1. Possible for pregnancy at risk for BSCL caused by *BSCL2* of *AGPAT2* mutations by analysis of fetal cell DNA obtained from amniocentesis or CVS, provided both disease-causing alleles of an affected family member must be identified previously
    2. Preimplantation genetic diagnosis (PGD) that may be available for families in which the disease-causing mutations have been identified
3. Management (Agarwal and Garg 2006; Patni and Garg 2015)
    1. Cosmetic management
        1. Facial reconstruction with free flaps, transposition of facial muscle, and silicone or other implants in the cheeks
        2. Liposuction or lipectomy for removal of excessive facial or neck fat
        3. Etretinate and fish oil that may improve acanthosis in some patients
    2. Diet
        1. Avoidance of weight gain to reduce the risk of developing diabetes and dyslipidemia
        2. Need sufficient energy to allow for growth and maturation in childhood
        3. Low-fat diet for extreme hypertriglyceridemia to minimize chylomicron formation
        4. Reduction in saturated fat and cholesterol intake to reduce LDL or non-HDL cholesterol levels that reduces atherosclerosis risk
    3. Hypoglycemic drugs
        1. Require rigorous glycemic control by oral hypoglycemic drugs and/or insulin therapy
        2. Require large dose of insulin to control hyperglycemia and prevent long-term

complications of diabetes, such as nephropathy, retinopathy, neuropathy, and possibly atherosclerosis

4. Lipid-lowering drugs
    1. Fibrates and, if needed, n-3 polyunsaturated fatty acids
    2. Avoid estrogens for oral contraception or postmenopausal hormone replacement therapy in women because it can accentuate hypertriglyceridemia
5. Adipocytes hormone leptin-replacement therapy that has shown a marked reduction in the blood glucose and lipids and reverse hepatic steatosis, allowing discontinuation of several medications (Oral et al. 2002; Petersen et al. 2002; Savage and O'Rahilly 2002; Cortés and Fernández-Galilea 2015)
6. Elucidation of the pathways underlying genetic lipodystrophies expected to help in developing innovative therapeutic strategies for treating diabetes, hyperlipidemia, hepatic steatosis, and other metabolic complications

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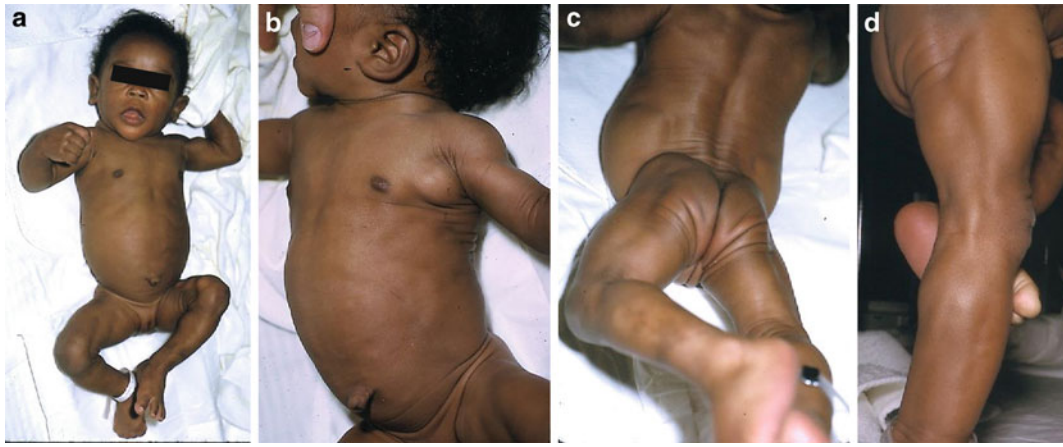

Fig. 1 (**a**–**d**) An infant with congenital generalized lipodystrophy showing extreme paucity (near complete absence) of adipose tissue from birth, resulting in a generalized prominent muscular appearance

Congenital Hemihyperplasia

Contents

In 1822, Meckel (1822) first described congenital hemihypertrophy. Hemihypertrophy, also called hemihyperplasia, is defined as asymmetric body overgrowth of one or more body parts. The overgrowth may involve an entire half of the body, a single limb, and one side of the face or combinations thereof. There may be accompanying asymmetric visceromegaly. Hemihyperplasia can be isolated or can occur as part of a syndrome. It is frequently not possible to determine if the enlargement is due to an increase in the size of cells (hypertrophy) or to an increase in the number of cells of normal size (hyperplasia) (Ballock et al. 1997).

Synonyms and Related Disorders

Beckwith-Wiedemann syndrome; Congenital hemihypertrophy; Congenital infiltrating lipomatosis of the face; Isolated hemihyperplasia/hemihypertrophy; Klippel-Trenaunay-Weber syndrome; McCune-Albright syndrome; Neurofibromatosis I; Overgrowth syndromes; Proteus syndrome; Russell-Silver syndrome

Genetics/Basic Defects

1. The asymmetric overgrowth, traditionally termed "hemihypertrophy," is more accurately referred to as hemihyperplasia, since the pathologic growth process involves an abnormal proliferation of cells (hemihyperplasia), rather than an increase in the size of existing cells (hemihypertrophy).
2. Isolated hemihyperplasia (IHH)
    1. Usually isolated: estimated prevalence as 1 in 13,200 to 1 in 86,000 live births
    2. Familial occurrence (Burchfield and Escobar 1980; Stoll et al. 1993; Heilstedt and Bacino 2004)
    3. *LIT1* and *H19* methylation defects in isolated hemihyperplasia (29.6%) (Martin et al. 2005)
3. Part of well-defined syndrome
    1. Beckwith-Wiedemann syndrome
    2. Proteus syndrome
    3. Russell-Silver syndrome
    4. Neurofibromatosis type I (NF I)

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5. Klippel-Trénaunay-Weber syndrome
6. McCune-Albright syndrome

Clinical Features

1. Clinical characteristics of isolated hemihyperplasia
    1. Birth incidence: 1:86,000 live births
    2. Females outnumber males two to one.
    3. Increased birth weight (mean 3.8 kg).
    4. Diagnosis by exclusion.
    5. Variable degree of asymmetry (mild cases are easily overlooked).
    6. Asymmetry becoming more pronounced or less noticeable with age with predominance of right-sided overgrowth.
    7. Involves a discrepancy in both length and circumference of the affected limb in comparison to the contralateral side.
    8. Observation of the enlargement of one kidney, adrenal, testis, or ovary with medullary sponge kidney, often an attendant finding.
    9. Nervous system accompaniments include unilateral peripheral nerve enlargement, sciatica, and hemimegalencephaly with frequent mental retardation.
    10. Facial involvement may be present (cheek, lip, nasal, external ear, palpebral fissure, tongue, maxillary, mandibular, palatal, and/or tooth asymmetry).
    11. Natural history of IHH varies markedly.
        1. Average life span.
        2. Prognoses for long-term survival may be modified by serious associated anomalies.
        3. Leg length discrepancy may lead to pelvic tilt and scoliosis.
        4. Renal function may be impaired by medullary sponge kidney.
    12. Predisposition to neoplasia (cancer) in isolated hemihyperplasia (Furukawa and Shinohara 1981; Geormaneanu et al. 1983; Viljoen et al. 1984; Clericuzio and Martin 2009; Craiglow et al. 2014) well known
        1. An overall incidence of intra-abdominal embryonal malignancies (5.9%)
        2. Embryonal neoplasms: similar to those noted in other overgrowth disorders
            1. Wilms tumor: hemihypertrophy occurs in approximately 3% of Wilms tumor cases.
            2. Adrenal cell carcinomas.
            3. Hepatoblastoma.
            4. Leiomyosarcoma.
2. Three types of hemihyperplasia/hemihypertrophy (Lee et al. 2013)
    1. Total: involves an entire half of the body
    2. Regional: involves an anatomical territory such as a limb
    3. Crossed: if opposite parts of the body are overgrown (e.g., left arm and right leg)
3. Malformation syndromes associated with hemihyperplasia (Hoyme et al. 1998; Cohen 1989)
    1. Beckwith-Wiedemann syndrome
        1. Omphalocele
        2. Hypoglycemia
        3. Generalized overgrowth
        4. Macroglossia
        5. Visceromegaly
        6. Earlobe pits and creases
        7. Predisposition to neoplasia
        8. Inheritance: heterogeneous (autosomal dominant, autosomal recessive, dup 11)
    2. Neurofibromatosis
        1. Café au lait spots
        2. Hypopigmented patches
        3. Axillary freckling
        4. Neurofibromas
        5. Iris Lisch nodules
        6. Macrocephaly
        7. Scoliosis
        8. Hypertension

9. CNS tumors
10. Inheritance (autosomal dominant)

3. Klippel-Trénaunay-Weber syndrome:
    1. Hemangiomata
    2. Lymphatic anomalies
    3. Poly-/syndactyly
    4. Oligodactyly
    5. Macrocephaly
    6. Glaucoma
    7. Cataracts
    8. Inheritance (unknown, sporadic)
4. Proteus syndrome
    1. Lipomata
    2. Hemangiomata
    3. Macrocephaly
    4. Scoliosis
    5. Macrodactyly
    6. Gyriform changes on soles of feet
    7. Inheritance (unknown, sporadic)
5. McCune-Albright syndrome
    1. Fibrous dysplasia of bones
    2. Irregular hyperpigmentation
    3. Precocious puberty
    4. Hyperthyroidism
    5. Hyperparathyroidism
    6. Other endocrinopathies
    7. Inheritance (unknown, sporadic, female predominance)
6. Epidermal nevus
    1. Epidermal nevi
    2. Pigmentary changes
    3. Mental deficiency
    4. Seizures
    5. CNS malformations
    6. Kyphoscoliosis
    7. Potential for malignancy
    8. Inheritance (heterogenous, usually sporadic but autosomal dominant and recessive inheritance described)
7. Triploid/diploid mixoploidy
    1. Large placenta with hydatidiform changes
    2. Incomplete calvarial ossification
    3. Microretrognathia
    4. Microphthalmia
    5. Colobomata
    6. Cataracts
    7. Irregular skin pigmentation
    8. Syndactyly
    9. Chromosomal diploid/triploid mosaicism (may be found only in fibroblasts)
8. Langer-Giedion syndrome
    1. Multiple exostoses
    2. Unusual facies with bulbous nose
    3. Long simple philtrum
    4. Microcephaly
    5. Loose skin in infancy
    6. Sparse scalp hair
    7. Deafness
    8. Inheritance (heterogenous, chromosome anomaly del(8)(q23q24), autosomal dominant)
9. Multiple exostoses
    1. Juxtaepiphyseal exostoses
    2. Forearm bowing
    3. Short stature
    4. Malignant transformation (sarcoma) in adulthood
    5. Inheritance (autosomal dominant)
10. Maffucci syndrome
    1. Enchondromata
    2. Hemangiomata (especially phlebectasia)
    3. Bowing of long bones
    4. Chondrosarcoma
    5. Inheritance (unknown, sporadic)
11. Osteochondromatosis (Ollier disease)
    1. Bilateral, asymmetric enchondromata
    2. Fractures
    3. Chondrosarcoma
    4. Inheritance (unknown, sporadic)
12. Trisomy 18 mosaicism
13. Translocation 7p;13q
14. Constitutional uniparental disomy (UPD) for chromosome 11p15
    1. Not common in patients with idiopathic hemihyperplasia (Bliek et al. 2008)
    2. Can result from various genomic changes including molecular

alterations of 11p15 (paternal UPD) and alterations of methylation at two imprinting centers at 11p15: IC1 (H19) and IC2 (*KCNQ1OT1*) (Shuman et al. 2006)

15. Hemihyperplasia/multiple lipomatosis syndrome (Boybeyi et al. 2010; Craiglow et al. 2014)
    1. Asymmetric nonprogressive overgrowth
    2. Multiple lipomas
    3. Superficial vascular malformations
16. *PIK3CA*-related overgrowth spectrum with overlapping clinical features (Keppler-Noreuil et al. 2015)
    1. Hemihyperplasia
    2. Overgrowth
    3. Vascular anomalies
    4. Skin abnormalities
    5. Tumors
    6. Scoliosis
    7. Others

4. Extent of involvement
    1. Range from enlargement of a single digit to an entire half of the body
    2. Segmental, unilateral, or crossed (affecting different anatomic areas on either side of the body)
    3. System involvement
        1. A single system
            1. Muscular
            2. Vascular
            3. Skeletal
            4. Nervous
        2. Combination of all systems
    4. Total hemihypertrophy
        1. Right side more affected than the left.
        2. Males appear to be affected more frequently.
    5. Associated anomalies found in about 50% of affected individuals
    6. Onset and course of asymmetry
        1. Almost always evident at birth
        2. May be accentuated at puberty
        3. Appears to be constant once developed
5. Facial involvement
    1. Involvement of the face only
    2. Unilateral facial enlargement accompanied by enlargement of the complete half of the body
    3. Variable degree of involvement
6. Skin and skin appendages
    1. Involved side
        1. Thicker with increased function of the sebaceous and sweat glands
        2. Pigmentation as well as early development of varicose veins or a medusa-like plexus of veins in the lower abdomen and groin area
        3. Supernumerary nipples as well as an enlarged breast
        4. Thicker and coarser hair
        5. Abnormal nail growth
    2. Either involved or contralateral side: telangiectasia and increased numbers of nevi
7. Skeletal system
    1. Unilaterally enlarged bones
    2. Other lesions
        1. Macrodactyly
        2. Polydactyly
        3. Syndactyly
        4. Lobster claw deformity
        5. Scoliosis
        6. Tilting of the pelvis
        7. Clubfoot
8. Central nervous system
    1. Mental retardation in 15–20% of affected individuals
    2. Sciatica probably resulting from pelvic tilt
    3. Dilatation of the anterior basal cisterna
    4. Dilatation of the pupil on the affected side
9. Genitourinary system
    1. The kidney and adrenal: most frequently enlarged on the involved side
    2. Other anomalies
        1. Hypospadias
        2. Cryptorchidism
        3. Elevated level of urinary gonadotropin and short stature
        4. Adrenogenital syndrome
        5. Embryonal tumors

6. Wilms tumor
7. Adrenal cortical carcinoma

10. Enlarged oral lesions on the involved side
    1. Enlarged and thickened tongue
    2. Oral soft and hard tissues such as lips, uvula, maxilla, mandible, tongue, alveolar process, and some teeth

Diagnostic Investigations

1. Serum alpha-fetoprotein measurement every 3 months until 4 years (Clericuzio and Martin 2009)
2. Radiographic studies of hemihypertrophy
3. Abdominal ultrasound for visceromegaly (tumor) (Ballock et al. 1997)
4. Brain MRI for hemihyperplasia
5. Chromosome analysis, UPD analysis, or gene mutation studies depending on the types of the malformation syndromes

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Isolated case: a low recurrence risk.
        2. Familial case: recurrence risk depends on mode of transmission:
            1. Autosomal dominant: a low recurrence risk if parents are normal
            2. Autosomal recessive: a 25% risk
            3. Imprinting mechanism such as in Beckwith-Wiedemann syndrome
    2. Patient's offspring
        1. Isolated case: a low recurrence risk.
        2. Autosomal dominant: a 50% risk.
        3. Autosomal recessive: recurrence risk does not increase unless the spouse is a carrier or affected.
2. Prenatal diagnosis
    1. Prenatal ultrasound/radiography for fetal hemihyperplasia
    2. Chromosome analysis from amniocentesis or CVS for triploidy or mixoploidy
3. Management
    1. Screening abdominal ultrasounds every 3–6 months to monitor Wilms tumor development in patients with idiopathic hemihypertrophy
    2. Orthopedic management for hemihypertrophy
    3. Management for neoplasm

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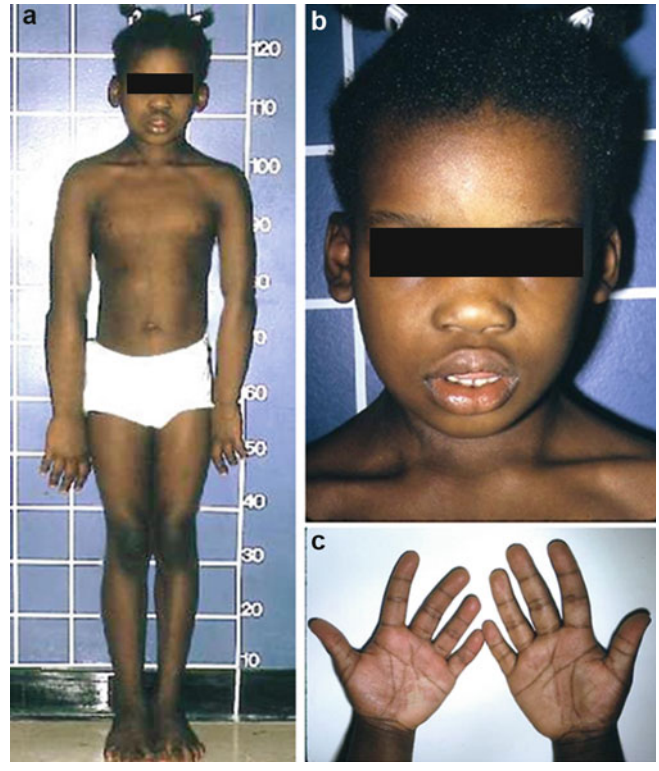

Fig. 1 (**a**–**c**) A girl with hemihypertrophy of the *right side* of the body

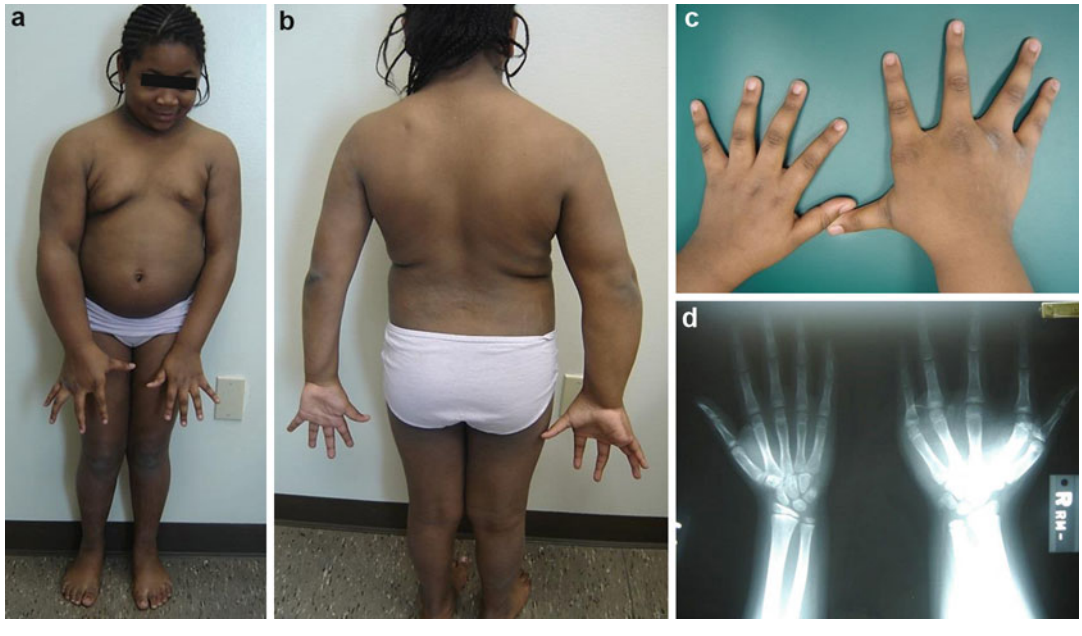

Fig. 2 (**a**–**d**) A 7-year-old girl with hemihypertrophy of the *right upper* extremity. The radiograph of the forearms and hands showed osseous and soft tissue hypertrophy. She is otherwise normal

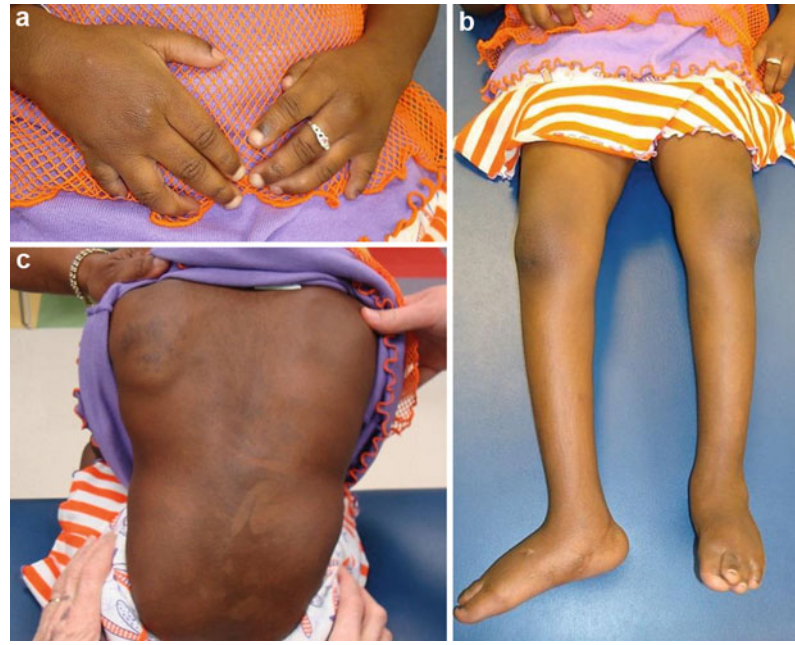

Fig. 3 (**a**–**c**) A 6-year-old girl with hemihypertrophy of the *right upper* and *lower* extremities. She also had talipes equinovarus (corrected) and abnormal pigmentation on the back

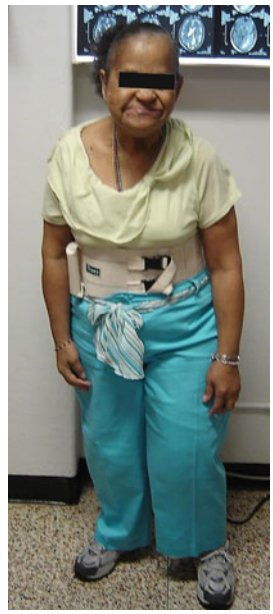

Fig. 4 A 60-year-old female was evaluated for mental retardation associated with *left* hemihypertrophy

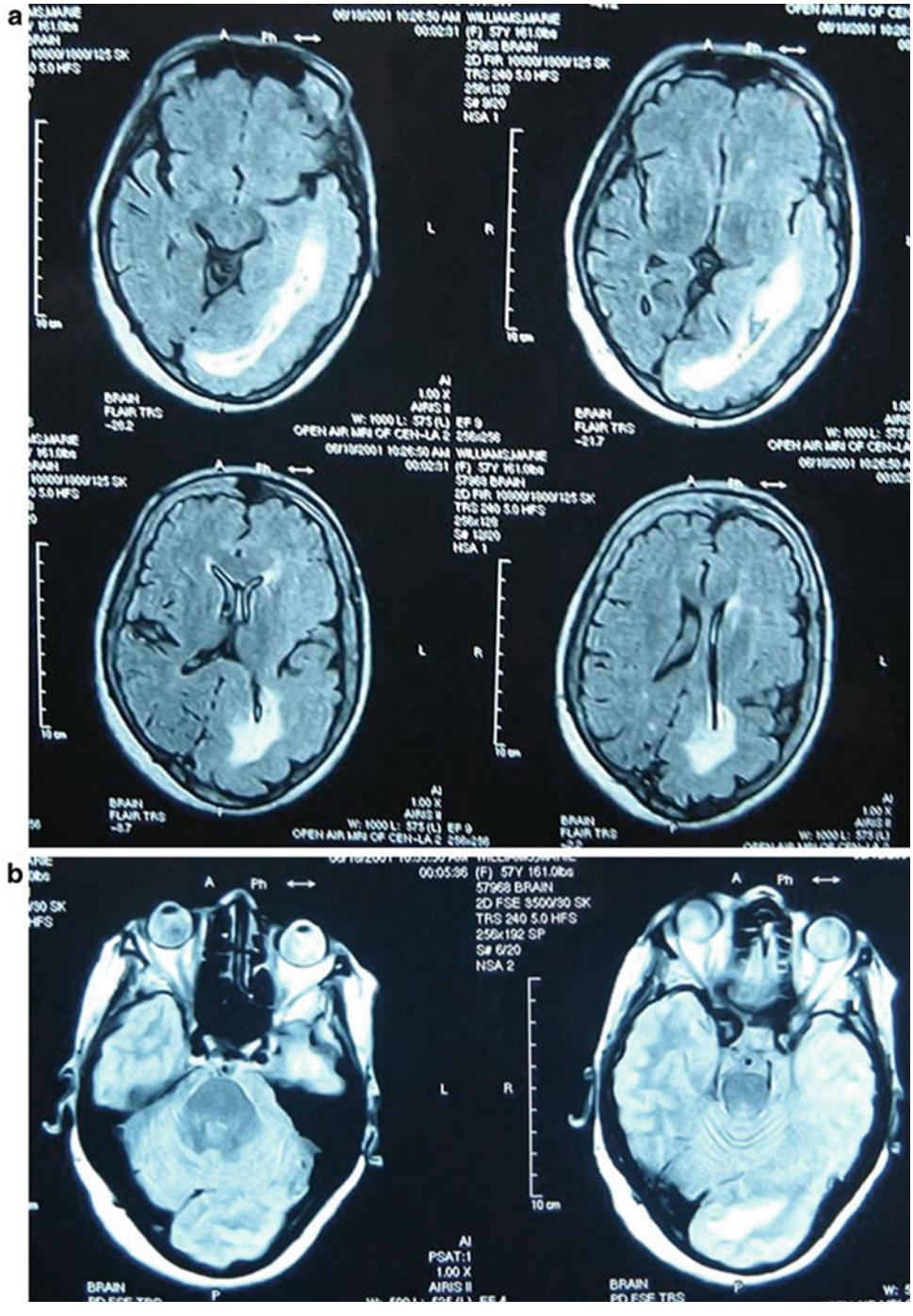

Fig. 5 (**a**, **b**) The patient's MRI of the brain showed cerebral asymmetry with *left* temporal, occipital, and parietal lobe hypertrophy associated with areas of macrogyria and lissencephaly, consistent with a congenital neuronal migration abnormality

Congenital Hydrocephalus

Contents

Congenital hydrocephalus is one of the most common CNS congenital anomalies. The incidence of congenital hydrocephalus is estimated as 3 per 1,000 live births. Hydrocephalus is defined as an increase in the cerebral spinal fluid (CSF) volume within the ventricular system independent of the actual head circumference.

Synonyms and Related Disorders

Infantile hydrocephalus; Neonatal hydrocephalus; Non-syndromic autosomal recessive hydrocephalus; Pediatric hydrocephalus; X-linked hydrocephalus with aqueduct stenosis

Genetics/Basic Defects

1. Physiology of CSF production and absorption
    1. Production of CSF: by the choroid plexus of lateral ventricles
    2. Pathway of CSF flow
        1. From lateral ventricles to the third ventricle through the foramen of Monro
        2. From the third ventricle to the fourth ventricle through the aqueduct of Sylvius
        3. Out of the ventricular system: from the fourth ventricle to spinal subarachnoid spaces through the foramen of Magendie or to the basal cisterns through two lateral foramina of Luschka
    3. Site of CSF resorption into the venous system: primarily through the superior sagittal sinus via arachnoid granulations
2. Pathophysiologic consequences of hydrocephalus (Del Bigio 2001b)
    1. Hydrocephalus-induced damage is dependent on:
        1. The rate and magnitude of ventricular dilatation
        2. The proximity to the ventricle
        3. The developmental stage at which the disturbance occurs
    2. Developmental processes, including myelin production, can be impaired.
    3. The potential for reversal of damage by shunting diminishes as the duration and severity of hydrocephalus increase.
3. Types and causes of hydrocephalus (Aronyk 1993)
    1. Overproduction of CSF: usually caused by choroid plexus tumors (very rare)
    2. Noncommunicating hydrocephalus

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1. Mechanical obstruction within the ventricular system causing impaired CSF absorption
    1. Foramen of Monro
    2. Aqueduct of Sylvius
    3. The fourth ventricle and its outlet channels
2. Causes
    1. Tumors
    2. Cysts
    3. Inflammatory scarring
    4. Intraventricular hemorrhage
    5. Rarely genetic disorders

3. Communicating hydrocephalus:
    1. Obstruction distally at the arachnoid granulations causing impaired absorption into bloodstream
    2. Causes
        1. Meningitis
        2. Trauma
        3. Intraventricular hemorrhage

4. Causes of pediatric hydrocephalus (Kahle et al. 2015)
    1. Acquired hydrocephalus
        1. Inflammatory
            1. Subarachnoid hemorrhage or infection: arachnoid scar (dysfunctional subarachnoid space)
            2. Intraventricular hemorrhage or infection: ependymal scar (ventricular obstruction)
        2. Neoplasm
            1. Parenchymal brain tumor: mass effect (ventricular obstruction)
            2. Spinal cord tumor: altered CSF composition (dysfunctional subarachnoid space)
            3. Disseminated tumor: tumors with meningeal infiltration – e.g., primitive neuroectodermal tumor (dysfunctional subarachnoid space)
            4. Choroid plexus tumor: altered CSF composition (dysfunctional subarachnoid space)
            5. Choroid plexus tumor: mass effect (ventricular obstruction)
            6. Choroid plexus tumor or hyperplasia: altered choroid plexus function (CSF overproduction – or hyperdynamic intraventricular pulsations)
        3. Vascular
            1. Vascular malformation: ventricular obstruction, e.g., vein of Galen malformation; venous hypertension, e.g., arteriovenous malformation (ventricular obstruction, decreased venous compliance – or decreased CSF absorption)
            2. Disordered cerebral venous function: extrinsic venous obstruction, e.g., skeletal dysplasias; intrinsic venous obstruction, e.g., venous sinus thrombosis; and idiopathic venous dysfunction, e.g., congenital idiopathic hydrocephalus (decreased venous compliance – or decreased CSF absorption)
    2. Congenital or developmental hydrocephalus
        1. Congenital aqueduct stenosis: third ventricle outlet obstruction (ventricular obstruction)
        2. Neural tube defects – e.g., myelomeningocele and Chiari II malformation: third or fourth ventricle outlet obstruction; altered venous compliance; arachnoid or ependymal scar (variable)
        3. Posterior fossa malformations: fourth ventricle outlet obstruction – e.g., Dandy-Walker complex; Chiari I malformation (ventricular obstruction)
        4. Developmental cysts: mass effect (ventricular obstruction)
        5. Congenital foramen of Monro atresia: lateral ventricle outlet obstruction (ventricular obstruction)

5. Etiology of congenital hydrocephalus (Schrander-Stumpel and Fryns 1998; Pattisapu 2001)
    1. Tumors blocking CSF pathway
        1. Benign tumors such as choroid plexus papilloma (Rickert and Paulus 2001)
        2. Malignant tumors
    2. CNS malformations/syndromes
        1. Congenital atresia of the foramina of Monro, Magendie, or Luschka

2. Dandy-Walker syndrome
    1. Atresia of the foramina of the fourth ventricle
    2. Dilation of the fourth ventricle
    3. Extreme dolichocephaly
    4. Sac formation at the caudal end of the cerebellum filling the posterior cranial fossa
3. Aqueductal stenosis
4. X-linked hydrocephalus, Bickers-Adams syndrome characterized by
    1. Stenosis of the aqueduct of Sylvius
    2. Severe mental retardation
    3. An adduction-flexion deformity of the thumb
5. Chiari II malformation
6. Cerebellar agenesis
7. Neural tube defects
    1. Meningomyelocele
    2. Encephalocele
8. Other Mendelian conditions with congenital hydrocephalus
    1. Walker-Warburg syndrome
    2. Hydrolethalus syndrome
    3. Meckel syndrome
    4. Smith-Lemli-Opitz syndrome

3. Chromosome abnormalities
    1. Trisomy 13
    2. Trisomy 18
    3. Trisomy 9 and 9p (mosaic)
    4. Triploidy
    5. Other aneuploidies
4. Skeletal dysplasias
    1. Achondroplasia
    2. Craniosynostosis syndromes such as Crouzon syndrome or Apert syndrome
    3. Fanconi anemia
    4. Hurler and Hunter syndromes
5. Infections
    1. Congenital CMV infection
    2. Congenital toxoplasmosis
    3. Congenital rubella infections
    4. Congenital syphilis
    5. Meningitis
    6. Ventriculitis
    7. Abscess
6. Vascular malformation
7. In utero intraventricular hemorrhage
8. Birth trauma
9. Destructive lesions
    1. Hydranencephaly
    2. Porencephaly
    3. Perinatal leukomalacia

6. Genetic abnormalities associated with pediatric hydrocephalus (Kahle et al. 2015)
    1. X-linked hydrocephalus with aqueduct stenosis (Online Mendelian Inheritance in Man (OMIM) identifier 307000): *L1CAM*
    2. Non-syndromic autosomal recessive hydrocephalus (HYC, OMIM 236600 [HYC1], OMIM 615219 [HYC2]): *CCDC88C* and *MPDZ*
    3. Fried-type syndromic mental retardation (OMIM 304340): *AP1S2*
    4. Walker-Warburg syndrome (multiple subtypes): *POMT1*, *POMT2*, *POMGNT1*, and others
    5. Neural tube defects (folate-sensitive [OMIM 601634] and folate-insensitive [OMIM 182940] forms)
        1. Multiple susceptibility genes involved in planar-cell polarity – e.g., *FUZ*, *VANGL1/2*, *CCL2*, and others
        2. Folate-sensitive neural tube defects associated with genes in folate synthesis pathway (*MTR*, *MTRR*, *MTHFR*, *MTHFD*)
    6. Primary ciliary dyskinesia and other ciliopathies (including the many heterogeneous subtypes of Meckel-Gruber syndrome and Joubert syndrome): multiple genes involved in cilia structure, function, and regulation – e.g., *CC2D2A*, *TMEM67*, *MKS1*, and others
    7. RAS-opathies – e.g., neurofibromatosis type 1, Noonan's syndrome, Costello's syndrome, and cardio-facio-cutaneous syndrome
        1. NF1
        2. Ras-Raf-MEK-ERK pathway genes – e.g., *KRAS*, *BRAF*, *PTPN11*, and others
    8. VACTERL-H (association of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies plus hydrocephalus) (OMIM 276950): *PTEN*
    9. X-linked VACTERL-H (OMIM 300515): *FANCB*

7. Familial (X-linked) aqueductal stenosis (HSAS, hydrocephalus-stenosis of the aqueduct of Sylvius sequence)
    1. X-linked recessive inheritance.
    2. Linked to chromosome Xq28.
    3. Mutations in *L1-CAM* (Weller and Gärtner 2001; Sztriha et al. 2002), the major gene for X-linked hydrocephalus (accounting for 7–27% of all male cases).
    4. *L1-CAM*, a neuronal surface glycoprotein, has been implicated in neuronal migration and axon fasciculation.
8. Traits known to be due to allelic mutations of *L1-CAM*
    1. HSAS
    2. MASA (Jouet et al. 1994)
        1. *M*ental retardation
        2. *A*phasia
        3. *S*huffling gait
        4. *A*dducted thumbs
    3. SP1 (complicated spastic paraparesis, type 1)
    4. MR-CT (mental retardation-clasped thumbs)
    5. ACC-DCC (agenesis or dysgenesis of the corpus callosum)
9. Pathogenesis of hydrocephalus-induced brain dysfunction, complex
    1. Chronic ischemia in white matter related to changes in intracranial pressure and in the vasculature
    2. Physical damage to periventricular axons with disconnection of neurons
    3. Alterations in the extracellular chemical environment of neurons

Clinical Features

1. Children <2 years
    1. Relatively benign course because infants can expand their cranium
    2. Early signs
        1. Increased head circumference (macrocephaly)
        2. Full anterior fontanelle
        3. Split cranial sutures
        4. Prominent scalp veins
        5. Poor feeding
        6. Vomiting
        7. Irritability
        8. Reduced activity
        9. Delay or loss of developmental milestones
        10. Hypertonia
        11. Hyperreflexia
    3. Late signs
        1. Lethargy
        2. Sixth cranial nerve palsy
        3. Limitation of upgaze resulting in a chronic downward deviation of the eyes (sunsetting sign)
2. Children >2 years
    1. Symptoms and signs more related to increased intracranial pressure due to inability of the cranium to expand sufficiently to offset the mounting volume of CSF
    2. Headaches
    3. Nausea
    4. Vomiting
    5. Lethargy
    6. Loss of milestones
    7. School performance and behavioral change
    8. Sunsetting of the eyes
    9. Sixth cranial nerve palsy
    10. Papilledema
3. Natural history of untreated childhood hydrocephalus: poor.
4. Handicaps resulting directly from hydrocephalus include the following (Vinchon et al. 2012)
    1. Impaired mobility and ambulation (e.g., cerebral palsy)
    2. Impaired cognition (mental delay, behavior)
    3. Sensory deficits (vision, hearing)
    4. Endocrine dysfunction (growth, puberty, weight balance, fertility)
    5. Epilepsy
    6. Depression
    7. Pain (chronic headache)
5. Most common clinical features of progressive hydrocephalus in the non-shunted group (Kirpatrick et al. 1989)
    1. Symptoms
        1. Asymptomatic (49%)
        2. Headache or irritability (33%)
        3. Vomiting (16%)

2. Signs
    1. Inappropriately increasing occipitofrontal circumference (76%)
    2. Tense anterior fontanelle (65%)
    3. Splayed sutures (39%)
    4. Scalp vein distension (33%)
    5. Sunsetting or loss of upward gaze (22%)
    6. Neck retraction or rigidity (14%)
6. Most common clinical features of progressive hydrocephalus in the shunted group (Kirpatrick et al. 1989)
    1. Symptoms
        1. Vomiting (48%)
        2. Drowsiness or lethargy (46%)
        3. Headache (46%)
        4. Behavioral change (including irritability) (38%)
        5. Anorexia (18%)
    2. Signs
        1. No clinical signs (25%)
        2. Decreased conscious level (18%)
        3. Acute strabismus (18%)
        4. Neck retraction (11%)
        5. Distended retinal veins (11%)
7. X-linked neurological syndromes
    1. HSAS (*h*ydrocephalus-*s*tenosis of the *a*queduct of *S*ylvius sequence)
        1. Hydrocephalus
        2. Macrocephaly
        3. Adducted thumbs
        4. Spasticity
        5. Agenesis of the corpus callosum
        6. Mental retardation
    2. MASA syndrome
        1. *M*ental retardation
        2. *A*phasia
        3. *S*huffling gait
        4. *A*dducted thumbs
        5. Hydrocephalus

Diagnostic Investigations

1. Fundoscopic examination
    1. Bilateral papilledema secondary to high intracranial pressure
    2. Normal finding in some cases of acute hydrocephalus
2. Lumbar puncture for measuring intracranial pressure
    1. Avoid if an increase in intracranial pressure is suspected due to obstruction since relief of pressure may cause herniation of the brainstem.
    2. Perform only after imaging studies rule out an obstruction.
3. TORCH titers on the infant and mother if intrauterine infection is suspected.
4. Chromosome analysis in cases of associated multiple congenital anomalies.
5. Cranial sonography (provided anterior fontanelle is still open)
    1. Ventriculomegaly
    2. Intraventricular hemorrhage
6. CT scans (Barkovich and Edwards 1992)
    1. Ventriculomegaly
    2. Cerebral edema
    3. Mass lesions
        1. Colloid cyst of the third ventricle
        2. Thalamic tumor
        3. Pontine tumor
7. MRI (Barkovich and Edwards 1992; Bradley 2001)
    1. Ventriculomegaly.
    2. Mass lesions.
    3. Associated brain anomalies
        1. Agenesis of the corpus callosum
        2. Chiari malformations
        3. Disorders of neuronal migration
        4. Vascular malformations
    4. More sensitive than CT
        1. For detecting interstitial edema (transependymal flow of cerebrospinal fluid [CSF])
        2. For detecting hyperdynamic CSF flow seen with shunt-responsive normal-pressure hydrocephalus (NPH)
        3. The presence of deep white matter ischemia that may contribute to the cause of the idiopathic form of NPH
    5. Phase-contrast MRI (PC-MRI) and/or 3D-Space methods (Kartal and Algin 2014)
        1. Relatively simple for evaluating true CSF flow and determining the obstruction level.

2. Provide additional physiological information.
3. Three-dimensional sampling perfection with application-optimized contrasts using different flip angle evolution (3D-SPACE) technique seems to be the most efficient and rapid for evaluating hydrocephalus, ETV and the shunt catheter.

6. PC-MRI, 3D-heavily-T2W, and/or contrast material-enhanced MR cisternography (CE-MRC) images may prevent false-negative or false-positive results (Kartal and Algin 2014).

8. Molecular genetic diagnosis to identify *L1CAM* mutations, identified in 22.4% (15/67) of sporadic cases of clinically or prenatally suspected L1 disease (Senat et al. 2001).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Sporadic: low (4%)
      2. Multifactorial trait (e.g., neural tube defect or in female infants with congenital hydrocephalus due to stenosis of the aqueduct of Sylvius): low recurrence risk (4%) for subsequent sibling (Váradi et al. 1988), 10% risk if there are two affected siblings
      3. Autosomal recessive traits (e.g., Dandy-Walker syndrome): 25% affected, 50% carriers, and 25% normal
      4. X-linked hydrocephalus: 50% of brothers are affected and 50% of sisters are carriers if the mother is a carrier, negligible in males with "sporadic" hydrocephalus representing a new X-linked mutation
   2. Patient's offspring
      1. Sporadic: low (4%).
      2. Multifactorial trait: 3–4.5% recurrence risk.
      3. Autosomal recessive traits: not increased unless the spouse is a carrier or affected.
      4. X-linked hydrocephalus: all daughters will be carriers in case of an affected father.
2. Prenatal diagnosis (Habib 1981)
   1. Ultrasonography
      1. Etiologic heterogeneity of fetal hydrocephalus diagnosed by ultrasound (Harrod et al. 1984)
      2. Fetal ventriculomegaly
      3. Additional CNS malformations
      4. Extracerebral malformations
   2. Sonographic findings in HSAS (Senat et al. 2001) or MASA syndromes (Pomili et al. 2000)
      1. Male fetus
      2. Hydrocephalus
      3. Hypoplasia or agenesis of the corpus callosum
      4. Bilateral adducted thumbs
   3. The specific sonographic appearance of fetal isolated aqueductal stenosis (Emery et al. 2015)
      1. Symmetric severe CNS ventriculomegaly
      2. Thinning of the brain parenchyma, both anteriorly and posteriorly
      3. A dangling choroid plexus
      4. A dilated third ventricle
      5. A preserved posterior fossa
   4. Amniocentesis
      1. Alpha-fetoprotein and cholinesterase determination from amniotic fluid for neural tube defects
      2. Chromosome analysis for suspected chromosomal disorder
   5. Molecular genetic diagnosis
      1. DNA diagnosis often requested in families with "isolated" hydrocephalus case due to high rate of de novo mutations, small family size, and the improved sensitivity of prenatal ultrasound scanning
      2. Molecular diagnosis of prenatally suspected L1 spectrum disorders (Finckh and Gal 2000; Senat

et al. 2001), even in cases without positive family history

3. Management (Kanev and Park 1993; Del Bigio 2001a; Hamid and Newfield 2001; Kestle 2003)
    1. Folic acid intake before and during the first trimester reduces the incidence of neural tube defects, thereby the incidence of hydrocephalus.
    2. Poor intellectual outcome (Futagi et al. 2002), significantly correlated with the following:
        1. An early onset
        2. A high lateral ventricular width/hemispheral width ratio at diagnosis of hydrocephalus
    3. Different types of shunt surgeries, depending on the location of the proximal and distal shunt catheters (Toma 2015)
        1. Insufficient evidence to demonstrate an advantage for one shunt hardware design over another in the treatment of pediatric hydrocephalus (Baird et al. 2014).
        2. Ventriculoperitoneal (VP) shunting devices with pressure-controlled valves under the scalp close to the burr hole: the most common type.
        3. Ventriculopleural shunt: the distal catheter is placed within the pleural cavity.
        4. Ventriculoatrial shunt: the distal catheter is placed at the right atrium through the internal jugular vein.
        5. Lumboperitoneal shunts: a proximal catheter in the lumbar theca and distal catheter in the peritoneal cavity. These are only used in communicating hydrocephalus, commonly in pseudotumor cerebri.
        6. Examples of less common types of shunt
            1. Syringopleural shunt (draining spinal cord syrinx into the pleural cavity)
            2. Lumbopleural shunt (lumbar theca to the pleural cavity)
        7. It does not completely reverse the pathologic alterations in the brain, and, unfortunately, treatment by shunting is associated with frequent complications.
    4. Major complication associated with shunt treatment, 81% of children with shunts suffer at least one and usually several malfunctions necessitating hospitalization
        1. Shunt obstruction
        2. Valve malfunction
        3. Disconnection
        4. Hematoma
        5. Overdrainage
        6. Outgrown shunt
        7. Shunt fracture
        8. Shunt-related infections, most often caused by *Staphylococcus aureus*, with unexplained fever or frank meningitis
        9. Signs of increased intracranial pressure with headache, lethargy, and vomiting
        10. Abdominal complications
            1. Peritonitis
            2. Perforation of an abdominal organ
            3. Peritoneal cysts
            4. Development of hydroceles in boys
        11. Seizures
        12. Allergic reaction to material
    5. A trial of in utero ventriculoamniotic shunt for treating congenital hydrocephalus (Al-Anazi et al. 2008).
    6. Fetal ventriculoamniotic shunting for isolated AS (Emery et al. 2015)
        1. Mechanical shunting was attempted in the 1980s but was abandoned because of the inability to accurately identify suitable candidates.
        2. Advances in prenatal diagnosis and fetal therapy in the intervening decades may allow for the identification of a patient population amenable to in utero intervention, namely, fetuses with isolated AS diagnosed in the midtrimester.

3. Proposing an evidence-based reassessment of ventriculoamniotic shunting through the North American Fetal Therapy Network (NAFTNet).

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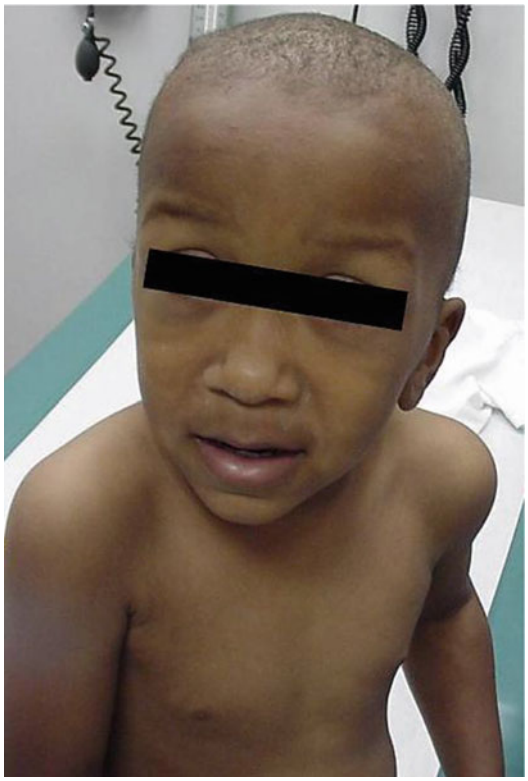

Fig. 1 A child with hydrocephalus which was shunted

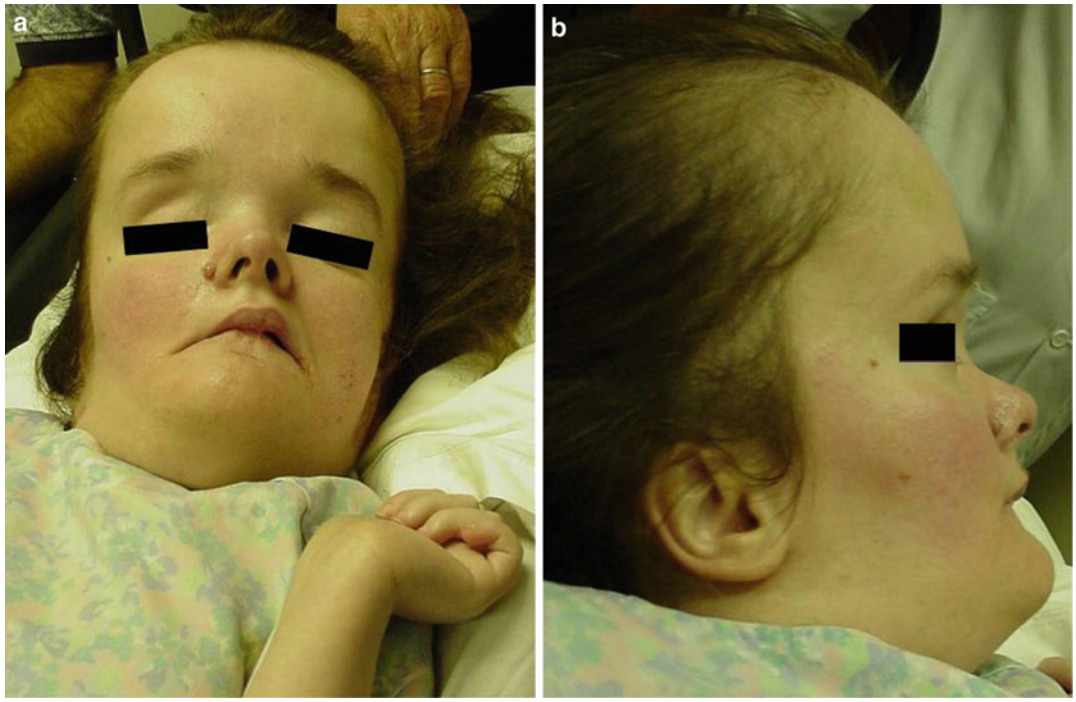

Fig. 2 (**a**, **b**) An adult with severe congenital hydrocephalus and mental retardation

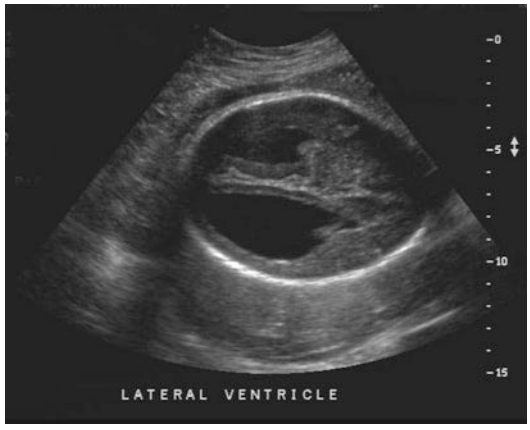

Fig. 3 Prenatal ultrasound at 33 weeks showing markedly dilated lateral ventricles

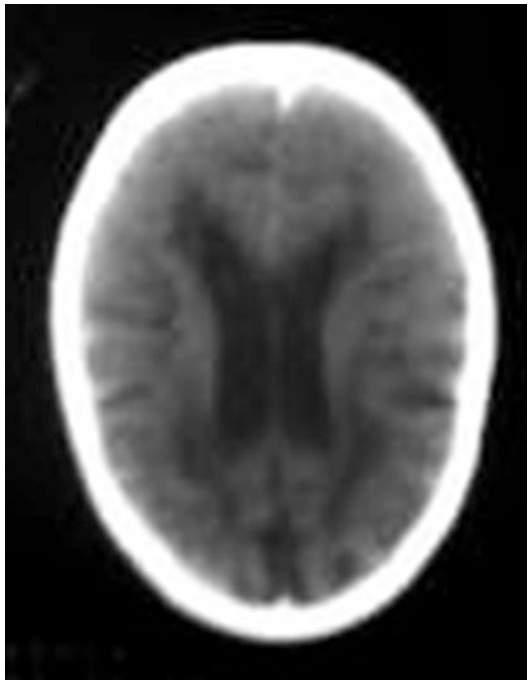

Fig. 4 CT scan of the head of a patient showing ventriculomegaly with congenital hydrocephalus

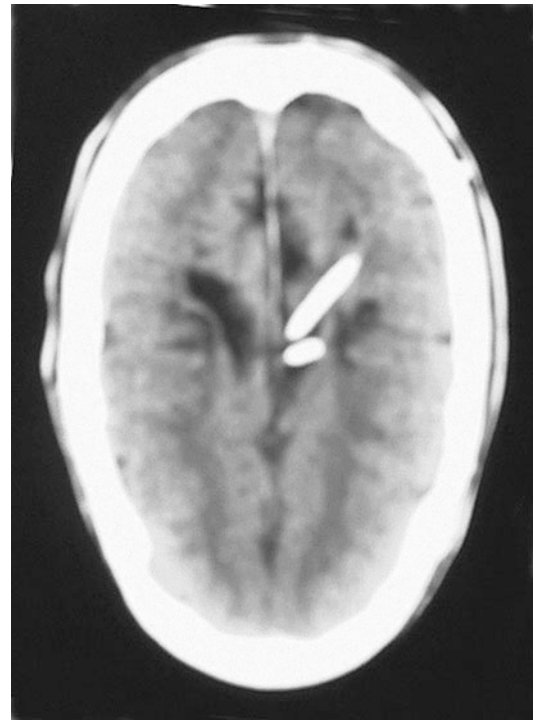

Fig. 5 CT scan of the head of a patient after ventriculoperitoneal shunt

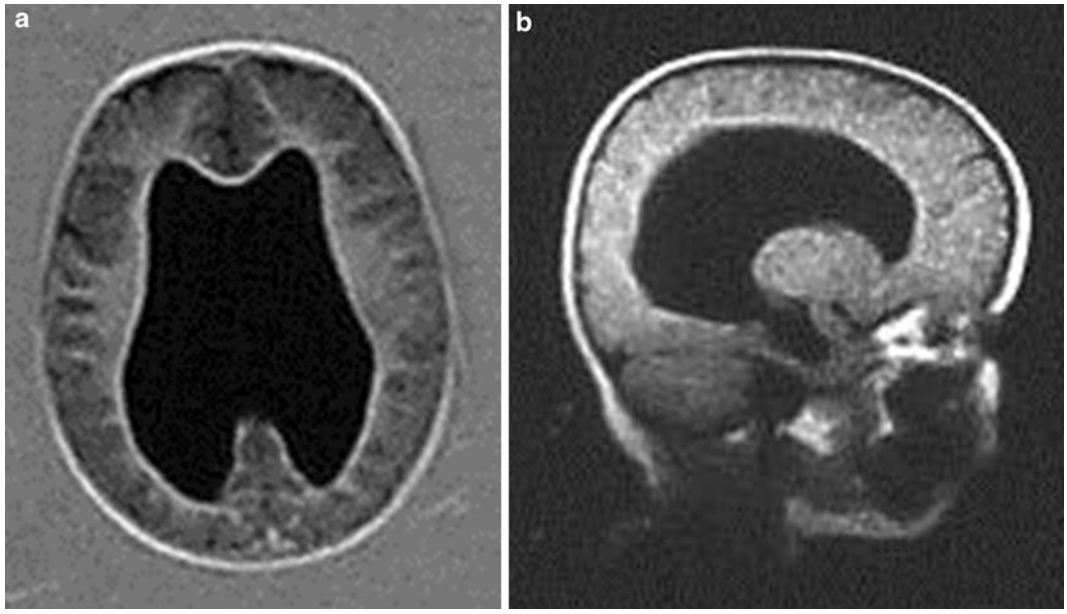

Fig. 6 (**a**, **b**) MRI of the brain of a patient showing hydrocephalus due to aqueduct stenosis

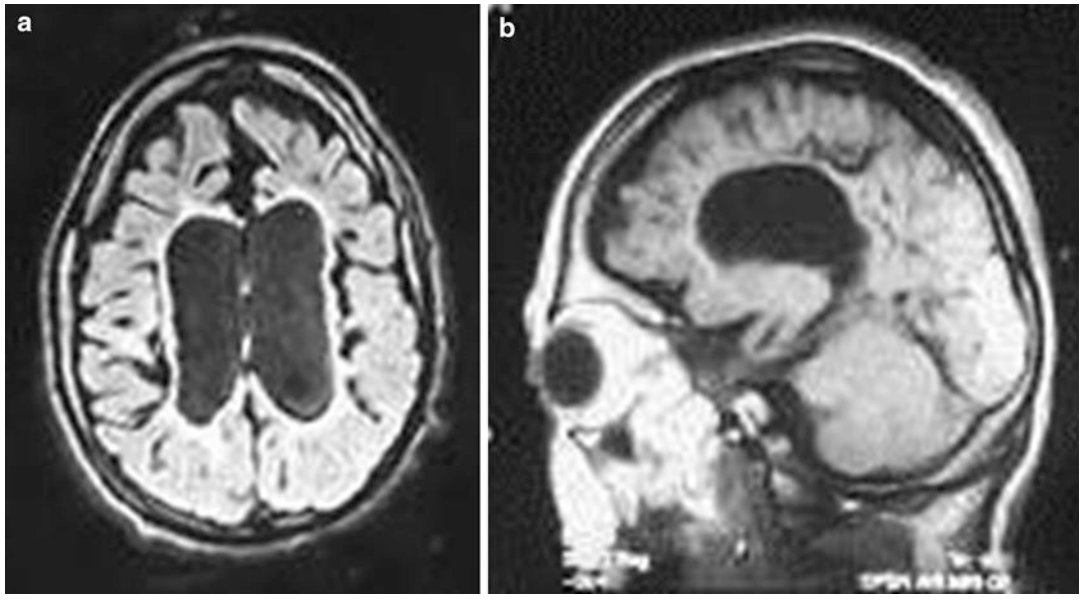

Fig. 7 (**a**, **b**) CT scans of the brain of a patient showing dilatation of the lateral ventricles with stretching of the corpus callosum and cortical atrophy

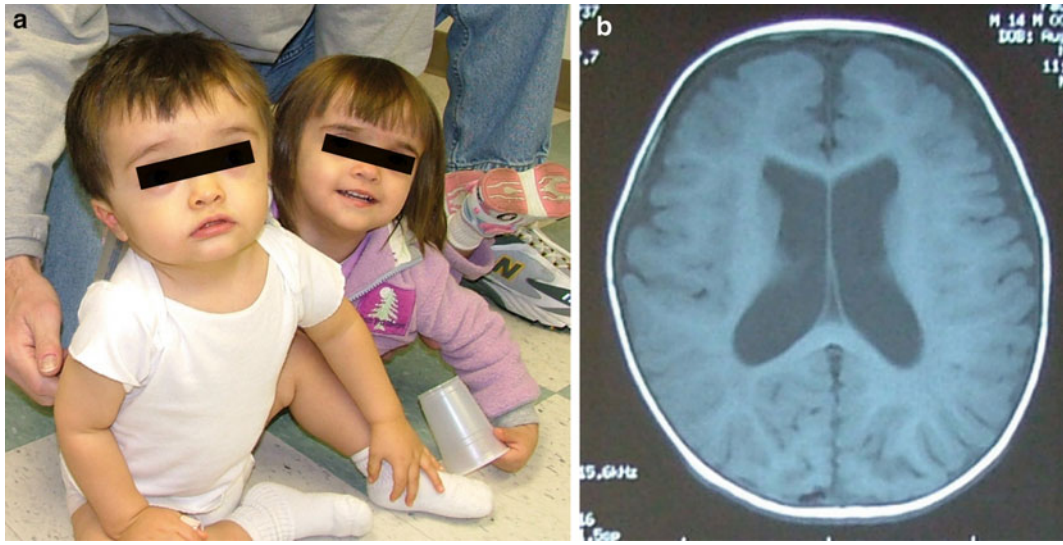

Fig. 8 (**a**, **b**) A brother (16 months) and a sister (29 months) with benign familial hydrocephalus. An MRI of the brain of the brother showed mild ventriculomegaly

Congenital Hypothyroidism

Contents

All forms of congenital hypothyroidism occur in 1 in 4,000 live births worldwide. The dysgenetic form affects twice as many females as males. It is the most prevalent congenital endocrine disease. The incidence is approximately 1 in 32,000 in Blacks and 1 in 2,000 in Hispanics.

Synonyms and Related Disorders

Ectopic thyroid gland; Thyroid agenesis; Thyroid dysgenesis; Thyroid hypoplasia; Thyrotropin resistance

Genetics/Basic Defects

1. Inheritance (Ambrugger et al. 2001)
    1. Thyroid dysgenesis (Fisher 1997)
        1. The most frequent cause of congenital hypothyroidism (85% of cases)
        2. Morphological classification
            1. Ectopic thyroid gland: the most frequent malformation, observed most frequently at the base of the tongue
            2. Athyreosis (absence of any detectable thyroid tissue)
            3. Hypoplasia (partially absent thyroid)
        3. Sporadic in most cases
        4. Genetic factors contributing to the development of thyroid dysgenesis in 2% of cases with a positive familial history (Castanet et al. 2001)
        5. Molecular defects clarified only in few cases of thyroid dysgenesis (Grüters et al. 2002)
            1. TSH receptor gene (thyroid hypoplasia, "apparent athyreosis") (Abramowicz et al. 1997b)
            2. Transcription factors: thyroid-specific transcription factor-1 (TTF-1) (hypothyroidism, chorea, choreoathetosis, respiratory distress), TTF-2 (thyroid hypoplasia, cleft palate, choanal atresia, curly hair, developmental delay) (Clifton-Blight et al. 1998), PAX-8 (thyroid hypoplasia, ectopy)
            3. NKX2A (athyreosis, hypoplasia, normally developed gland, choreoathetosis, pulmonary problems, mental retardation, pituitary abnormalities)
    2. Autosomal recessive defects of thyroid hormone biosynthesis with identification of the

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following candidate genes for congenital hypothyroidism
1. A homozygous mutation of the *betaTSH* gene (Biebermann et al. 1999)
2. Thyroid peroxidase (*TPO*) gene
    1. A hemoprotein responsible for tyrosine iodination and coupling
    2. Intriguing role of *TPO* mutations in the development of thyroid tumor
3. Sodium-iodide symporter (*NIS*) gene
4. Thyroglobulin (*TG*) gene
5. Pendrin (*PDS*) gene (Pendred syndrome) (Coyle et al. 1998)
6. Thyroid oxidase 2 (*THOX2*) gene (Moreno et al. 2002; Pfarr et al. 2006)
7. Inactivating mutation of the thyrotropin receptor causing profound hypoplasia of the thyroid gland (Abramowicz et al. 1997a)
8. Mutations in the gene encoding thyroid transcription factor-1 (*TTF-1*) are not a frequent cause of congenital hypothyroidism with thyroid dysgenesis (Abramowicz et al. 1997b)

3. Autosomal dominant transmission of congenital hypoplasia due to loss-of-function mutation of *PAX-8* (Macchia et al. 1998; Vilain et al. 2001)

2. Etiology of primary (permanent) hypothyroidism (thyroidal congenital hypothyroidism) (Macchia et al. 1999; Macchia 2000; De Vijlder 2003; Jain et al. 2008; Rastogi and LaFranchi 2010)
    1. Thyroid dysgenesis (aplasia, hypoplasia, hemiagenesis, or ectopia) (85% of cases with congenital hypothyroidism)
        1. Hypothyroidism due to a developmental anomaly
        2. Associated mutations (these account for only 2% of thyroid dysgenesis cases; 98% unknown)
            1. *TTF-2*
            2. *NKX2.1*
            3. *NKX2.5*
            4. *PAX-9*
    2. Thyroid dyshormonogenesis (hypothyroidism due to impaired hormone production) (10–20%)
        1. Sodium-iodide symporter defect
        2. Thyroid peroxidase defects
            1. Hydrogen peroxide generation defects (*DUOX2*, *DUOXA2* gene mutations)
            2. Pendrin defect (Pendred syndrome)
            3. Thyroglobulin defect
            4. Iodotyrosine deiodinase defect (*DEHAL1*, *SECISBP2* gene mutations)
    3. Resistance to TSH binding or signaling
        1. TSH receptor defect
        2. G-protein mutation: pseudohypoparathyroidism type 1a
3. Etiology of central (hypothalamic-pituitary) hypothyroidism (secondary hypothyroidism) (Rastogi and LaFranchi 2010)
    1. Isolated TSH deficiency (TSH β subunit gene mutation)
    2. Thyrotropin-releasing hormone deficiency
    3. Isolated, pituitary stalk interruption syndrome (PSIS), hypothalamic lesion, e.g., hamartoma
    4. Thyrotropin-releasing hormone resistance
    5. TRH receptor gene mutation
    6. Hypothyroidism due to deficient transcription factors involved in pituitary development or function
    7. *HESX1, LHX3, LHX4, PIT1, PROP1* gene mutations
4. Etiology of peripheral hypothyroidism (Rastogi and LaFranchi 2010)
    1. Resistance to thyroid hormone
    2. Thyroid receptor β mutation
    3. Abnormalities of thyroid hormone transport
    4. Allan-Herndon-Dudley syndrome (monocarboxylate transporter 8 [*MCT8*] gene mutation)
5. Etiology of syndromic hypothyroidism (Rastogi and LaFranchi 2010)
    1. Pendred syndrome (hypothyroidism, deafness, goiter): Pendrin mutation

2. Bamforth-Lazarus syndrome (hypothyroidism, cleft palate, spiky hair): *TTF-2* mutation
3. Ectodermal dysplasia (hypohidrotic, hypothyroidism, ciliary dyskinesia)
4. Hypothyroidism (dysmorphism, postaxial polydactyly, intellectual deficit)
5. Kocher-Deber-Semilange syndrome (muscular pseudohypertrophy, hypothyroidism)
6. Benign chorea (hypothyroidism)
7. Choreoathetosis (hypothyroidism – neonatal respiratory distress): *NKX2.1*/*TTF-1* mutation
8. Obesity, colitis (hypothyroidism, cardiac hypertrophy, developmental delay)

6. Etiology of transient form of primary congenital hypothyroidism (Moreno et al. 2002; Jain et al. 2008; Rastogi and LaFranchi 2010)
   1. Occurs in 5–10% of infants detected by newborn screening
   2. Represents about 5% of cases with congenital hypothyroidism
   3. Etiology
      1. Maternal thyrotropin binding inhibitory immunoglobulins (Schwingshandl et al. 1993)
      2. Exposure to goitrogens (iodides or antithyroid drugs)
      3. Transient hypothyroidism of prematurity
      4. Sick euthyroid syndrome
      5. Exposure to excess iodine in the perinatal period
         1. Use of iodinated disinfectants
         2. Use of contrast agents
      6. Heterozygous mutations of *THOX2* or *DUOXA2*
      7. Congenital hepatic hemangioma/hemangioendothelioma
7. Down syndrome: congenital hypothyroidism occurs approximately 28 times more common among infants with Down syndrome than in the general population with an incidence of 1% detected by newborn screening
8. Pathogenesis of mental retardation in congenital hypothyroidism: due to the central role of thyroid hormones in brain development, which takes place during fetal life and early postnatal life up to the second or third year of age (DeLange 1997)

Clinical Features

1. Coarse facies and growth failure in infants: suspect congenital hypothyroidism or acquired (autoimmune) hypothyroidism (Beltroy et al. 2003)
2. Severe dysgenetic and athyreotic hypothyroidism (Smith et al. 1975; Brown 2015)
   1. Early symptoms
      1. Poor feeding
      2. Constipation
      3. Growth failure
      4. Hoarse cry
   2. Signs and symptoms in infants and toddlers
      1. Delayed linear growth
      2. Hypotonia
      3. Decreased activity
      4. Lethargy
      5. Prolonged jaundice
      6. Bradycardia
      7. Hypothermia
      8. Cold to touch
      9. Pallor
      10. Dry/puffy/thick skin
      11. Sparse hair
      12. Characteristic craniofacial appearance
          1. Coarse facial feature
          2. Puffy eyes
          3. Myxedematous facies
          4. Large fontanelles
          5. A broad, flat nose
          6. Pseudohypertelorism
          7. Large, protruding tongue (macroglossia)
      13. Delayed tooth eruption
      14. Occasional cardiomegaly
      15. Protuberant abdomen with umbilical hernia
      16. Constipation

17. Poor nail growth
18. Delayed return of the deep tendon reflexes
19. Irreversible growth failure and mental retardation

Diagnostic Investigations

1. Newborn screening (American Academy of Pediatrics AAP Section on Endocrinology and Committee on Genetics and American Thyroid Association Committee on Public Health 1993): ideally universal screening at 3–4 days of age should be done for detecting CH. Abnormal values on screening (T4 < 6.5 ug/dL, TSH > 20mu/L) should be confirmed by a venous sample (using age-appropriate cutoffs) before initiating treatment.
    1. Successful identification of infants with congenital hypothyroidism
    2. Enables early diagnosis and treatment of infants and prevention of mental retardation in the majority of children (>90%) with congenital hypothyroidism if therapy is commenced within the first 2 weeks of life, making neonate screening for this disorder the most successful population-based screening test in pediatrics (Grüters and Krude 2012)
    3. Newborn screening measures either TSH or T_4 in neonatal blood placed on filter paper
    4. Confirmation with a serum sample if the filter paper result is abnormal
        1. Primary congenital hypothyroidism
            1. Low serum T_4 levels
            2. Elevated serum TSH
        2. Hypopituitary hypothyroidism
            1. Low total T_4 levels
            2. Low or normal TSH
        3. Thyroxine-binding globulin (TBG) deficiency
            1. Low total T_4 but normal serum-free T_4 levels
            2. Normal TSH
    5. Screening programs for congenital hypothyroidism in premature newborns (Kugelman et al. 2009)
        1. Sick premature infants may display transient hypothyroxinemia secondary to immaturity of the hypothalamic-pituitary axis.
        2. Therefore, early screening programs of such infants may be misleading.
        3. Recommendations.
            1. Screening programs should report thyroid-stimulating hormone (TSH) as well as thyroxin (T4) levels in premature infants, which will allow the treating physicians to be aware of possible abnormality that needs to be followed.
            2. Sick premature infants and other populations at risk should undergo a full serum thyroid function evaluation including free T4 and TSH beyond the screening program at discharge or at 30 days of age, whichever comes first.
            3. Physicians should use their clinical judgment and experience even in the face of normal newborn thyroid screening test and reevaluate for hypothyroidism when there is a clinical suspicion.
    6. Pendred syndrome (Banghova et al. 2008)
        1. An autosomal recessive disorder characterized by sensorineural hearing loss and thyroid dyshormonogenesis
        2. Caused by mutations in the *PDS*/*SLC26A4* gene
        3. Present from birth
        4. Can be diagnosed by newborn screening
2. Diagnostic studies for evaluation of congenital hypothyroidism (Jain et al. 2008; Agrawal et al. 2015).
    1. Laboratory diagnosis
        1. Thyroid function tests
            1. Elevated serum TSH
            2. Low serum T_4 levels
        2. Determine antithyroglobulin and antithyroid peroxidase antibodies if indicated

3. Determine thyroxine-binding globulin (TBG) levels for suspected TBG deficiency
4. ^{123}I uptake
5. Serum thyroglobulin levels
    1. Reflects thyroid mass
    2. Generally elevated with increased thyroid activity
    3. Elevated thyroglobulin levels with radionuclide scan finding of absent uptake: suggest presence of thyroid gland and the neonate may have a TSH receptor inactivating mutation trapping defect or maternal thyroid receptor blocking antibodies (TRB-ab) rather than aplasia
6. Urinary iodine estimation
    1. 24 h urinary iodine excretion approximates daily iodine excretion.
    2. The normal range in neonates approximately 50–100 mg/24 h.
    3. Measurement of urinary iodine may confirm iodine deficiency or excess.

2. Imaging studies
    1. Radiography for bone age
    2. Thyroid ultrasonography
        1. Considered as the best noninvasive method for the anatomical assessment of the thyroid gland
        2. Can detect thyroid aplasia or ectopic thyroid glands
3. Radionuclide scan (thyroid scintigraphy) using ^{99m}Tc or ^{123}I (DeLange 1997; Jain et al. 2008)
    1. To demonstrate the presence of ectopic thyroid tissue or thyroid aplasia (Kreisner et al. 2003)
    2. Iodide transport defect
        1. Low or absent uptake of ^{123}I
        2. Response to therapeutic doses of potassium iodide
    3. Defective organification of iodide
        1. Rapid uptake of ^{123}I
        2. Marked decrease in thyroid radioactivity when perchlorate or thiocyanate is administered 2 h after administering radioiodine
        3. Occasional sensorineural hearing loss (Pendred syndrome)
    4. Iodotyrosine-coupling defect
        1. Rapid uptake of ^{123}I
        2. No discharge by perchlorate
        3. Very high thyroid gland content of monoiodotyrosine (MIT) and diiodotyrosine (DIT)
        4. Virtually undetectable T_4 and T_3
        5. Adequately iodinated thyroglobulin
    5. Defects in thyroglobulin gene expression and thyroglobulin secretion
        1. Elevated uptake of ^{123}I
        2. No discharge by perchlorate
        3. Abnormal serum iodoproteins
        4. Elevated protein-bound/T_4 iodine ratio
        5. Low or borderline serum thyroglobulin
    6. Iodotyrosine deiodinase defect
        1. Rapid uptake and turnover of ^{123}I
        2. Elevated serum and urinary iodotyrosines (MIT, DIT)
        3. Response to iodine supplementation
    4. Suspected autoimmune thyroid disease: maternal and neonatal serum TBII measurement (not routinely available)
    5. Suspected iodine exposure or deficiency: urinary iodine measurement
    6. Ancillary test to determine severity of fetal hypothyroidism: radiograph of knee for skeletal maturation
3. Intelligence quotient (IQ) measurement for testing neuropsychological progress and outcome
4. Molecular genetic diagnosis (Grüters and Krude 2012)
    1. Mutations causing thyroid dysgenesis
        1. Due to the low frequency of mutations in patients with thyroid dysgenesis, genetic testing should be initiated only in those patients with either a suggestive clinical manifestation (*FOXE1*, *NKX2-1*, and *NKX2-5* gene mutations).
        2. Or with a familial occurrence of thyroid dysgenesis (*PAX8* and *TSHR* gene mutations).

2. Mutations causing thyroid dyshormonogenesis
    1. *TPO* and *TG*: the partial or complete loss of activity of the enzyme thyroid peroxidase (PO) or thyroglobulin (encoded by the *TG* gene) leads to severe hypothyroidism with a large goiter.
    2. *SLC26A4* gene: encodes pendrin, a protein expressed in follicular cells and in cells of the inner ear that transports iodine into the thyroid follicle.
    3. *DUOX*: defects in the H_2O_2-generating oxidase system (DUOX2, DUOX2a).
    4. *GNAS* mutations can cause central and primary congenital hypothyroidism.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Sporadic cases: low recurrence risk
        2. Autosomal recessive inheritance: 25%
        3. Autosomal dominant inheritance: low recurrence risk unless a parent is affected
    2. Patient's offspring
        1. Sporadic cases: low recurrence risk
        2. Autosomal recessive inheritance: low recurrence risk unless the spouse carries the recessive gene
        3. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis (Agrawal et al. 2002)
    1. Ultrasonography and percutaneous fetal blood sampling (Noia et al. 1992; Abuhamad et al. 1995)
        1. Detection of fetal goiter (the second trimester)
            1. Presence of two echogenic masses in the fetal neck
            2. A rare yet potentially dangerous condition
            3. A large goiter may cause hyperextension of the neck of the fetus caused by a large goiter, resulting in malpresentation and complicating labor and delivery
            4. Possibility of compressing the trachea and asphyxiating the neonate after birth
        2. Fetal blood sample (28 weeks)
            1. Elevated TSH
            2. Low T4
            3. A repeat cordocentesis at 35 weeks showed normalization of fetal thyroid function
    2. Amniocentesis
        1. Determination of TSH concentration (markedly elevated TSH level) in amniotic fluid in the second trimester for the offspring of a couple both known to have an iodide (iodothyronine synthesis) enzymatic organification defect
        2. Affected fetus with markedly increased TSH level in the amniotic fluid sample for the trimester
    3. Molecular genetic diagnosis possible by sequencing of select exons on fetal DNA for previously identified mutations in a research laboratory
3. Management
    1. Sodium L-thyroxine
        1. The treatment of choice.
        2. Early therapy (within 14 days) with appropriate doses of thyroxine (about 10 μg/kg/day) will prevent any brain damage even in case of evidence of fetal hypothyroidism, since thyroxine of maternal origin will reach and protect the fetus (DeLange 1997).
        3. Avoid overtreatment to prevent the following adverse effects (LaFranchi 1999):
            1. Premature cranial suture fusion
            2. Acceleration of growth and skeletal maturation
            3. Problems with temperament and behavior
    2. X-linked dominant thyroxine-binding globulin deficiency (causing a low total T4 but normal free T4): no need for thyroid hormone replacement
    3. Intrauterine treatment of fetus with a large goiter (Perelman et al. 1990; Davidson

et al. 1991; Noia et al. 1992; Abuhamad et al. 1995; Agrawal et al. 2002)
   1. Indicated because of the morbidity associated with compression of the trachea and mechanical interferences during delivery.
   2. Intra-amniotic injections of T_3/thyroxine present the least invasive approach to fetal treatment.
      1. Rapid decrease in the fetal goiter size
      2. Normalization of fetal thyroid function
4. Intrauterine treatment of fetus affected with iodide organification defect with synthroid (Hirsch et al. 1990)
5. Intrauterine treatment of dyshormonogenetic fetal goiter due to defective thyroglobulin synthesis (Medeiros-Neto et al. 1997)

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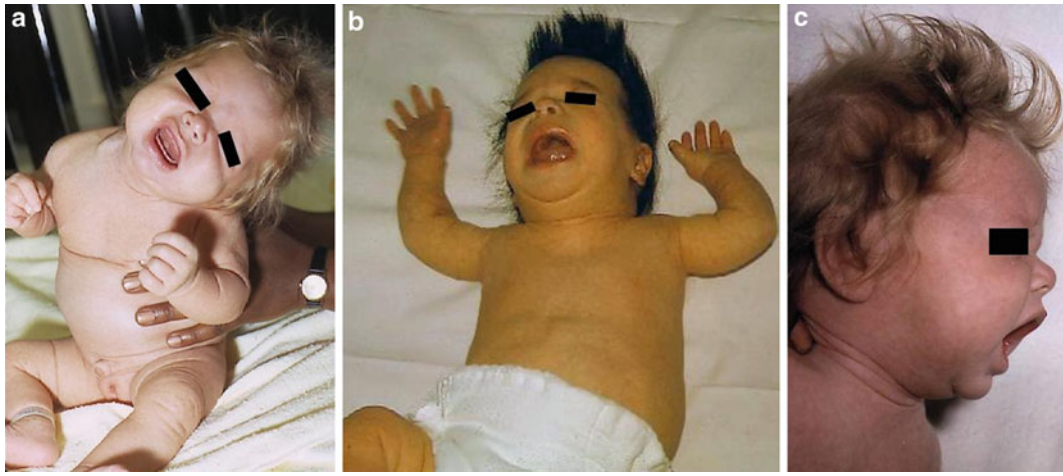

Fig. 1 (**a**–**c**) A neonate with congenital hypothyroidism showing coarse facial features, hypotonia, macroglossia, and umbilical hernia

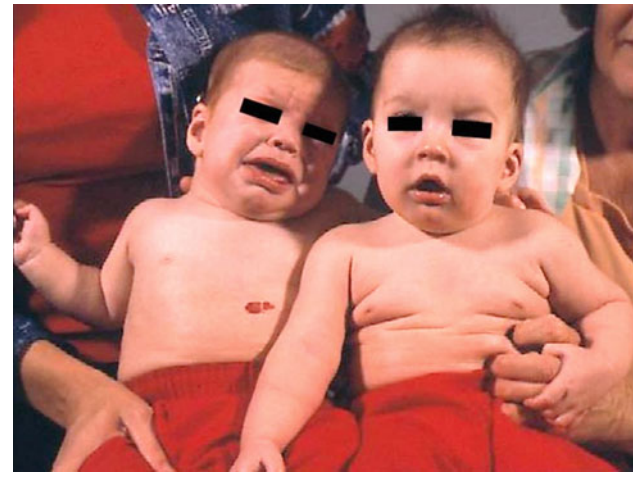

Fig. 2 A twin affected with congenital hypothyroidism (*left*) shows coarse facial features. The normal co-twin is on the *right*

Congenital Infiltrating Lipomatosis of the Face

Contents

In 1983, Slavin et al. described a new entity termed "congenital infiltrating lipomatosis of the face" (CIL-F). It differs from the other lipomatosis in its exclusive facial location, its effects on adjacent structures, its congenital nature, and its precise histologic characteristics (Bouletreau et al. 2000).

Synonyms and Related Disorders

Facial infiltrating lipomatosis; *PIK3CA*-related overgrowth spectrum; *PIK3CA*-related segmental overgrowth

Genetics/Basic Defects

1. Etiology (Shenoy et al. 2015)
    1. Hamartomatous origin (Slavin et al. 1983).
    2. Aberrant differentiation in situ of mesenchymal cells into lipoblasts (Chen et al. 2002).
    3. Cytomegalovirus (CMV) infection (Donati et al. 1990; Patel and Gondalino 1991).
    4. Recently, patients with facial infiltrating lipomatosis, characterized by hemifacial soft tissue and skeletal overgrowth, precocious dental development, macrodontia, hemimacroglossia, and mucosal neuromas, were diagnosed with *PIK3CA*-activating mutations (Maclellan et al. 2014). The strategy used to identify somatic mutations in patients with facial infiltrating lipomatosis is applicable to other somatic mosaic disorders that have allelic heterogeneity.
2. Pathogenesis
    1. Unclear (Singh et al. 2011)
    2. Current theories
        1. Mutation in the PIK3CA gene, leading to lipomatous change through trauma, chronic irradiation, muscular metaplasia, degenerative processes with fatty transformation, influence of hormones on multipotential cells, and alteration in chromosome 12 (Mahadevappa et al. 2012; Sahai et al. 2013).
        2. CIL-F is at one end of a spectrum of overgrowth syndromes including Proteus syndrome, supporting the role of somatic mosaicism and sporadic occurrence with no age or sex predilection (Padwa and Mulliken 2001).
        3. Possibly due to sporadic, spontaneous somatic mutation involving local increase in tissue growth factor (Tadisina et al. 2015).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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Clinical Features

1. Onset: typically presents itself at birth or in early childhood
2. Unilateral swelling of the cheek with ill-defined borders
3. Progressive increase in the size of the swelling with a prominent soft tissue enlargement infiltrating muscle and soft tissues, making excision difficult and recurrence likely
4. Commonly ipsilateral macroglossia and macrodontia, in addition to enlargement of underlying bone (MacMillan et al. 1990), which can lead to a bite deformity (Bouletreau et al. 2000)
5. May involve the underlying bony structures of the temporomandibular joint, coronoid process, and zygomatic bone causing bony ankylosis and trismus (Keramidas et al. 2012)
6. Tooth abnormalities: common (Sun et al. 2013)
    1. Accelerated tooth formation
    2. Premature eruption
    3. Root malformations
7. Bony asymmetry becoming more prominent with age
8. A completely benign lesion with no evidence of malignant transformation
9. The rest of the clinical examination: normal with no trunk or limb anomalies
10. Differential diagnosis (Kim et al. 2010)
    1. Hemifacial hyperplasia
        1. Hemifacial and hemitongue enlargement: common
        2. Presence of mucosal neuromas and infiltration of soft tissue by mature adipocytes: not common
    2. Lymphangioma
        1. Diffuse neck swelling
        2. Histopathological analysis: typical lymphatic channels
    3. Lipoblastoma, lipoblastomatosis, or liposarcoma (Langhans et al. 2015)
        1. More localized soft tissue enlargements of the neck.
        2. Histopathological analysis: undifferentiated or immature adipocytes.
        3. Cytogenetic analyses identified a characteristic rearrangement of the long arm on chromosome 8 (8q11–8q13) occurring in nearly 90% of the lipoblastomas (Bruyeer et al. 2012; Coffin and Alaggio 2012).
        4. Cytogenetic analyses demonstrate a distinctive translocation t(12;16)(q13;p11) and a FUS-DDIT3 gene fusion in 95% of myxoid liposarcomas (Miller et al. 1997; Hicks et al. 2001; Kåbjörn Gustafsson et al. 2014).
    4. MEN2B, Cowden syndrome, and Bannayan–Riley–Ruvalcaba syndrome
        1. Presence of mucosal neuromas
        2. Testing positive for *RET* or *PTN* mutations
    5. Infiltrating angiolipoma or facial angioma: lack skeletal findings and mucosal neuromas
    6. Lipomatosis in Proteus syndrome: involve areas outside of the head and neck
    7. Encephalocraniocutaneous lipomatosis (also called Haberland syndrome) (Rizzo et al. 1993; Kocak et al. 2015)
        1. Unilateral skin lesions such as lipoma, connective tissue nevi, and alopecia
        2. Ipsilateral ophthalmological and cerebral malformation with or without psychomotor and mental retardation and early-onset seizure
    8. Nasopalpebral lipoma–coloboma syndrome
        1. Extremely rare, predominantly autosomal dominant disorder characterized by nasopalpebral lipomatous growth, accompanying eyelid colobomas, telecanthus, and maxillary hypoplasia (Babu et al. 2011).
        2. This is the second of two syndromes where lipomatous growth is isolated to the face.

9. *PIK3CA*-related segmental overgrowth: caused by heterozygous (usually somatic mosaic) *PIK3CA* mutations of (Mirzaa et al. 2013)
    1. Megalencephaly–capillary malformation syndrome
    2. Hemimegalencephaly
    3. Segmental body overgrowth
        1. Congenital *l*ipomatous asymmetric overgrowth of the trunk, lymphatic, capillary, venous, and combined-type vascular malformations, epidermal nevi, skeletal and spinal anomalies (CLOVES) syndrome
        2. Fibroadipose hyperplasia
10. *PIK3CA*-related overgrowth spectrum (Keppler-Noreuil et al. 2014)
    1. Absence of the term "segmental" because there are patients having the *PIK3CA* somatic mutation who present with bilateral and systemic involvement
    2. Inclusion of the term "spectrum" to emphasize that there are different but related phenotypes rather than one specific phenotype

Diagnostic Investigations

1. CT: typically showing a nonencapsulated diffusely infiltrating low-attenuation mass that usually measures between −65 H and −125 H (Hounsfield unit) in addition to bony changes (Malik et al. 2004)
2. MRI
    1. Probably the most helpful study
    2. Showing diffuse fatty infiltration and increased thickness of subcutaneous fat on the affected side
    3. A bright signal on both T1- and T2-weighted spin echo sequences with fatty extension into adjacent soft tissue (Ha et al. 1994)
3. Histopathological findings
    1. Important in obtaining the correct diagnosis.
    2. Infiltration of normal tissue by mature adipocytes versus undifferentiated or immature adipocytes in lipoblastomatosis (Shear 1967) and liposarcoma (Sauk 1971).
    3. Areas of normal tissue involved include submucosa, dermis, skeletal muscle, and parotid, submandibular, and minor salivary glands.
    4. An increased number of small vessels and mucosal neuromas are also seen.
4. Molecular study
    1. Patients were found to be negative to genetic testings: While FIL is thought to be caused by a somatic mutation involving local increase in tissue growth factors, molecular studies can be useful to rule out other disorders.
    2. Testing for *RET* mutation (MEN2B) and *PTEN* mutation (Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome) is recommended (Padwa and Mulliken 2001; Kim et al. 2010).

Genetic Counseling

1. Recurrence risk (Mirzaa et al. 2013)
    1. Patient's sib: the risk to sibs of a proband with somatic mosaicism for a mutation in *PIK3CA* would be expected to be the same as in the general population.
    2. Patient's offspring: no instances of vertical transmission of this disorder.
2. Prenatal diagnosis: usually not indicated for family members since CIL-F is not inherited
3. Management (Tadisina et al. 2015)
    1. Nonsurgical management
        1. Anti-angiogenic agents/anti-inflammatory therapy
        2. Chemotherapy with imatinib (Tracy et al. 2013) (in conjunction with excision)
    2. Surgical management
        1. Partial excision (complete excision not possible due to diffuse nature)
        2. Reconstruction of craniofacial deformity

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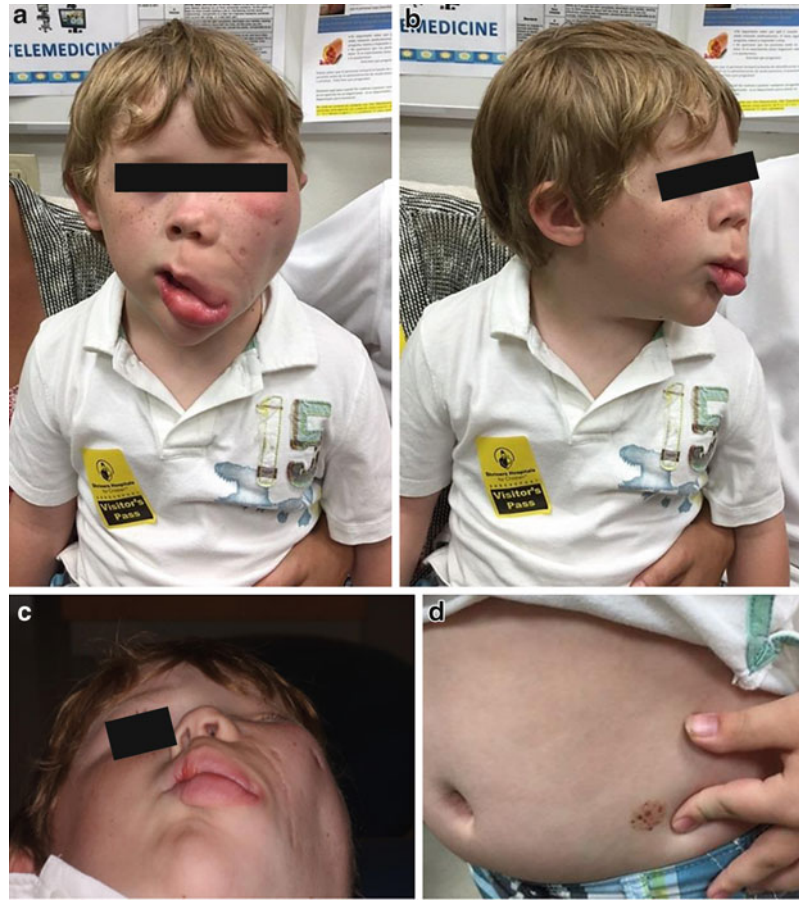

Fig. 1 (**a**–**d**) This 6-year-old boy was seen for segmental overgrowth of his left face consistent with congenital infiltrating lipomatosis of the face. Considerable disfigurement and enlargement of the soft tissues around the left side of his face were noted (**a**–**c**). He had decreased movement of the gingiva, particularly on the left side and inside his mouth. A small nevus spilus was present on the left flank (**d**). Other physical features were normal. He was delivered at 32 weeks gestation with birth weight of 5 lb 5 oz and an obvious left side facial overgrowth. He met all of his developmental milestones at the appropriate age. He had received multiple debulking surgeries since birth. He has history of stable bicuspid valve, obstructive sleep apnea, and vision changes in the left eye (Courtesy of Dr. Jennifer Woerner and Dr. Ghali Ghali)

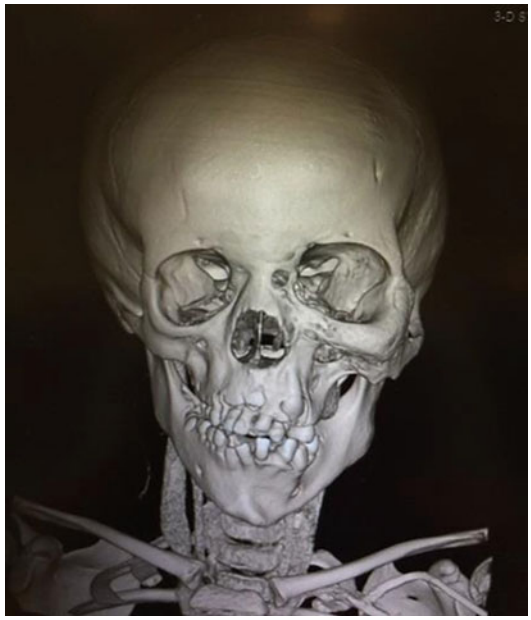

Fig. 2 3D reconstructed CT of his face, head, and neck showed hypertrophy of the left maxilla, left zygomatic arch, and left mandible. The left orbital cavity was distorted. There was a predominantly fatty lesion over the left side of his face, enhancing soft tissue and fatty infiltration into the left tongue and the floor of the mouth region. The CT of the neck also showed mild subcutaneous fat hypertrophy over the left side of the neck

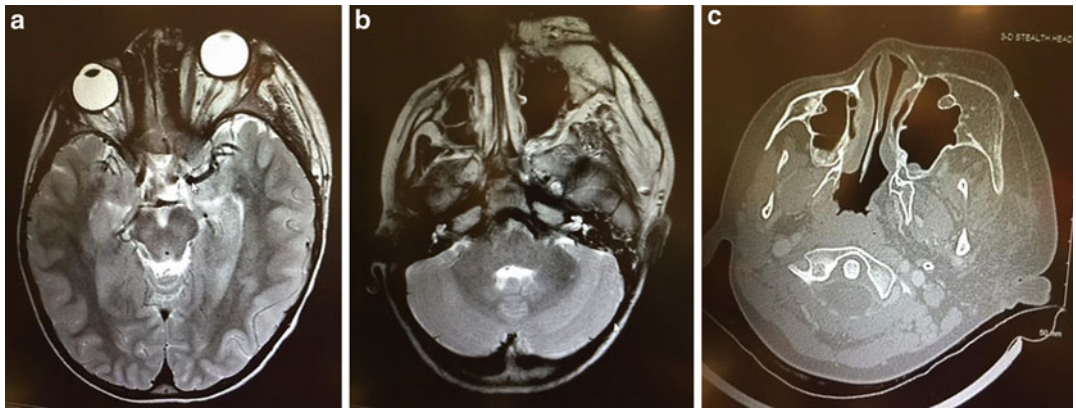

Fig. 3 (**a**–**c**) MRI of the brain and orbits showed extensive fatty tissue infiltration in the left side of the face with involvement of the orbit, infraorbital fissure, and inferior portion of the left cavernous sinus. There was proptosis involving the left orbit. There was thickening of the left medial rectus muscle compared to the right side. The brain parenchyma and ventricular system appeared unremarkable

Congenital Muscular Dystrophy

Contents

Congenital muscular dystrophy (CMD) refers to a group of genetic disorders in which weakness and an abnormal muscle biopsy are present at birth.

Synonyms and Related Disorders

Merosin-negative CMD; Merosin-positive CMD (rigid spine disease, Ullrich disease, pure CMD); Merosin-positive CMD with mental retardation and neuronal migration defects (Fukuyama CMD, muscle-eye-brain disease, Walker-Warburg syndrome)

Genetics/Basic Defects

1. Inheritance.
    1. Genetic heterogeneity
    2. Most are autosomal recessive (Muntoni and Voit 2004)
    3. Autosomal dominant (Leyten et al. 1986)
2. Caused by genetic defects in proteins of the sarcolemmal membrane or its supporting structures. The proteins may also be expressed in the central nervous system, and many forms of CMD are associated with structural brain and eye anomalies.
3. Classification of CMD (Guicheney et al. 1997; Topaloglu et al. 1990; Voit 1998; Cardamone et al. 2008; Mercuri and Muntoni 2012; Sparks et al. 2012; Iannaccone and Castro 2013; Bonnemann et al. 2014).
    1. Extracellular matrix protein
        1. Merosin (lamin-α2) (*LAMA2*): merosin-deficient CMD (MDC1A) (Helbling-Leclerc et al. 1995; Allamand and Guicheney 2002; Kang et al. 2015)
            1. Autosomal recessive merosinopathy
            2. Demyelinating neuropathy
            3. White matter signal changes on brain MRI
        2. Collagen VI (*COL6A1*, *COL6A2*, *COL6A3*) (Kang et al. 2015): Ullrich CMD, Bethlem CMD
            1. Proximal contractures
            2. Distal hyperextensibility
            3. Sandpaper rash
        3. Integrin α7 (*ITGA7*) deficiency (Lopate 2015)
            1. Described only in a few children
            2. Hypotonia in infancy with delayed motor milestones
            3. One patient with mental retardation

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Another patient with contractures and respiratory failure
5. One patient required noninvasive ventilation at age 8 and became wheelchair bound at age 12

2. Sarcolemmal protein (Plectin, *PLEC1*): CMD with epidermolysis bullosa (Lopate 2015)
    1. Blistering skin rash from birth
    2. Nail dystrophy
    3. Scalp alopecia
    4. Progressive proximal muscle weakness, often leading to wheelchair bound by the second decade and may correlate with residual plectin function
    5. Myasthenic syndrome: may respond to pyridostigmine
        1. Ptosis
        2. Ophthalmoplegia
        3. Facial weakness
    6. Other systemic features
        1. Growth retardation
        2. Anemia
        3. Laryngeal webs
        4. Tooth decay
        5. Pyloric atresia
        6. Infantile respiratory insufficiency
        7. Cardiomyopathy.
3. Glycosyltransferases: autosomal recessive dystroglycanopathies (Kang et al. 2015)
    1. Fukuyama CMD (Toda et al. 1993, 2000; Kondo-Iida et al. 1999), Walker-Warburg syndrome
        1. *FKTN* (Fukutin)
        2. Eye and structural brain anomalies
        3. Seizures
        4. Mental retardation
        5. Absent α-dystroglycan on muscle immunocytochemistry
    2. Muscle-eye-disease: can be caused by the following mutations (Lopate 2015):
        1. *POMT1*
        2. *POMT2*
        3. *POMGnT1*
        4. *FKRP*
        5. *LARGE*
    3. Protein O-mannose β-1,2-N-acetylglucosaminyltransferase 1 (POMGnT1): muscle-eye-brain disease
        1. Eye and structural brain anomalies
        2. Absent α-dystroglycan on muscle immunocytochemistry
    4. Protein *O*-mannosyltransferase 1 (*POMT1*): Walker-Warburg syndrome, limb-girdle muscular dystrophy, type 2 K
        1. Eye and structural brain anomalies
        2. Seizures
        3. Mental retardation
        4. Absent α-dystroglycan on muscle immunocytochemistry
    5. Protein *O*-mannosyltransferase 2 (*POMT2*)
        1. Walker-Warburg syndrome: hydrocephalus
        2. Muscle-eye-brain disease: severe structural brain anomalies, absent α-dystroglycan on muscle immunocytochemistry
    6. Unknown protein: congenital muscular dystrophy type 1B (muscle hypertrophy, early respiratory failure)
    7. Fukutin-related protein (*FKRP*) (Brockington et al. 2001a, b): limb-girdle muscular dystrophy type 21, congenital muscular dystrophy type 1C, Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome
        1. Duchenne phenocopy
        2. Cardiomyopathy
        3. Absent α-dystroglycan on muscle immunocytochemistry
    8. LARGE congenital muscular dystrophy: congenital muscular dystrophy type 1D
        1. Severe mental retardation
        2. White matter signal changes on brain MRI
    9. SIL1 (*SIL1*): Marinesco-Sjögren syndrome
        1. Cerebellar ataxia
        2. Congenital cataracts

4. Endoplasmic reticulum protein
    1. Rigid spine muscular dystrophy (Schara et al. 2008)
        1. Caused by mutations in *SEPN1* (selenoprotein N, 1) and *FHL1* (four-and-a-half LIM domain 1) (Kang et al. 2015)
        2. Extends the phenotypic spectrum of *ACTA1* myopathies to include congenital muscular dystrophy associated with rigid spine (O'Grady et al. 2015)
        3. Thin habitus
        4. Spinal rigidity
    2. Multicore myopathy: early respiratory failure
    3. Congenital fiber-type disproportion
    4. Myofibrillar myopathy
5. Nuclear envelope protein (Lamin A/C, *LMNA*): variable phenotype
    1. Emery-Dreifuss MD
    2. Limb-girdle muscular dystrophy type 1B
    3. Congenital muscular dystrophy
    4. Dilated cardiomyopathy
    5. Charcot-Marie-Tooth disease (CMT) type 2B1
6. RYR1 (ryanodine receptor 1)-related myopathy (Bharucha-Goebel et al. 2013)
    1. Autosomal recessive
    2. CMD presentation: dropped head syndrome, axial and scapuloperoneal involvement, absent or early loss of ambulation
    3. Milder presentations fuse with early-onset Emery-Dreifuss muscular dystrophy
7. CHKB-related CMD (Kobayashi et al. 1996; Nishino et al. 1998; Mitsuhashi et al. 2011; Bonnemann et al. 2014)
    1. Autosomal recessive
    2. Congenital weakness
    3. Cognitive impairment
    4. Pruritus
    5. Giant mitochondria in biopsy
8. PTRF-related PCGLP4 with CMD (Bonnemann et al. 2014)
    1. Autosomal recessive
    2. Congenital onset generalized progressive lipodystrophy
    3. Later rippling muscle

Clinical Features

1. Typical features
    1. Present in the first year of life.
        1. Hypotonia and weakness
        2. Respiratory insufficiency
        3. Bulbar dysfunction
        4. Arthrogryposis
    2. Hypertrophy of the tongue and limb muscles, scoliosis, and contractures may develop with age.
    3. Weakness is static or slowly progressive.
2. Merosin-negative CMD
    1. Demonstrating clinical homogeneity
        1. Severe hypotonia
        2. Multiple contractures
        3. Delayed developmental milestones
        4. Normal mentation
        5. Variable degrees of central hypomyelination seen on neuroimaging
    2. Patients with complete merosin deficiency
        1. Typically presenting as floppy infants
        2. May or may not require ventilatory assistance
        3. Most patients stabilize and able to continue developing without mechanical ventilation
        4. Feeding difficulty leading to recurrent aspiration and poor nutrition in some patients
        5. The best motor milestone achieved: standing with support
        6. Unable to ambulate
        7. Cognitive development
            1. Generally normal
            2. Mental retardation in patients with brain anomalies
        8. Epilepsy

3. Patients with partial merosin deficiency
    1. Wide clinical spectrum
        1. Marked hypotonia at birth, contractures, and severely delayed motor milestones
        2. Limb-girdle muscular dystrophy-like presentation in the teen
        3. An adult-onset proximal limb-girdle weakness with elevated CK concentration
    2. White matter abnormalities by MRI in all patients with documented merosin gene mutations
3. Merosin-positive CMD
    1. Rigid spine disease (Flanigan et al. 2000)
        1. Infantile hypotonia, with prominent neck muscle weakness and poor head control in the early years of life
        2. Initial improvement in muscle strength which parallels development, followed by stabilization or only minimal decrease in muscle strength, with marked loss of muscle bulk
        3. Contractures of the spine, resulting in rigidity in flexion and, to a lesser extent, contractures of limb joints
        4. Skeletal abnormalities, particularly scoliosis, which appear by age 5 years and may progress to require surgical intervention
        5. Early respiratory insufficiency, with onset before adolescence, often requiring nocturnal ventilatory support
        6. Normal intellectual function
        7. Essentially normal cardiac function
    2. Ullrich disease (Lopate 2015)
        1. Proximal joint contractures
        2. Distal joint laxity
        3. Delayed motor milestones
            1. Ability to walk in some cases
            2. Wheelchair dependent in majority of cases
        4. Normal intelligence
    3. Classic or "pure" CMD (Kobayashi et al. 1996; Leyten et al. 1996)
        1. Onset at birth or during the first year of life
        2. Respiratory difficult in early infancy
        3. Hypotonia and generalized muscular weakness
        4. Multiple joint contractures evident in the first year of life
        5. Clinical course nonprogressive or slowly progressive
        6. Normal or subnormal mental development (in any case IQ $>$ 50)
        7. CT/MRI: cerebral atrophy (24%) and areas of white matter lucency (11%)
    4. Other merosin-positive CMD
4. Merosin-positive CMD with mental retardation and neuronal migration defects
    1. Fukuyama CMD (Fukuyama et al. 1981; Fukuyama and Ohsawa 1984; Yoshioka and Kuroki 1994)
        1. An autosomal recessive disorder.
        2. Prevalent in Japan.
        3. Early onset (before 9 months).
        4. Muscle weakness.
        5. Accompanied by joint contractures.
        6. Hypotonia/hypokinesia.
        7. Small fraction of patients acquire the capacity to walk unassisted (Kondo-Iida et al. 1997).
        8. Severe mental retardation.
        9. Epilepsy.
        10. Eye anomalies (Chijiiwa et al. 1983).
            1. Entropion of lower lids
            2. Pathological myopia with astigmatism
            3. Congenital nystagmus
            4. Cortical blindness
            5. Optic nerve pallor/atrophy
            6. Irregular grayish subretinal mottling
            7. Choreoretinal degeneration
        11. Brain anomalies (cobblestone lissencephaly; type 2 lissencephaly).
            1. Micropolygyria
            2. Pachygyria
            3. White matter lucency
            4. Minor cerebellar alterations (cortical dysplasia)
    2. Muscle-eye-brain disease (Santavuori et al. 1977; Sparks et al. 2012)
        1. An autosomal recessive disorder

2. Mimics Walker-Warburg syndrome but overall changes tend to be much milder
3. Present as a floppy infant with suspected blindness
4. Severe mental retardation
5. Extensive neuronal migration disorder
    1. Pachygyria and polymicrogyria
    2. Brainstem hypoplasia
    3. Cerebellar dysgenesis
    4. Hydrocephalus
6. Muscle involvement: typical features of muscular dystrophy with ongoing de- and regeneration
7. Brain anomalies
    1. Frontoparietal pachygyria
    2. Polymicrogyria
    3. Vermis hypoplasia
    4. Cerebellum cyst/dysplasia
8. Normal expression of laminin α2

3. Walker-Warburg syndrome (Sparks et al. 2012)
    1. An autosomal recessive disorder
    2. Type II lissencephaly (Cormand et al. 2001)
        1. Micropolygyric "cobblestone" cortex
        2. Extensive white matter abnormalities
        3. Hydrocephaly with enlarged ventricles
        4. Brainstem hypoplasia
        5. Hypoplasia of the cerebellum, particularly the cerebellar vermis
    3. Ocular dysgenesis
        1. Megacornea
        2. Buphthalmos
        3. Corneal clouding
        4. Cataracts
        5. Abnormal vitreous
        6. Retinal hypopigmentation
        7. Hypoplasia of the optic nerve
        8. Clinically blind
    4. Muscular dystrophy
        1. Variable in severity: ranges from myopathy with increased variation of fiber size to severe, end-stage muscular dystrophy
        2. Well-preserved expression of laminin α2
    5. Brain anomalies
        1. Cobblestone lissencephaly
        2. Severe cerebellum hypoplasia
    6. Complete lack of psychomotor development (severe mental retardation) for those who survive for some years
5. Lethal congenital muscular dystrophy with arthrogryposis multiplex congenita (Sombekke et al. 1994)
    1. Maternal polyhydramnios.
    2. Arthrogryposis multiplex congenita.
    3. Severe muscle wasting.
    4. Lung hypoplasia.
    5. Hydrops.
    6. The muscle biopsies showed fibrosis, variation in fiber size, and extensive fat replacement compatible with muscular dystrophy.

Diagnostic Investigations

1. Serum creatine kinase (CPK) levels (Lopate 2015).
    1. Normal to mildly elevated (≤5 times normal): Ullrich congenital muscular dystrophy, rigid spine with muscular dystrophy (deficiency of selenoprotein N), and integrin-α7 deficiency
    2. Usually more than 1000: congenital muscular dystrophy with familial junctional epidermolysis bullosa
    3. Mildly to markedly elevated (2–150 times normal) in most patients with congenital muscular dystrophy due to abnormal glycosylation or with laminin-α2 mutations
2. Nerve conduction studies (NCV) may show demyelinating neuropathy in merosin-deficient CMD (Quijano-Roy et al. 2004).
3. Electromyography/NCV testing: useful to rule out a peripheral neuropathy associated particularly in LAMA2-related CMD (Quijano-Roy et al. 2004).

4. Muscle biopsy shows typical dystrophic changes (degeneration and regeneration of muscle fibers and proliferation of fatty and connective tissue).
5. Immunocytochemistry enables analysis of merosin, α-dystroglycan, collagen VI, and other muscle proteins (Jones and North 2003; Muntoni and Voit 2004; Bertini et al. 2011).
6. Muscle MRI.
    1. Particularly useful when suspecting a *COL6*-, *SEPN1*-, or *LMNA*-related CMD, showing specific or preferential involvement of certain muscle groups for each condition.
    2. In *COL6*-related disorders, the muscle MRI shows a characteristic pattern with diffuse fatty infiltration within thigh muscles taking the form of a rim of hypodensity at the periphery of muscles, particularly in vasti muscles, with a relative sparing of the central part and with relative sparing of the sartorius, gracilis, and adductor longus muscles.
    3. Particularly in the mild phenotypes of Bethlem myopathy, MRI shows a systematic fatty infiltration in the rectus femoris muscle and specifically takes the form of a central hypodensity described as a "central shadow sign."
    4. In selenoproteinopathies, selective involvement of sartorius and adductor longus muscles but sparing of the gracilis muscle is highly suggestive of the diagnosis.
7. Cerebral magnetic resonance imaging (MRI) may show abnormalities of neuronal migration and white matter signal.
    1. Pachygyria (with normal cognitive function)
    2. Cerebellar hypoplasia (with normal cognitive function but delay of speech development)
    3. Cerebellar cysts (in connection with pure CMD)
    4. Diffuse and symmetrical increase in signal in the white matter of the cerebral hemispheres (merosin-deficient CMD) (Caro et al. 1999)
    5. Large lissencephalic changes
    6. Hydrocephalus
8. Cardinal brain MRI findings of Fukuyama CMD (Aida 1998).
    1. Abnormalities of cerebral cortices, including cerebral polymicrogyria with preferential involvement of the frontal lobe and temporo-occipital pachygyria or type I1 lissencephaly
    2. Cerebellar polymicrogyria with parenchymal cysts
9. Molecular genetic analyses.
    1. Fukuyama CMD: sequencing of entire coding region or select exons of *FCMD* gene
    2. Muscle-eye-brain disease: sequencing of entire coding region or select exons or targeted mutation analysis of *POMGnT1* gene
    3. Walker-Warburg syndrome: sequencing of entire coding region or select exons or mutation scanning of *POMT1* gene
    4. Successful application of targeted sequencing in conjunction with next-generation sequencing to screen for mutations in hundreds of exons in a genetically heterogeneous human disorder, such as congenital muscular dystrophy (Valencia et al. 2012)

Genetic Counseling

1. Recurrence risk (Sparks et al. 2012).
    1. Patient's sib
        1. Autosomal recessive: a 25% recurrence risk
        2. Autosomal dominant (Ullrich congenital muscular dystrophy): a low recurrence risk but greater than that of the general population if both parents are clinically unaffected or if the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, because of the possibility of germline mosaicism
    2. Patient's offspring:
        1. Autosomal recessive
            1. Many individuals not living long enough to reproduce.

2. All offspring are carriers.
3. Recurrence risk to offspring probably less than 1%.

2. Autosomal dominant: a 50% risk

2. Prenatal diagnosis.
   1. Possible for pregnancies at 25% risk for complete merosin deficiency, provided complete merosin deficiency has been documented in the muscle of the proband.
      1. The diagnostic testing must be done on a sample of direct and flesh-frozen chorionic villi obtained at about 10–12 weeks of gestation by immunostaining.
      2. Using molecular testing for mutations that have been previously identified in the proband by CVS or amniocentesis.
   2. Complete merosin deficiency (Guicheney et al. 1997, 1998): concerning families with a CMD child having complete merosin deficiency, microsatellite analysis can be used for prenatal diagnosis with or without a direct assessment of the laminin α2 chain in fetal chorionic villous biopsies.
   3. Partial merosin deficiency (Guicheney et al. 1997, 1998).
      1. Heterogeneous
      2. Important to detect laminin α2 chain gene defects in order to perform prenatal diagnoses by direct mutation analysis
   4. A combination of immunocytochemistry and linkage analysis can be used for the prenatal diagnosis of merosin-deficient CMD. The results are easy to interpret in families with total absence of the protein, while caution is required when dealing with families where partial expression occurs (Naom et al. 1997).
   5. Since laminin α2 chain is expressed in placental trophoblasts, the demonstration of its deficiency in chorionic villi is a useful aid to prenatal diagnosis of laminin-deficient CMD (Nass et al. 1999).
   6. Prenatal diagnosis by DNA mutation analysis is available for pregnancies at increased risk of Fukuyama MD (Kondo et al. 1996; Takai et al. 1998), muscle-eye-brain disease, Walker-Warburg MD, congenital muscular dystrophy type 1C and 1D, and congenital muscular dystrophy with early spine rigidity by analysis of fetal DNA, obtained by amniocentesis or CVS, provided both disease-causing alleles of an affected family member have been identified.
3. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the disease-causing mutations have been identified in an affected family member (Sparks et al. 2012).
4. Management (Sparks et al. 2012).
   1. No definitive treatment available
   2. General approaches
      1. Weight control to avoid obesity
      2. Physical therapy and stretching exercises
         1. To promote mobility
         2. To prevent contractures
      3. Using mechanical devices to help ambulation and mobility
      4. Surgical interventions for scoliosis and foot deformity
      5. Medications for seizure control
      6. Respiratory aids as needed
      7. Social and emotional support

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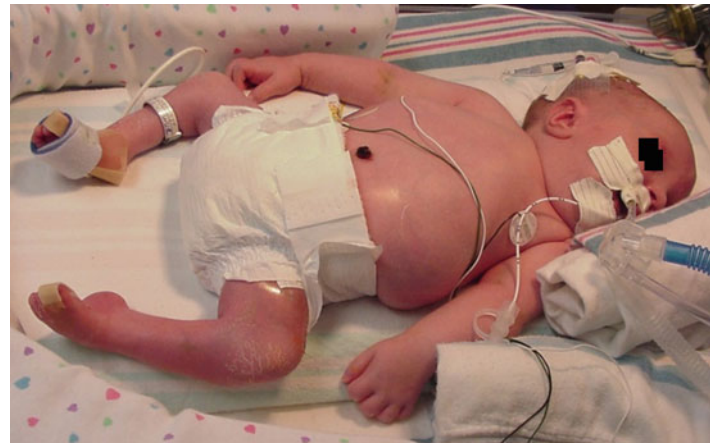

Fig. 1 An infant with congenital muscular dystrophy showing hypotonic frog-leg posture, the chest deformity due to weakness of the intercostal muscles, and contractures of joints

Congenital Radioulnar Synostosis

Contents

Although congenital proximal radioulnar synostosis is an uncommon malformation of the upper extremity, first described by Sandifort in 1973 (Simmons et al. 1983), congenital radioulnar synostosis (RUS) is the most common congenital functional disorder of the elbow joint (Siemianowicz et al. 2010). In most cases, RUS is an isolated defect involving only one limb. However, bilateral RUS is usually familial and affects males more than females (Figs. 1–3).

Synonyms and Related Disorders

Proximal radioulnar synostosis

Genetics/Basic Defects

1. Etiology (Rizzo et al. 1997; Elliott et al. 2010; Wurapa 2012)
    1. Isolated or congenital radioulnar synostosis types I and II (Davenport et al. 1924)
    2. Familial cases: inherited as autosomal dominant trait (Hansen and Andersen 1970; Spritz 1978; Rizzo et al. 1997)
    3. Association of RUS and chromosome anomalies: well known (Rizzo et al. 1997; Kidszun et al. 2012)
        1. X chromosome anomalies: polysomy X in both male and female patients with supernumerary X chromosomes (49,XXXXY, 49,XXXXX, 48, XXXX, 48,XXXY, 48,XXYY, 47, XXY)
        2. Y chromosome anomalies (De Smet and Fryns 2008; Syed and Quinton 2008)
        3. Other chromosome anomalies:
            1. Del(10)(pter-p13)
            2. Del(11)(q23)
            3. Del(13)(q22-qter)
            4. Dup(12)(q24-qter)
            5. Dup(14)(q23-qter)
            6. Partial trisomy 11q
            7. Trisomy 8 mosaicism
            8. Trisomy 18p
    4. Association of RUS with various syndromes
        1. Apert syndrome
        2. Arthrogryposis
        3. Berant syndrome (radioulnar synostosis and craniosynostosis)
        4. Carpenter syndrome

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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5. Cenani-Lenz syndactyly: a form of syndactyly resembling that of Apert syndrome but with additional features such as severe shortening of the ulna and radius with fusion, fusion of the metacarpals, "disorganization" of phalangeal development, and less severely affected feet (Cenani and Lenz 1967)
6. De Lange syndrome
7. Der Kaloustian syndrome (radioulnar synostosis, short stature, retinal changes)
8. Fetal alcohol syndrome (Froster and Baird 1992)
9. Fetal thalidomide syndrome (Smithells and Newman 1992)
10. Fetal vitamin A syndrome (Rizzo et al. 1991)
11. Holt-Oram syndrome
12. Jorgenson syndrome (blepharophimosis and radioulnar synostosis)
13. Mandibular dysostoses
14. Michels syndrome (clefting, ocular anomalies, radioulnar synostosis)
15. Multiple dysostosis
16. Nail-patella syndrome
17. Noonan syndrome
18. Poland syndrome
19. Williams syndrome
20. Others

5. Developmental gene(s) responsible has not been identified in isolated RUS (Elliott et al. 2010)
    1. Mutations in the homeobox A11 (*HOXA11*) gene resulting in autosomal dominant RUS with megakaryocytic thrombocytopenia in two pedigrees have been reported (Thompson and Nguyen 2000)
    2. The HOX genes: critical developmental genes in limb development
    3. Not all patients with the gene mutation demonstrated marrow failure

2. Developmental basis of proximal radioulnar synostosis (Elliott et al. 2010)
    1. The upper limb bud arises from the body wall at approximately 26 days of development (after conception)
    2. The elbow is first discernible at 35 days: presence of three connected cartilaginous anlagen which will eventually develop into the humerus, radius, and ulna
    3. Soon afterward, longitudinal segmentation produces separation of the distal radius and ulna. However, briefly, their proximal ends are united and share a common perichondrium (Lewis 1901)
    4. Abnormal genetic or environmental factors operating at this time in development could interrupt subsequent proximal radioulnar joint morphogenesis (Mital 1976)
    5. Such interference would allow for later ossification of the entire proximal cartilaginous model and produce complete bony synostosis. If joint development continued before the developmental arrest occurred, this could lead to a smaller area of coalition and the presence of a rudimentary radial head (Simmons et al. 1983)
    6. These two scenarios also represent related primary anomalies of radioulnar differentiation/segmentation. The final specific defect of this spectrum is influenced by subtle differences in developmental timing

Clinical Features

1. 2 types of radioulnar synostosis (Wilkie 1914; Bauer and Jonsson 1988)
    1. Type 1
        1. Proximal smooth fusion of 2–6 cm between the radius and ulna
        2. Absent radial head
        3. Resulting in a limitation of pronation and supination of the forearm
    2. Type 2
        1. A fusion just distal to the proximal radial epiphysis

   2. Association with congenital dislocation of the radial head
   3. Resulting in a limitation of pronation and supination of the forearm and a restriction of extension at the elbow
2. Pain
   1. Not always associated with radioulnar synostosis
   2. Occurrence of pain: usually thought to be due to progressive, symptomatic radial head subluxation (Sachar et al. 1994)

Diagnostic Investigations

1. Radiographic types (Cleary and Omer 1985)
   1. Type I (19%): fibrous synostosis with a reduced normal-appearing radial head
   2. Type II (8%): visible bony synostosis with a reduced radial head
   3. Type III (56%): visible bony synostosis with a hypoplastic and posteriorly dislocated radial head
   4. Type IV (17%): short bony synostosis with an anteriorly dislocated mushroom-shaped radial head
2. CT scans recommended especially in cases in which plain radiographs show no osseous fusion (Karatosun et al. 2004)
3. MRI: demonstrates soft tissue anatomy better

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Sporadic: probably not increased
      2. Autosomal dominant inheritance: not increased unless a parent is affected
   2. Patient's offspring
      1. Sporadic: probably not increased
      2. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis of bilateral radioulnar synostosis by ultrasonography in a fetus of 49, XXXXY female at the second trimester of gestation (Martini et al. 1993)
3. Management
   1. Patients with congenital radioulnar synostosis in nearly neutral rotation could perform activities of daily living with the aid of compensatory movements of the shoulder and elbow (Kasten et al. 2009).
   2. Surgical intervention (Mostert and Tulp 2002):
      1. Usually not recommended, except in bilateral cases or in hyperpronation
      2. Optimal age for surgery difficult to define
         1. 4–5 years of age in cases of hyperpronated hand
         2. 12 years of age in the case of bilateral synostosis
   3. Derotational osteotomy at the shafts of the radius and ulna for congenital radioulnar synostosis (Murase et al. 2003).
   4. Surgical treatment with radial head excision yielded resolution of pain and restoration of elbow flexion (VanHeest et al. 2013).

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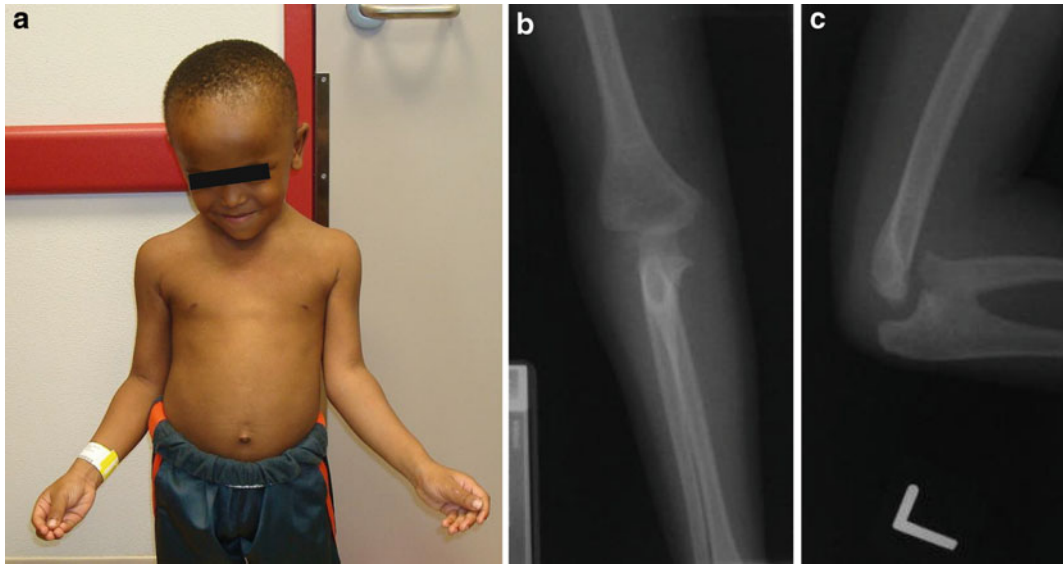

Fig. 1 (**a**–**c**) This 3½-year-old boy was evaluated for familial bilateral proximal radioulnar synostosis (shown by radiograph) (**b**, **c**). He had a large head, frontal bossing, and depressed nasal bridge is and unable to supinate both wrists (**a**)

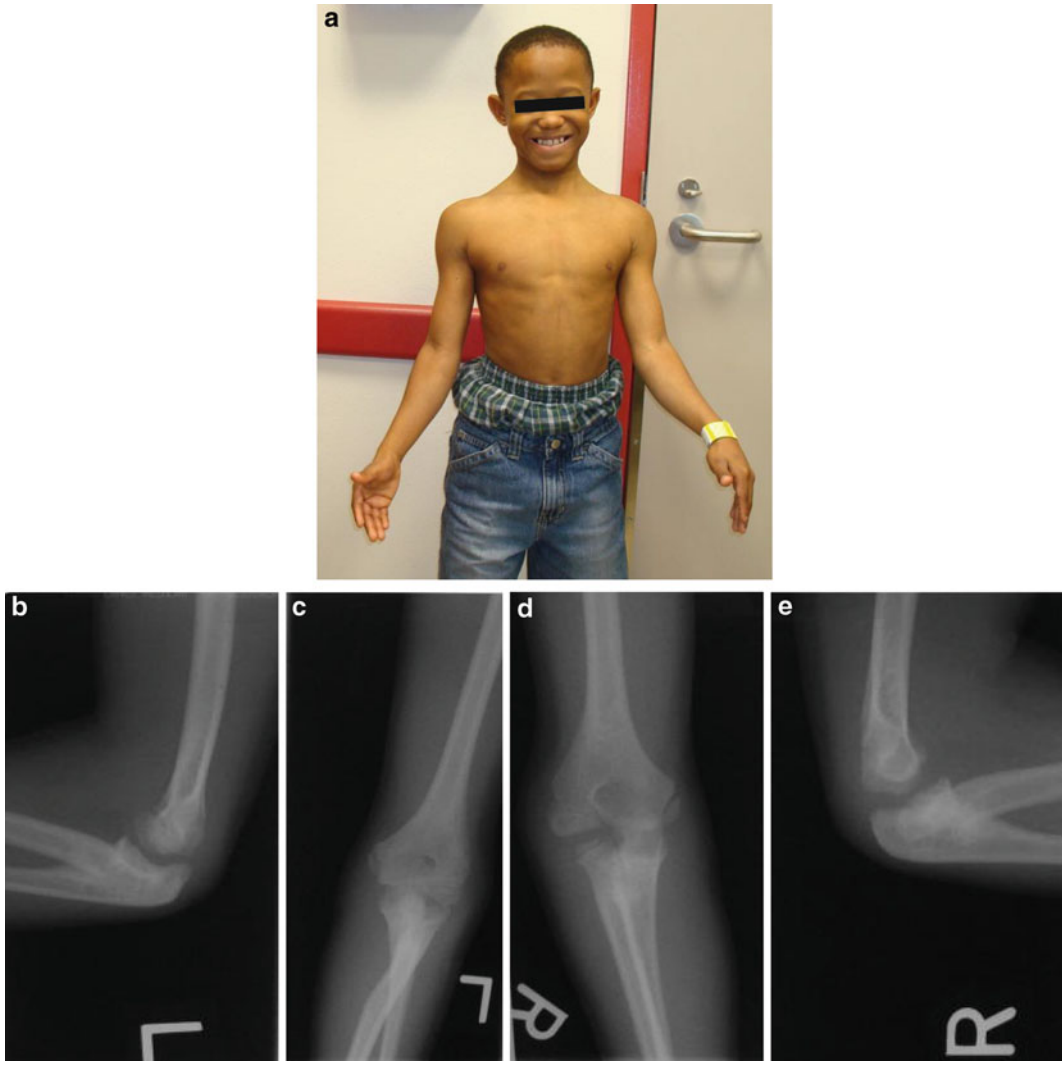

Fig. 2 (**a**–**e**) The 10-year-old brother also had bilateral proximal radioulnar synostosis, shown by radiographs (**b**–**e**) with similar clinical features (**a**)

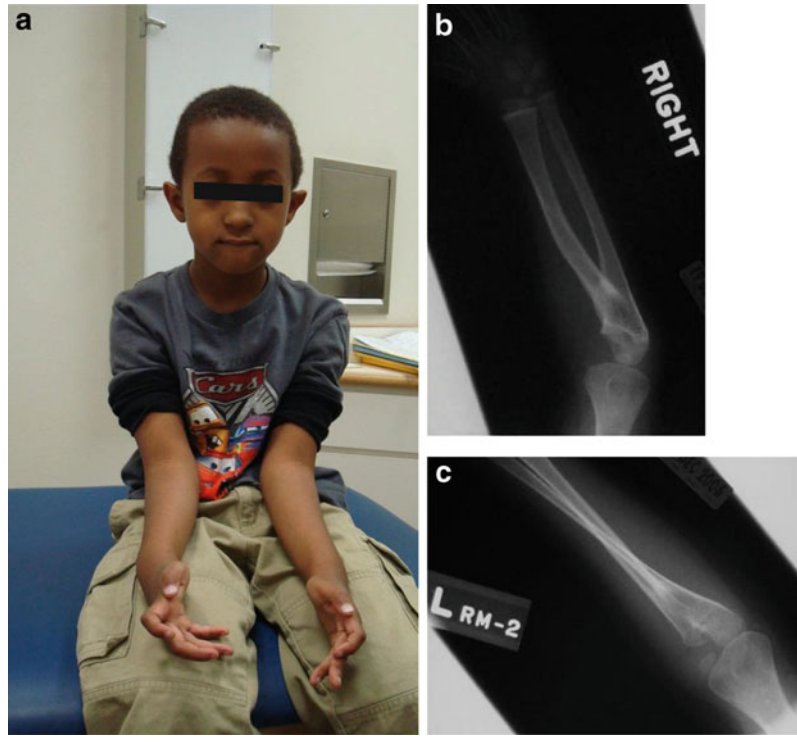

Fig. 3 (**a**–**c**) This young boy was evaluated because of bilateral cubitus valgus (**a**). He could not extend his forearms fully and supinate his wrists. Radiographs showed bilateral proximal radioulnar synostosis (**b**, **c**)

Congenital Toxoplasmosis

Contents

Acute infection in a pregnant woman with a parasite, *Toxoplasma gondii*, can have serious consequences on the fetus, ranging from fetal loss to severe neurologic or ocular lesions. In other cases, infected newborns are asymptomatic at birth but are at risk for developing retinal diseases during childhood or adolescence on *Toxoplasma* reactivation (Wallon et al. 2004). In the United States, the incidence of congenital toxoplasmosis is estimated to be 1 in 1,000 to 1 in 10,000 births, and approximately 400–4,000 cases of congenital toxoplasmosis occur each year.

Synonyms and Related Disorders

Toxoplasma gondii infection in pregnancy

Genetics/Basic Defects

1. *Toxoplasma gondii* (Beasley and Egerman 1998; Black and Boothroyd 2000; Jones et al. 2003)
    1. A protozoan parasite
    2. The causative agent of toxoplasmosis, a common infection throughout the world with estimated one billion people infected worldwide
    3. Life cycle: exists in three forms
        1. The oocysts, or soil form
        2. The tachyzoite, or active infectious form
        3. The tissue cyst, or latent form
2. Hosts
    1. Cats
        1. The primary host
        2. Maintain the intestinal-epithelial sexual cycle of *Toxoplasma* development with the production of oocysts
    2. All other animals (humans, birds, rodents, and domestic animals)
        1. The intermediate or secondary hosts
        2. Have an extraintestinal asexual cycle with resultant parasitemia and the production of tissue cysts
3. Routes by which *Toxoplasma* is transmitted to humans
    1. Principal routes:

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_56

1. Acquired: risk factors for contracting toxoplasmosis (Kaye 2011; Maenz et al. 2014; Robert-Gangneux 2014)
    1. Cats in the home or stray cats in or around the home
    2. Any job or activity that requires contact with dirt, soil, or other material that could contain cat feces
    3. Ingestion of raw or inadequately cooked infected meat (beef, pork, or lamb), raw eggs, or unpasteurized milk
    4. Drinking untreated water
    5. Ingestion of unwashed fruit or vegetables
    6. Not washing hands thoroughly after handling raw meat or gardening
    7. Ingestion of oocysts, an environmentally resistant form of the organism that cats pass in their feces and human exposure to cat litter or contaminated soil (from gardening or unwashed fruits or vegetables)
2. Congenital: transplacental infection of unborn fetus by the newly infected mother

2. Rare routes:
    1. Blood and blood product transfusion
    2. Organ transplant
    3. Laboratory accident
3. No evidence of direct human-to-human transmission other than from mother to fetus

4. Seventy percent of the obstetric population with negative antibodies: at risk for transmission to the fetus.
5. Congenital toxoplasmosis usually occurs as a result of primary maternal infection.
6. Maternal-fetal transmission rate depends on gestational age at the time of maternal infection:
    1. Less than 5% before fifth week of gestation
    2. Twenty-five percent in the first trimester
    3. Seventy-five percent in the third trimester
    4. Greater than 90% in the last few weeks of pregnancy
7. Severity of the fetal infection inversely related to gestational age: the earlier infections being the most severe.
8. Untreated maternal infections: About 50% of cases transmit to the fetus.
9. An immunocompetent woman previously infected is considered immune and will not transmit *T. gondii* to her offspring. *Toxoplasma* infection leads to lifelong immunity with the presence of *T. gondii*-specific IgG antibodies. Acute toxoplasmosis in the adult is often asymptomatic and usually does not result in complications.
10. Reactivation can occur in immunocompromised pregnant woman (i.e., HIV) leading to parasitemia and fetal infection.

Clinical Features

1. Unpredictable manifestations in the fetus and in the newborn
2. Maternal infections
    1. Generally asymptomatic in immunocompetent mothers
    2. Subtle symptoms in about 15–20% of infected mothers
        1. Cervical lymphadenopathy: the most common clinical manifestation
        2. Fatigue
        3. Flu-like symptoms
    3. In immunocompromised mothers
        1. Chorioretinitis
        2. Encephalitis
        3. Pneumonitis
        4. Myocarditis
    4. Maternal infections early in pregnancy
        1. Less likely to be transmitted to the fetus than infections later in pregnancy
        2. More likely to be severe than later infections
3. Fetal infections
    1. Usually resulting from a primary maternal infection with risk of developing congenital abnormalities. Reactivation of *T gondii* in an immunocompromised patient can render the fetus susceptible to infection.

2. Infectivity: The incidence and severity of the fetal infection depend on the gestational age at the time of the maternal infection. The later the gestation, the higher the infectivity. However, the postnatal sequelae are severer when infection occurs early in gestation.

4. Natural history of congenital toxoplasmosis (Hall 1992)
   1. Free of symptoms at birth in vast majority of cases with congenital infection (70–90% of cases) (Bollani et al. 2013)
   2. About 15% of the infected children with signs or symptoms at birth or neonatal period
      1. Maculopapular rash
      2. Generalized lymphadenopathy
      3. Hepatosplenomegaly
      4. Jaundice
      5. Thrombocytopenia
      6. Consequences of intrauterine meningoencephalitis
         1. CSF abnormalities
         2. Hydrocephalus
         3. Microcephaly
         4. Chorioretinitis
         5. Seizures
      7. Signs of the "classic triad" (hydrocephalus, intracranial calcifications, and chorioretinitis) without systemic signs of disease
   3. Sequelae during childhood or early adult life in 50–90% of cases
      1. Learning disability
      2. Visual impairment
      3. Chorioretinitis: the most frequent congenital manifestation and is progressive in >80% of patients by 20 years of age
      4. Mental retardation
      5. Hearing loss
   4. Ocular lesions: the most frequent manifestations of congenital toxoplasmosis (Metz 2001; Hovakimyan and Cunningham 2002; Melamed et al. 2010)
      1. Chorioretinal scars: a clinical hallmark of ocular toxoplasmosis (79%)
      2. Strabismus (33%)
      3. Nystagmus (27%)
      4. Microphthalmia (13%)
      5. Phthisis (4%)
      6. Microcornea (19%)
      7. Cataract (10%)
      8. Active vitritis (11%)
      9. Active retinitis (11%)
      10. Optic atrophy (20%)
   5. Severely affected congenital infection
      1. Die in utero
      2. Die within a few days of life

Diagnostic Investigations

1. Serological testing (Beasley and Egerman 1998; Lynfield and Eaton 1995)
   1. IgM anti-*Toxoplasma* antibodies
      1. Produced 1–2 weeks after an infection
      2. Levels detectable for years after the acute infection
   2. IgM elevations (Alford et al. 1974)
   3. IgG anti-*Toxoplasma* antibodies
      1. Levels peak approximately 2 months after the initial infection
      2. Remain positive for life
   4. IgA anti-*Toxoplasma* antibodies
      1. Parallels IgM production
      2. Peak levels occur approximately 2 months after the initial infection and then rapidly decline
   5. IgE anti-*Toxoplasma* antibodies
      1. Detected early after an acute infection
      2. Usually present for 4–8 months
      3. May provide useful information regarding the timing of an acute infection
   6. *Toxoplasma gondii* recombinant antigens as tools for serodiagnosis of human toxoplasmosis (Holec-Gasior 2013)
2. Detection of antibodies to toxoplasmosis in the neonatal period (Naessens et al. 1999)
   1. Specific *T. gondii* IgM antibody
      1. A positive IgM antibody in the newborn: diagnostic of congenital toxoplasmosis
      2. A negative IgM antibody in the newborn does not exclude the diagnosis and may be due to the following reasons:

1. Lack of production of IgM
2. Waning of the IgM response by the time of birth
3. Insensitivity of the assay

3. A positive IgM antibody in the mother
   1. Associated with recent maternal infection
   2. Would support the diagnosis of congenital toxoplasmosis

2. Specific *T. gondii* IgA antibody: more sensitive test than IgM antibodies
3. Neonatal screening with IgM or IgA antibodies fails to detect majority of children with congenital toxoplasmosis when the maternal infection occurred before the 20 week of pregnancy

3. Definitive postnatal diagnosis of congenital toxoplasmosis
   1. Detection of parasites in material collected from the newborn (blood, cerebrospinal fluid, or other clinical material) by inoculation into mice or tissue culture
   2. Detection of persisting specific IgG antibodies at the age of 1 year
   3. Reappearance of specific IgG antibodies in the child after cessation of postnatal antibiotic therapy
   4. Diffuse cerebral calcifications and hydrocephalus detected by radiography, ultrasonography, CT scan, or MRI of the brain
4. Other diagnostic evaluation of the infants
   1. Physical examination
   2. Dilated retinal examination
   3. Examination of the cerebrospinal fluid
      1. Protein
      2. Glucose
      3. Cell count
      4. Antibody determination
   4. Audiologic screen
   5. Examination of the placenta
      1. Evidence of infection, although the gross appearance may not parallel the severity of fetal disease
      2. Inoculation of the placental tissue into mice or tissue culture to attempt isolation of the parasite
      3. The feasibility of placental analysis, in terms of sample recovery and rapid *T. gondii* detection by PCR, makes it a useful diagnostic tool for early monitoring and treatment of neonates at risk for congenital infection (Robert-Gangneux et al. 2010)
   6. Diminution or resolution of intracranial calcifications was an unexpected and remarkable finding in infants with treated, congenital toxoplasmosis, consonant with their improved neurologic functioning (Patel et al. 1996)

Genetic Counseling

1. Recurrence risk: women with previous infection not at risk for delivering a fetus with congenital toxoplasmosis unless immunosuppressed
2. Prenatal diagnosis (Daffos et al. 1988; Hezard et al. 1997)
   1. Seroconversion during pregnancy
      1. Absence of specific *Toxoplasma gondii* IgG antibodies in the first serum sample obtained during gestation
      2. Detection of specific IgG and IgM antibodies in the follow-up sample at a later prenatal visit or at birth
   2. Suggestive but not diagnostic signs by prenatal ultrasonography (Beasley and Egerman 1998)
      1. Ventriculomegaly: the most common sonographic finding in utero
      2. Intracranial calcifications
      3. Hydrops
      4. Microcephaly
      5. Choroid plexus cysts
      6. Growth retardation
      7. Hepatomegaly
      8. Splenomegaly
      9. Ascites
      10. A thickened placenta
   3. Prenatal diagnosis of acute infection in the fetus
      1. Amniocentesis or cordocentesis (Fricker-Hidalgo et al. 1997; Foulon et al. 1999a; Antsaklis et al. 2002)

1. Detection of parasites in amniotic fluid or in fetal blood by inoculation into tissue culture or mice
2. Detection of anti-*Toxoplasma gondii* IgM, IgA, and IgE antibodies in the fetal blood. The diagnosis of fetal *T. gondii* infection before 22 weeks using cordocentesis is not possible because fetal IgM or IgA may not be produced before 22 weeks' gestation
3. Detection of *T. gondii* DNA (B1 gene) by gene amplification in amniotic fluid: the best diagnostic tools for the detection of vertical transmission in pregnancies with seroconversion during pregnancy and more accurate and faster diagnosis of congenital toxoplasmosis (Hohlfeld et al. 1994)

2. Chorionic villus sampling not helpful because it will show placental but not fetal infection

3. Management
   1. Prevention of *Toxoplasma* infection
      1. Cook meat to a safe temperature to kill *Toxoplasma*.
      2. Peel or thoroughly wash fruits and vegetables before eating.
      3. Clean cooking surfaces and utensils after they have contacted raw meat, poultry, seafood, or unwashed fruits or vegetables.
      4. Avoid changing cat litter during pregnancy or use gloves and wash hands thoroughly.
      5. Do not feed raw or undercooked meat to cats and keep cats inside to prevent acquisition of *Toxoplasma* by eating infected prey.
      6. Avoid risk factors for *T. gondii* infection including careful adherence to simple hygienic measures during pregnancy (decrease *Toxoplasma* infection by 60%).
   2. Treat *Toxoplasma* infection with spiramycin, pyrimethamine, sulfonamides, and folinic acid (Hohlfeld et al. 1989; Roizen et al. 1995).
      1. Reduce sequelae of congenital infection by treating the mother as soon as possible after the serologic screening program identifies the infection (Foulon et al. 1999b).
      2. Treat infected neonates: The sooner the treatment, the better the outcome.
   3. Newborn screening for *Toxoplasma*-specific IgG and IgM allows the identification and treatment of subclinical cases so that the sequelae of infection with toxoplasmosis may be prevented or attenuated (Guerina et al. 1994).

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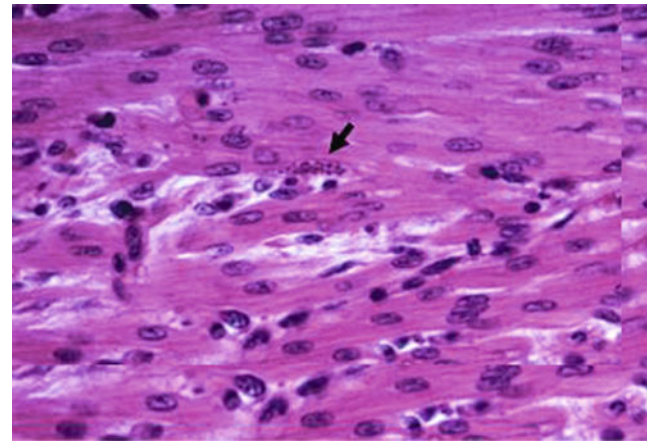

Fig. 1 A newborn died of congenital generalized *Toxoplasma* infection. The heart showed myocarditis with presence of *Toxoplasma* cyst (*arrow*) (H and E, ×400)

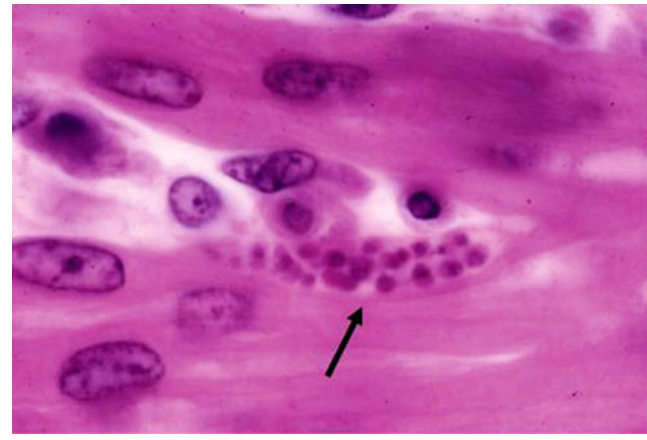

Fig. 2 *Toxoplasma* cyst seen in high magnification (*arrow*) (H and E, ×1,000)

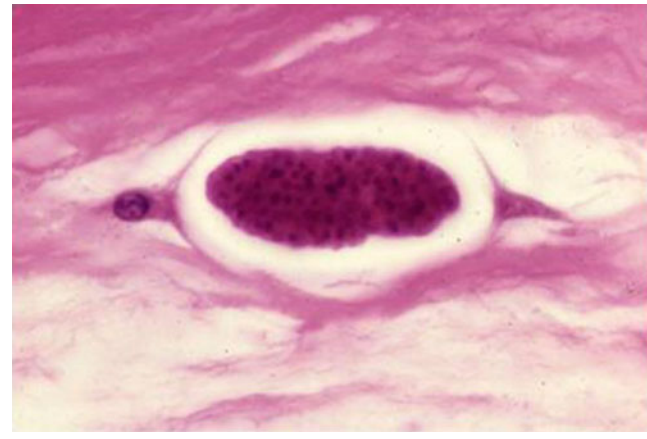

Fig. 3 Mild acute chorionitis associated with *Toxoplasma* infection. A *Toxoplasma* cyst was found in chorionic plate of the placental disk (H and E, ×1,000)

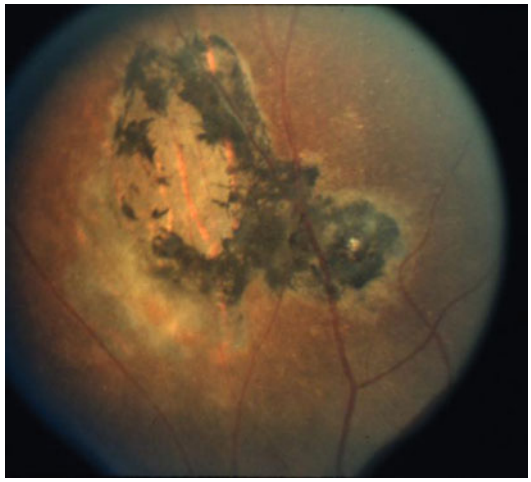

Fig. 4 A small area of resolving acute toxoplasmic retinochoroiditis adjacent to a larger area of healed congenital toxoplasmosis scar

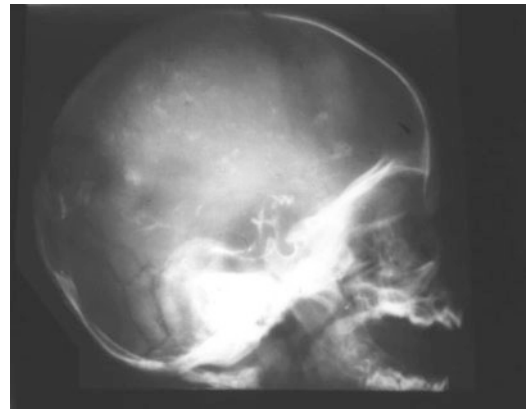

Fig. 6 Diffusely scattered punctate cerebral calcifications secondary to congenitally acquired toxoplasmosis

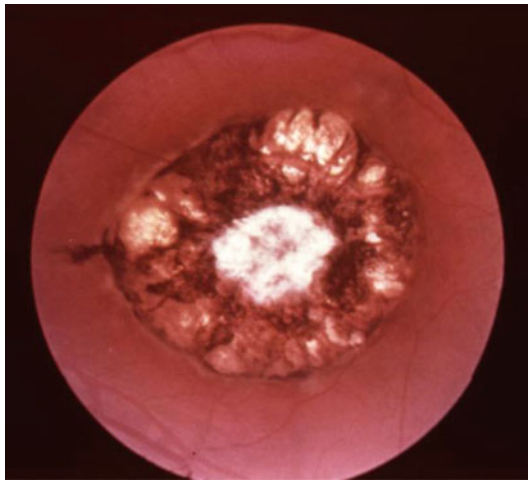

Fig. 5 Satellite lesions of acute exacerbation of toxoplasmic retinochoroiditis adjacent to a larger scar of healed congenital ocular toxoplasmosis

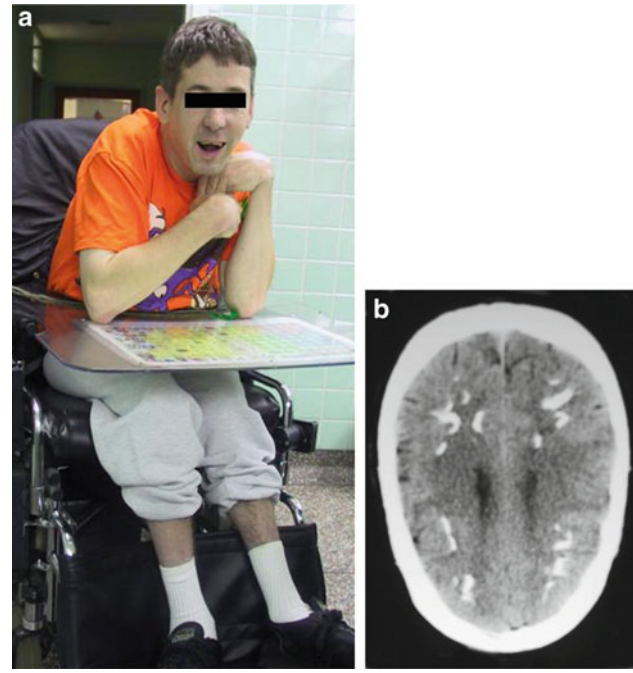

Fig. 7 (**a**, **b**) An adult with congenital toxoplasmosis who had mental retardation, seizures, and chorioretinitis. CT of the brain showed scattered multiple foci of intracerebral calcifications

Conjoined Twins

Contents

Conjoined twins are incompletely separated monozygotic twins. They have long fascinated both medical profession and lay public. Such events are rare and occur in 1/50,000–1/100,000 births and 1 in 400 sets of monozygotic twins. Over 60% succumb in utero or are stillborn (Spitz 2005). It is a complication of monochorionic twinning at 13–15 days after conception.

Synonyms and Related Disorders

Cephalopagus; Craniopagus; Dicephalus; Diprosopus; Epigastrius; Fetus in fetu; Ischiopagus; Omphalopagus; Pygopagus; Rachipagus; Thoracopagus

Genetics/Basic Defects

1. Conjoined twins
    1. Rare variants of monozygotic, monochorionic twins
    2. Two theories of conjoined twin formation
        1. Resulting from the secondary union of two originally separate monovular embryonic disks
        2. Resulting from an incomplete separation of the inner cell mass at around 13–15 days of gestation of the monovular twins
    3. Twins conjoining at any site from the cranium downward to the sacrococcygeal region
    4. Approximately 60% stillborn
    5. Female predominance (Edmonds & Layde 1982): approximately 3:1 female-to-male ratio
2. Embryologic classification of conjoined twins (Zimmermann 1967; Benirschke et al. 1978; Spencer 1996; Spencer 2000a, b; McHugh et al. 2006; Winkler et al. 2008): Greek word "pagus" added to denote fixing to union site
    1. Ventral union (87%)
        1. Rostral (48%)
            1. Cephalopagus (11%): fusion from top of the head to umbilicus; each twin having two arms and legs; separate lower abdomen and pelvis
            2. Thoracopagus (20–40 %): position face to face, with fused thoraces and with a shared heart or single interatrial vessel
            3. Omphalopagus (18–33 %): similar fusion to thoracopagus

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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without shared heart or interatrial vessel
2. Caudal (11%) (ischiopagus): a large, conjoined pelvis, more commonly joined end to end; can be face to face with a conjoined abdomen; always shared external genitalia and anus

2. Dorsal union (13%)
1. Craniopagus (5%): joined by any portion of the skull except the face and foramen magnum, shared cranium, meninges, and, occasionally, the brain
2. Rachipagus (2%): dorsal fusion above the sacrum
3. Pygopagus (6%): fused sacrococcygeal and perineal regions, typically with shared anus but separate rectums; shared spinal cord

3. Lateral union (28%): parapagus (side-to-side connection with shared pelvis and variable cephalad sharing), defined as follows:
1. Dithoracic parapagus (separate thoraces and heads)
2. Dicephalic parapagus (separate head with fused thoraces)
3. Diprosopus parapagus (two faces on the same side of a single head)

3. Anatomic classifications of conjoined twins, based on how the body axes of the twins are mutually oriented in the embryonic disk
1. Notochordal axes facing each other
1. Ventro-ventral
1. Thoracopagus
2. Xiphopagus
3. Omphalopagus
2. Cranial ventro-ventral (cephalothoracopagus)
3. Caudal ventro-ventral (ischiopagus)
4. Cranial end to end (craniopagus)
5. Caudal end to end (pygopagus)

2. Notochordal axes facing side by side
1. Dicephalus
2. Diprosopus

4. Anatomic classifications of conjoined twins, based on how the subsequent events of migration, growth, and body folding result in different types of conjoined twins
1. Dipygus
2. Fetus in fetu
1. A fetiform mass located within a basically normal fetus (Spencer 2001)
2. Inclusion of a monozygotic diamniotic twin within the bearer being the best explanation

5. Duplicitas symmetros (symmetrical conjoined twins resulting from incomplete fission of the uniovum) (Gilbert-Barness et al. 2003)
1. Terata katadidyma (twins joined at the lower part of the body and double above)
1. Dicephalus (twins with two separate heads and necks side by side with one body; lateral conjugation)
2. Diprosopus (twins with two faces side by side, one head, and one body)
3. Ischiopagus (twins joined by the inferior margins of the coccyx and sacrum with two completely separate spinal columns; caudal conjugation)
4. Pygopagus (twins joined by posterior surfaces of the coccyx and sacrum, back to back; posterior conjugation)
5. Craniothoracopagus
6. Ileothoracopagus

2. Terata anadidyma (twins joined at the upper part of the body and double below)
1. Craniopagus (twins joined at the top of cranial vaults; cephalic conjugation)
2. Dipygus (twins with one head, one thorax, one abdomen, and double pelvis with or without two sets of external genitalia and up to four legs; lateral conjugation)
3. Syncephalus (twins joined by the face; the faces turning laterally)

3. Terata anakatadidyma (twins joined by the midportion of the body)
1. Omphalopagus (twins joined from the umbilicus to xiphoid cartilage; anterior conjugation)
2. Xiphopagus (twins joined at xiphoid process)

3. Rachipagus (twins joined by the vertebral column; back to back)
4. Thoracopagus (twins joined at the chest wall; anterior conjugation)

6. Duplicatas asymmetros (asymmetrical conjoined twins resulting from unequal and incomplete fission of the uniovum and unequal placental circulation to twins)
   1. Cephalic conjugation
      1. Craniopagus parasiticus
      2. Janus parasiticus
      3. Epignathus heteropagus
   2. Anterior conjugation
      1. Thoracopagus parasiticus
      2. Epigastrius
   3. Posterior conjugation
      1. Ischiopagus parasiticus
      2. Pygopagus parasiticus
      3. Sacral parasiticus (Chou et al. 2001)

Clinical Features

1. Thoracopagus twins
   1. Represents 40% of conjoined twins
   2. Conjoined at the thoracic region
   3. Face to face
   4. Associated congenital heart defects
      1. Present in 75% of cases
      2. Presence of varying degree of pericardial sac fusion
      3. A conjoined heart with two ventricles and a varying number of atria (most frequent abnormality)
      4. Ventricular septal defect in virtually all patients
2. Omphalopagus twins (fused umbilical region)/xiphopagus twins (fused xiphoid process of the sternum) (Harper et al. 1980; Wilcox et al. 1998)
   1. Constitutes one third of all types of conjoined twins
   2. The most readily separable conjoined twins since their union perhaps involving only the skin and portions of the liver, occasionally including portions of the sternum
   3. Most omphalopagus twins joined by a skin bridge that contains the liver and bowel
   4. Conjoined liver in 81%
   5. Conjoined sternal cartilage in 26%
   6. Conjoined diaphragm in 17%
   7. Conjoined genitourinary tract in 3%
   8. Malformations of the abdominal wall (usually omphalocele) in at least one of the twins in 33%
   9. Congenital heart defects in at least one of the twins in 25%
      1. Ventricular septal defects
      2. Tetralogy of Fallot
   10. Concordant congenital heart defects in only 1 out of 9 sets of twins
3. Pygopagus twins
   1. Constitutes 19% of conjoined twins
   2. Conjoined at sacrum (buttocks and lower spine)
   3. Most commonly back to back (face away from each other)
   4. May share part of the sacral spinal canal
   5. May share common rectum and anus
   6. Often with fused genitalia
4. Ischiopagus twins
   1. Constitutes 6% of conjoined twins
   2. Conjoined back to back at the coccyx
   3. Often with a common large pelvic ring formed by the union of the two pelvic girdles
   4. May have four legs (ischiopagus tetrapus)
   5. May have three legs (ischiopagus tripus)
   6. Frequently share the lower gastrointestinal tract
      1. The intestines joined at the terminal ileum
      2. Emptying into a single colon
   7. May have a single bladder and urethra
   8. Displaced anus
   9. Common vaginal anomalies
   10. Common rectovaginal communications
5. Craniopagus twins (fused at the cranial vault) (2%)
   1. Classification according to the area of junction
      1. Frontal craniopagus

2. Parietal craniopagus (most common)
3. Temporal craniopagus
4. Occipital craniopagus

2. Classification based on surgical and prognostic purposes
    1. Partial type (brains separated by the bone or dura with each brain having separate leptomeninges)
    2. Complete type (presence of cerebral connection)

6. Rachipagus twins (fused upper spinal column; back to back)
7. Pygodidymus twins (fused cephalothoracic region; duplicate pelvi and lower extremities)
8. Pygopagus twins/pygomelus twins (joined back to back at the sacrum; additional limb or limbs at or near the buttock)
9. Iniopagus twins/craniopagus occipitalis twins (fused head, at parasitic occipital region)
10. Epicomus twins/craniopagus parasiticus twins (smaller, parasitic twin joined to larger autosite at occiput)
11. Monocephalus twins (single head with two bodies)
12. Diprosopus twins (single body with two faces)
13. Dicephalus twins (symmetric body with two heads)
14. Dipygus parasiticus twins (the head and thorax completely merged; the pelvis and lower extremities duplicated)
15. Cephalopagus conjoined twins
    1. The rarest type of conjoined twins
    2. Fused from the top of the head to the umbilicus
    3. Presence of two faces on the opposite sides of the head with one face usually being rudimentary
    4. Separation of the lower abdomen
    5. With four arms and four legs
    6. Prognosis dismal dependent on the following factors
        1. Presence of associated anomalies
        2. Degree of fusion of the intracranial, intrathoracic, and/or intra-abdominal structures
        3. Extent of venous connections
16. Epigastric heteropagus twins (Petit et al. 2001)
    1. A rare type of conjoined twinning
    2. Resulting from an ischemic atrophy of one fetus at an early stage of gestation
    3. The pelvis and lower limbs of the ischemic fetus (incomplete parasitic twin; heteropagus) attached to the epigastrium of the well-developed fetus (the autosite)
17. Fetus in fetu
    1. The parasites embodied in the autosite, usually within cranial, thoracic, and abdominal cavities during the developmental process of the asymmetrical conjoined twins
    2. Most likely arise from inclusion of a monochorionic, diamniotic, monozygotic twin within the bearer due to anastomoses of vitelline circulation (Nastanski and Downey 2001)
18. Prognosis
    1. A high mortality rate.
        1. Nearly 40% are stillborn.
        2. One third die within 24 h of birth.
        3. No prospect of survival when complex cardiac union is present.
    2. Causes of death
        1. Severely abnormal conjoined heart
        2. Pulmonary hypoplasia due to distortion of fused thoracic cages
19. Examples of historically famous conjoined twins (Guttmacher 1967; Sills et al. 2001; Gilbert-Barness et al. 2003; Spitz 2005)
    1. So-called Biddenden Maids (1100–1134) in England
        1. Probably pygopagus twins
        2. Their famous image imprinted on the "cakes"
        3. Walks with their arms around each other
        4. Lived together for 34 years and died within 6 h
    2. Chang and Eng Bunker (1811–1874) from Bangkok and settled in the USA ("Siamese twins")

1. Born on a riverboat in Siam
2. Joined at the xiphisternum by a short bank that stretched so they were eventually able to stand side by side
3. Taken by Hunter, a traveling Scottish merchant, to the USA where they were exhibited by the showman
4. Later married to twin sisters
5. Fathered 22 children
6. Lived together for 63 years and one dying shortly from other twin

3. Blažek sisters (1878–1922) from Bohemia
   1. Two heads
   2. Four arms
   3. Four legs
   4. Partially fused torso
   5. Combined reproductive organs
   6. Delivered an infant through a single vagina but the gestation occurring in the uterus of one of the twins

Diagnostic Investigations

1. Prenatal echocardiography
   1. Presence and extent of cardiac conjunction
   2. Associated cardiac defects
2. Prenatal radiography
3. Prenatal ultrasonography (including transvaginal and three-dimensional sonography) (Maymon et al. 1998), (the surface-rendered image of the conjoined twin and its demonstration on an axially rotating cine loop facilitates explanation of the precise nature of the abnormalities, especially in the case of cephalothoracopagus conjoining)
4. CAT scan and MRI of the abdomen and the chest
   1. Anatomy of the heart
   2. Anatomy of the livers
   3. Anatomy of the genitourinary systems
   4. CT scan allows prospective diagnosis of fetus in fetu (Awashi et al. 2001)
5. Gastrointestinal contrast studies to demonstrate the presence and level of conjunction of the intestinal tract
6. Ventrally fused conjoined twins (Gore et al. 1982)
   1. Prenatal radiography/ultrasonography
      1. Fetal body parts on the same level
      2. Constant relative fetal position
      3. Fetal extremities in unusual proximity
      4. Face-to-face fetal position
      5. Bibreech, less commonly bicephalic presentation
      6. Hyperextension of one or both cervical spines
   2. Prenatal ultrasonography
      1. Nonseparable continuous external skin contour
      2. Single heart sound by Doppler
      3. Solitary large liver and heart
      4. Multiple shared omenta
      5. Solitary umbilical cord with >3 vessels
7. Cephalothoracopagus (Chen et al. 1997; Kuroda et al. 2000)
   1. Prenatal radiographic criteria
      1. Both fetal heads at the same level
      2. Backward fusion of the cervical spines
      3. A narrow space between lower cervical and upper thoracic spines
      4. No change in fetal relative positions after maternal movement
   2. Prenatal sonographic criteria
      1. Fusion of the skulls, face, thorax, and upper abdomen
      2. Fetal body parts at the same level
      3. Constant relative fetal motion
      4. Fetal extremities in unusual positions
      5. Breech position
      6. Hyperextension of both cervical spines
      7. Nonseparable external skin contour
      8. A solitary umbilical cord with multiple vessels
      9. Polyhydramnios
      10. Two actively beating hearts
      11. Two sets of pelvi, limbs, and spine

Genetic Counseling

1. Recurrence risk
    1. Patients sib: not higher according to family study
    2. Patient's offspring: report of delivery of a healthy male infant to the pygopagus Blažek sisters
2. Prenatal diagnosis: imaging techniques utilized in prenatal diagnosis of conjoined twins (Baken et al. 2013)
    1. Conventional 2D ultrasound: sufficient in most cases
    2. 3D ultrasound and Doppler ultrasound: to gain extra and more precise information in an efficient way
    3. Computed tomography (CT) scan
    4. Magnetic resonance imaging (MRI)
    5. 3D virtual embryoscopy: provide additional diagnostic information in evaluating complex anatomical structures, especially when depth perception is needed; may contribute to earlier, more appropriate counseling and management
3. Management
    1. Early prenatal diagnosis: highly desirable, given the extremely poor prognosis of some types of conjoined twins (Benirschke 1998)
    2. Psychological and prognosis counseling
    3. Accurate preoperative investigation
    4. A team approach
    5. Previous experience
    6. Meticulous operative and postoperative management
    7. Substantial mortality rate related to the underlying conditions
    8. High likelihood of success if major associated anomalies are absent
    9. Options of obstetrical management
        1. Continuing the vaginal delivery and delivering the twins intact
        2. Delivering the twins vaginally after intrauterine separation or a destructive procedure
        3. Cesarean section and delivering the twins intact
        4. Cesarean section and delivering the twins after intrauterine separation or destruction
    10. Anesthetic management for separating operations (Keats et al. 1967)
        1. Extensive cross circulation
            1. Through a liver bridge
            2. Common cerebral venous sinus
        2. Mechanical problems
            1. One anesthetist required for each infant
            2. A third anesthetist to look after intravenous infusions and monitor
            3. A fourth anesthetist to look after massive blood loss, circulatory collapse, or other catastrophic occurrence
        3. Anticipating complex congenital heart defects that was not diagnosed preoperatively
    11. Four separate time frames of management (Spitz & Kiely 2002; Spitz 2005)
        1. Prenatal
            1. Define the anatomy of the union once the diagnosis of conjoined twins is suspected.
            2. Termination can be considered in the event of complex cardiac fusion in thoracopagus twins or extensive cerebral fusion in craniopagus twins: required detailed echocardiography and accurate ultrasonography complemented as necessary with MRI scanning.
            3. Obtain informed decision as to either terminate or proceed with the pregnancy.
            4. Delivery by Cesarean section at 36–38 weeks of gestation (Rudolph et al. 1967).
        2. Nonoperative treatment
            1. In the presence of complex cardiac fusion

2. Where a severe unacceptable deformity would follow separation

3. Emergency separation
    1. When one twin is dead or dying, threatening the survival of the remaining twin
    2. Presence of a life-threatening correctable congenital abnormality (e.g., intestinal atresia, malrotation with or without volvulus, ruptured omphalocele, or anorectal agenesis)
    3. Emergency separation carrying a significantly higher mortality rate compared with elective procedures
4. Elective separation
    1. Normally takes place between 2 and 4 months
    2. Allows time to stabilize, thrive, and carry out detailed investigation to define the nature and the extent of union, and detailed planning of the operative procedure with all members of the operating team
    3. Survival rate: approaches 80%

12. Bioethics of separating conjoined twins (Lee et al. 2011)
    1. Informed consent: is it ethical to impose a surgical procedure of unknown risk, where the goal is to improve quality of life of children who cannot provide informed consent and who may potentially not want the separation?
    2. Medical need is classically determined by the following criteria: likelihood of benefitting the patient, urgency of need, change in quality of life, and duration of benefit.
    3. To achieve an optimal physician-patient relationship, the health-care provider should be an advocate for his or her patient.

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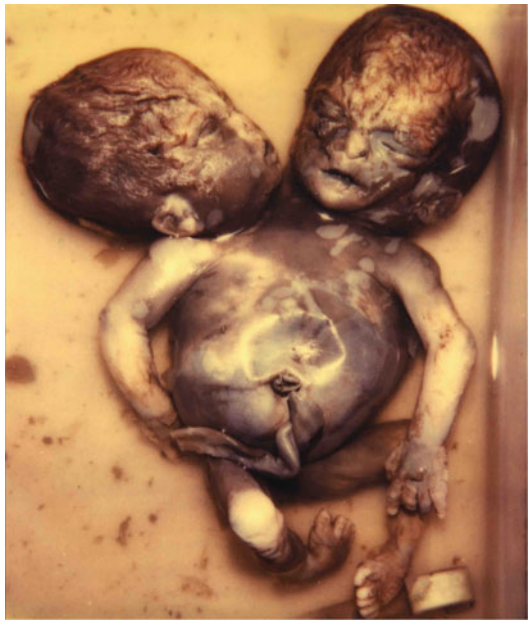

Fig. 1 A stillbirth with dicephalic conjoined twins

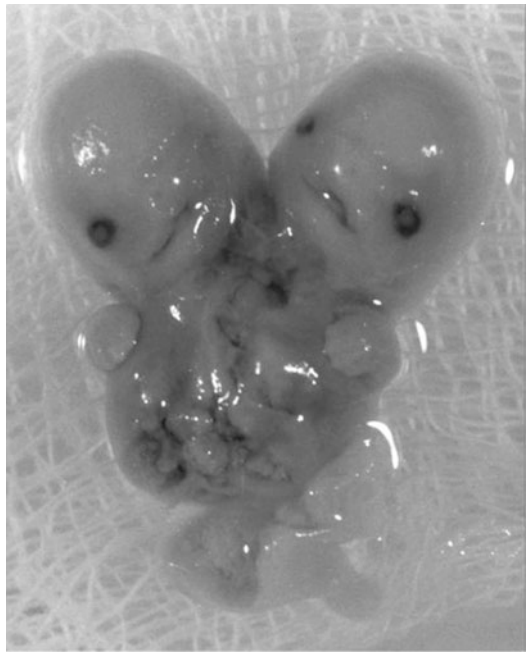

Fig. 2 A set of dicephalic conjoined twin embryos at 6–7 weeks of gestation

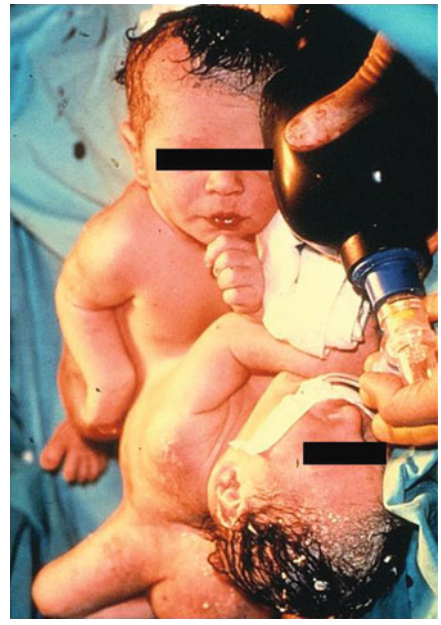

Fig. 3 The conjoined twins are joined at the level of abdomen from umbilicus to the xiphoid cartilage (xiphoomphalopagus). This type of conjoined twins is the one most amenable to successful surgical correction because the incidence of complex anatomical anomalies is low. Left twin was successfully separated from the right twin who succumbed shortly after surgery to multiple congenital anomalies including exstrophy of the cloaca, left Bochdalek hernia, hypoplastic kidney, hypoplastic lungs, imperforate anus, and a large sacral meningomyelocele

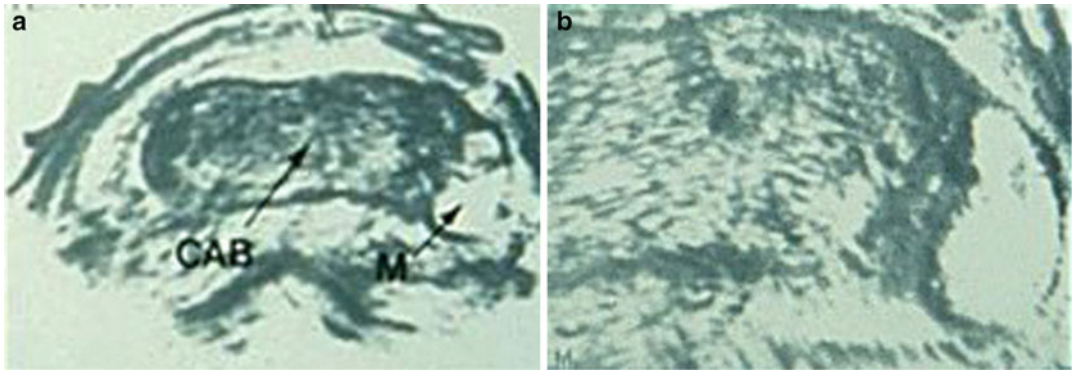

Fig. 4 Prenatal ultrasound (**a**) detected the above conjoined twins with a shared liver (CAB) and separate hearts, stomach, pelvis, and extremities. One fetus was noted to have a meningomyelocele (M). The magnified view (**b**) shows part of the shared liver and meningomyelocele

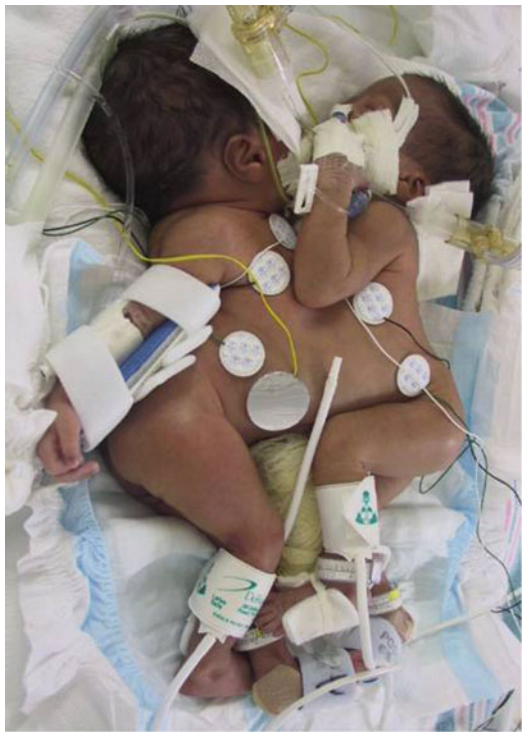

Fig. 5 These twins are thoraco-omphalopagus, connected at the thorax and upper abdomen. The heart showed complex anomalies with a common atrium and a single ventricle. Therefore, separation of the twins was not attempted

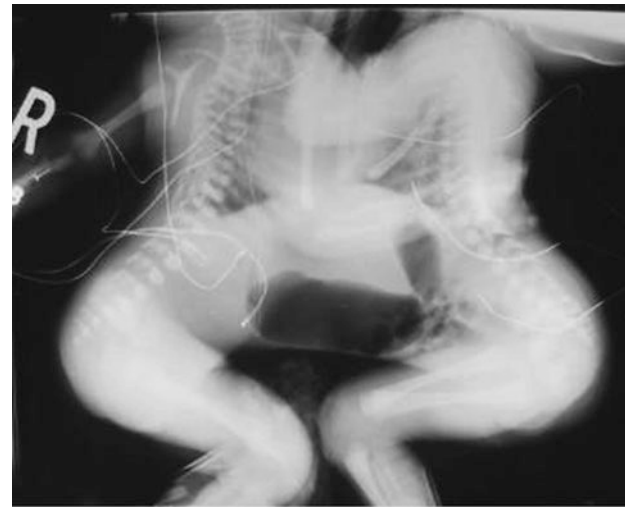

Fig. 6 The radiograph of the twins in Fig. 3 showing the connection at the thorax and the upper abdomen

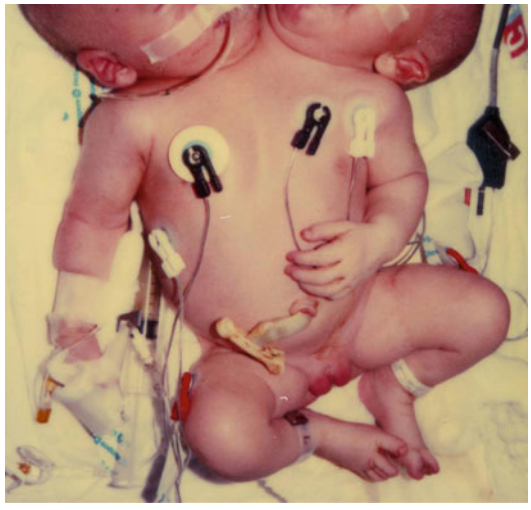

Fig. 7 Dicephalic conjoined twins. Two separate heads, two separate necks, and only one body are evident. The twins shared a common pericardium with complex cardiac anomalies, a common aorta at the level of iliac arteries, a common small intestine and other GI tract distally, a common bladder and urethra drained from a single kidney from each twin, and single normal female genitalia with normally placed fallopian tubes and ovaries. Surgical separation of the twins was deemed impossible and was not attempted

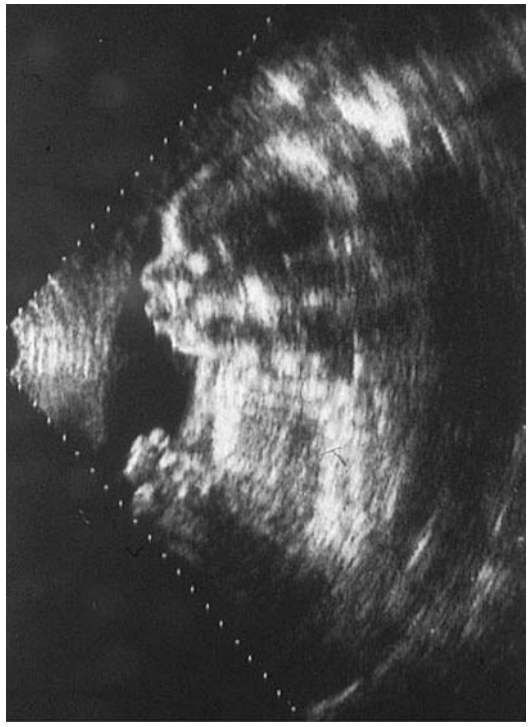

Fig. 8 Prenatal ultrasound study showed lateral view of the dicephalic twins with two heads side by side, one trunk with two overlapping vertebral columns, and two *upper* extremities

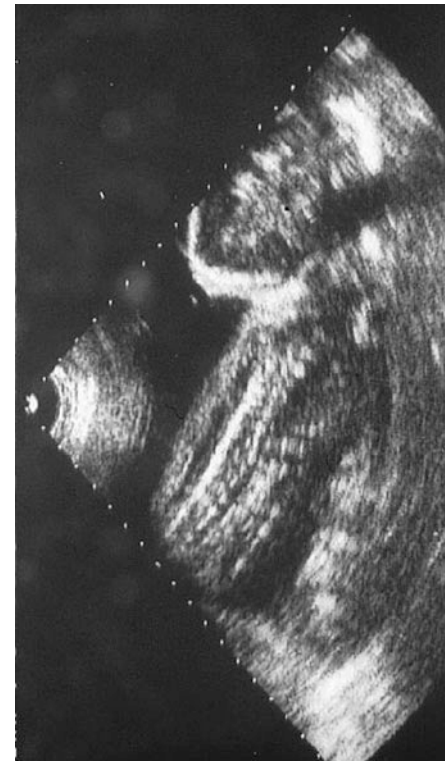

Fig. 9 Prenatal ultrasound study showed two separate vertebral columns

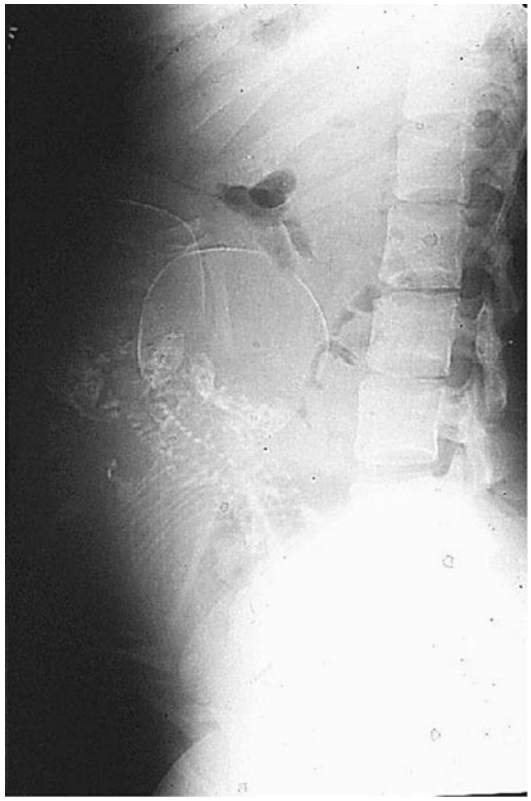

Fig. 10 Prenatal radiographic study showed dicephalic twins with two separate heads and two separate vertebral columns

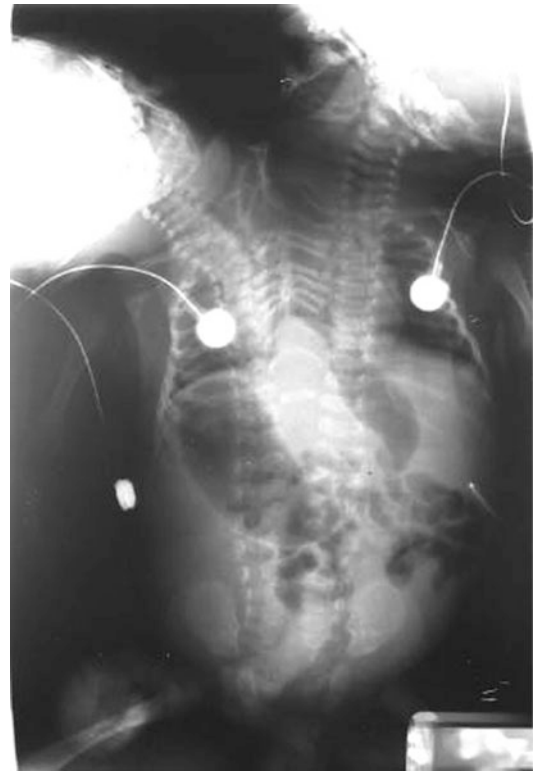

Fig. 11 The postnatal radiograph of the above conjoined twins showing separate heads, separate vertebrae, and separate *upper* GI tract. There is one pericardium sac and a fused liver

Corpus Callosum Agenesis/Dysgenesis

Contents

The corpus callosum is an interhemispheric structure that permits the integration of motor, sensory, and cognitive performance between the two cerebral hemispheres. Agenesis/dysgenesis of the corpus callosum is one among the most common brain developmental malformations with a wide spectrum of associated clinical and pathologic abnormalities. The prevalence and clinical significance are uncertain. It is estimated to be 0.3–0.7% in the general population and 2–3% in the developmentally disabled (Jeret et al. 1985).

Synonyms and Related Disorders

Agenesis of corpus callosum; Dysgenesis of corpus callosum

Genetics/Basic Defects

1. Markedly heterogeneous etiology of agenesis/dysgenesis of the corpus callosum (Vergani et al. 1994; Dobyns 1996; Palmer and Mowat 2014; Al-Hashim et al. 2015)
    1. Sporadic in most cases
    2. Environmental factors
        1. Antenatal alcohol exposure: associated with microcephaly, a general reduction in white matter
        2. Volume and hypoplasia of the corpus callosum (most severe in the splenium) as well as partial and complete agenesis of corpus callosum
        3. Maternal antenatal infections: e.g., cytomegalovirus, toxoplasmosis, rubella, and influenza
        4. Maternal phenylketonuria: rare, especially since neonatal screening introduced in many countries since 1960s
        5. Maternal diabetes
        6. Vascular/hypoxic insults: rare
    3. A multifactorial trait
    4. As a part of autosomal dominant syndrome
        1. Agenesis/dysgenesis of the corpus callosum
        2. Apert syndrome
        3. Basal cell nevus syndrome
        4. Miller-Dieker syndrome

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_58

5. Rubinstein-Taybi syndrome
6. Tuberous sclerosis

5. As a part of autosomal recessive syndrome
    1. Agenesis/dysgenesis of the corpus callosum
    2. Agenesis/dysgenesis of the corpus callosum with thrombocytopenia
    3. Acrocallosal syndrome
    4. Andermann syndrome (Casaubon et al. 1996)
        1. Agenesis/dysgenesis of the corpus callosum with peripheral neuropathy
        2. Mapping of the gene to a 5-cM region in chromosome 15q13-15
    5. Cerebro-oculo-facio-skeletal (COFS) syndrome
    6. Cogan syndrome (ocular motor apraxia)
    7. Craniotelencephalic dysplasia
    8. Dincsoy syndrome
        1. Multiple midline malformations
        2. Limb abnormalities
        3. Hypopituitarism
    9. Fukuyama congenital muscular dystrophy
    10. Hydrolethalis syndrome
    11. Joubert syndrome (cerebellar vermis agenesis)
    12. Leprechaunism
    13. Lissencephaly syndrome
    14. Lowry-Wood syndrome
        1. Epiphyseal dysplasia
        2. Microcephaly
        3. Nystagmus
    15. Meckel-Gruber syndrome
    16. Microcephalic osteodysplastic primordial dwarfism type I/III
    17. Neu-Laxova syndrome
    18. Opitz G syndrome
    19. Peters plus syndrome
        1. Peters anomaly
        2. Short-limb dwarfism
    20. Shapiro syndrome: a rare condition of spontaneous periodic hypothermia, corpus callosum agenesis, and hyperhidrosis which can occur at any age (Tambasco et al. 2014)
    21. Smith-Lemli-Opitz syndrome
    22. Toriello-Carey syndrome
        1. Agenesis/dysgenesis of the corpus callosum
        2. Facial anomalies
        3. Robin sequence
    23. Vici syndrome
        1. Agenesis/dysgenesis of the corpus callosum
        2. Immunodeficiency
        3. Cleft lip/palate
        4. Cataract
        5. Hypopigmentation
    24. Walker-Warburg syndrome
        1. Hydrocephalus
        2. Agyria
        3. Retinal dysplasia
    25. Warburg micro syndrome
        1. Microcephaly
        2. Microphthalmia
        3. Cerebral malformations
        4. Other anomalies
    26. Hypoplastic corpus callosum, microcephaly, severe mental retardation, preauricular skin tag, camptodactyly, growth retardation, and recurrent bronchopneumonia (Da-Silva et al. 1988)
6. As a part of X-linked syndrome
    1. Agenesis/dysgenesis of the corpus callosum
    2. Agenesis/dysgenesis of the corpus callosum with Hirschsprung disease
    3. Agenesis/dysgenesis of the corpus callosum with hypohidrotic ectodermal dysplasia
    4. Aicardi syndrome (retinovertebral anomalies in females)
    5. ATR-X syndrome (X-linked alpha thalassemia mental retardation syndrome)
    6. Craniofrontonasal syndrome
    7. Curatolo syndrome
        1. Agenesis/dysgenesis of the corpus callosum
        2. Chorioretinal abnormality
    8. FG (Opitz-Kaveggia) syndrome
        1. Mental retardation
        2. Large head
        3. Imperforate anus

4. Congenital hypotonia
5. Partial agenesis/dysgenesis of the corpus callosum

9. HSAS syndrome (*h*ydrocephalus due to congenital *s*tenosis of *a*queduct of *S*ylvius)
10. Lenz dysplasia
    1. Microphthalmia/anophthalmia
    2. Associated anomalies
11. Lujan-Fryns syndrome
    1. X-linked mental retardation
    2. Marfanoid habitus
12. MASA syndrome
    1. *M*ental retardation
    2. *A*phasia
    3. *S*huffling gait
    4. *A*dducted thumbs
13. MLS syndrome
    1. *M*icrophthalmia
    2. *L*inear *s*kin defects
14. Opitz G syndrome
15. Oral-facial-digital syndrome I
16. Proud syndrome
    1. X-linked syndrome
    2. Seizures
    3. Acquired micrencephaly
    4. Agenesis/dysgenesis of the corpus callosum
17. XLIS syndrome (X-linked lissencephaly)

7. As a part of unknown-genesis syndrome
    1. Calloso-genital dysplasia
    2. Delleman (oculocerebrocutaneous) syndrome
    3. Frontonasal dysplasia
    4. Opitz C trigonocephaly syndrome
    5. Sebaceous nevus syndrome
8. As a part of metabolic disorders
    1. Adenylosuccinase deficiency
    2. Adipsic hypernatremia
    3. β-Hydroxyisobutyryl coenzyme A deacyclase deficiency
    4. Desmosterolosis
    5. Fumarase deficiency
    6. Glutaric aciduria type II
    7. Histidinemia
    8. Hurler syndrome
    9. Leigh syndrome
    10. Menkes syndrome
    11. Neonatal adrenoleukodystrophy
    12. Nonketotic hyperglycinemia
    13. Pyruvate dehydrogenase deficiency
    14. Smith-Lemli-Opitz syndrome
    15. Zellweger syndrome
9. Associated chromosome abnormalities (Serur et al. 1988)
    1. Trisomy 18
    2. Trisomy 13
    3. Trisomy 8 mosaicism
    4. Trisomy 21
    5. Trisomy 22
    6. Other trisomies
    7. Deletions
    8. Translocations
    9. Duplications
    10. Variable rearrangements and submicroscopic copy number variants
10. Agenesis of the corpus callosum with interhemispheric cyst: a heterogeneous group of disorders that have in common callosal agenesis and extraparenchymal cysts, both of which are among the commonest CNS malformations (Barkovich et al. 2001)
11. Incidental finding in normal individuals (isolated dysgenesis of the corpus callosum)

2. Embryogenesis of the corpus callosum
    1. Development of the corpus callosum
        1. A late event in cerebral ontogenesis
        2. Taking place between 12 and 18 weeks of gestation
    2. An important brain commissure connecting the cerebral hemispheres (Achiron and Achiron 2001)
    3. Essential for efficient cognitive function (Achiron and Achiron 2001)
    4. Failure of development of the commissural fibers connecting the cerebral hemispheres produces dysgenesis or agenesis of the corpus callosum
    5. Diagnosis of agenesis: a challenge even for expert sonologists, particularly prior to 20 weeks of gestation

3. Types of agenesis
   1. Complete agenesis: commonly regarded as a malformation deriving from faulty embryogenesis
   2. Type I agenesis
      1. Not associated with other disorders
      2. Usually absent or associated with mild neurologic manifestations
   3. Type II agenesis
      1. Associated with other migrational, genetic, and chromosomal disorders
      2. Usually associated with severe neurologic manifestations
   4. Partial agenesis
      1. Referred to as dysgenesis
      2. Either a true malformation or a disruptive event occurring at any time during pregnancy
      3. Missing caudad portion (splenium and body) to varying degrees
4. Agenesis/dysgenesis of the corpus callosum (Da-Silva 1988)
   1. Without other associated brain anomalies
   2. Frequently associated with other brain anomalies
      1. Defects of septum pellucidum and fornix
      2. Hydrocephalus
      3. Dandy-Walker malformation
      4. Interhemispheric cyst
      5. Holoprosencephaly
      6. Porencephaly
      7. Polymicrogyria
      8. Macrogyria
      9. Cortical heterotopia and atrophy
      10. Lipoma
      11. Encephalocele
      12. Hypoplasia of cerebellum
   3. Frequently associated other anatomical anomalies
      1. Congenital heart defects
      2. Costovertebral defects
      3. Gastrointestinal anomalies
      4. Genitourinary anomalies

Clinical Features

1. Craniofacial abnormalities
   1. Microcephaly
   2. Macrocephaly
2. Developmental anomalies
   1. Nonspecific mental retardation
   2. Developmental delay
   3. Learning disabilities
   4. Behavioral disorder
   5. Mental retardation
   6. Failure to thrive
3. Infantile spasms/seizures (Lacey 1985)
4. Signs and symptoms related to type I and type II agenesis
   1. Type I
      1. Variable intelligence: normal to mild or moderate mental retardation
      2. Seizure disorder
      3. Impaired visual, motor, and/or bimanual coordination
      4. Mild impairment of crossed tactile localization and skills requiring matching of visual patterns
   2. Type II
      1. Mental retardation
      2. Seizures
      3. Hydrocephaly
      4. Microcephaly
      5. Hemiparesis
      6. Diplegia
      7. Spasticity
      8. Failure to thrive

Diagnostic Investigations

1. Psychometric tests (Finlay et al. 2000)
   1. Difficulties in motor coordination
   2. Difficulties in interhemispheric transfer of tactile information
   3. Difficulties in some areas of memory
   4. A marked difference in verbal IQ and performance IQ in children
2. EEG for seizure activities

3. CT and/or ultrasound of the brain (Gupta and Lilford 1995)
    1. Absence of the corpus callosum
    2. Absence of septum pellucidum
    3. Increased separation of the lateral ventricles
    4. Marked separation of the slit-like anterior horns of the lateral ventricles and dilatation of the occipital horns creating the typical "rabbit's ear" or "tear drop" appearance
    5. Upward displacement of the third ventricle
    6. Evidence of other migration disorders
4. Coronal radiographs showing a pathognomonic bat-wing ventricular pattern
5. Karyotyping for underlying chromosomal disorder
6. Metabolic studies for underlying inborn error of metabolism
7. Exome sequencing: Exome sequencing identifies recessive *CDK5RAP2* variants in patients with isolated agenesis of corpus callosum (Jouan et al. 2015)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: depending on the etiology and the mode of inheritance
        1. Isolated agenesis/dysgenesis of the corpus callosum
            1. Recurrence risk: 2–3% if no family history (Palmer and Mowat 2014)
            2. In isolated cases of ACC, long-term neurodevelopmental outcome is expected to be normal in approximately 75% of cases, meaning that continuation of pregnancy can be preferred (Pilu et al. 1993; Özyüncü et al. 2014)
        2. Environmental factor: recurrence risk not increased by avoiding the environmental factor
        3. Autosomal recessive inheritance: 25% of siblings affected, 50% siblings carriers, and 25% of siblings normal
        4. Autosomal dominant inheritance: recurrence risk not increased unless a parent is affected in which case the recurrence risk is 50%
        5. X-linked recessive inheritance
            1. Carrier mother (50% of brothers affected, 50% of sisters carriers)
            2. Affected father (all brothers normal, all sisters carriers)
        6. X-linked dominant inheritance
            1. Affected mother (50% of brothers and sisters affected)
            2. Affected father (all brothers normal, all sisters affected)
        7. Chromosomal disorder: recurrence risk increased, especially if a parent carries a balanced translocation
    2. Patient's offspring
        1. Environmental factor: recurrence risk not increased by avoiding the environmental factor
        2. Autosomal recessive inheritance: recurrence risk not increased unless the spouse is also a carrier, in which case the recurrence risk is 50%
        3. Autosomal dominant inheritance: 50%
        4. X-linked recessive inheritance
            1. Carrier female (50% of sons affected, 50% of daughters carriers)
            2. Affected male (all sons normal, all daughters carriers)
        5. X-linked dominant inheritance
            1. Affected female (50% of sons and daughters affected)
            2. Affected male (all sons normal, all daughters affected)
        6. Chromosomal disorder: recurrence risk increased, especially if a parent carries a balanced translocation
2. Prenatal diagnosis
    1. Ultrasonography (Pilu et al. 1993; D'Ercole et al. 1998)
        1. Prenatal detection of the agenesis of the corpus callosum usually not possible

before 22 weeks of gestation (Bennett et al. 1996)
2. Direct demonstration of the absence or partial absence of the corpus callosum
3. Failure to visualize the cavum septum pellucidum
4. Separated lateral ventricles
5. Upward displacement of third ventricle
6. Increased interhemispheric fissure
7. Radial disposition of the sulci on the internal aspects of the hemispheres
8. Third ventricle lying between widely separated lateral ventricles due to absent corpus callosum
9. Lateral ventricles more parallel to the midline than usual
10. A cyst arising from the superior aspect of the third ventricle communicating with the lateral ventricles
11. Vertical orientation of the gyri with agenesis instead of normal horizontal alignment
12. Colpocephaly (locally dilated occipital horns of the lateral ventricle) forming an appearance on axial views similar to bulls' horns
13. Absence of pericallosal artery
14. Up to 50% of cases with other associated anatomic defects
15. Variable developmental outcome on prenatal detection of an isolated agenesis of the corpus callosum

2. MRI (D'Ercole et al. 1998)
   1. Allows more detailed visualization of the fetal brain than ultrasonography
   2. Constitutes a useful additional procedure after ultrasonographic diagnosis or suspicion of corpus callosum agenesis
3. Amniocentesis recommended for karyotyping as there is 10–20% risk of aneuploidy associated with the agenesis of the corpus callosum
4. Cytogenetic findings (Alby et al. 2016)
   1. CNVp (copy number variation considered as pathogenic) detected by karyotype
      1. Duplication 1pter/deletion 1qter
      2. Interstitial del(1q44)
      3. Del(4p) (9 Mb)/dup(8p) (7 Mb)
      4. Del(6q) (4 Mb)
      5. Dup(7q) (55 Mb)
      6. Monosomy 7q36.3 (1.4 Mb)/Trisomy 8p23.3 (0.8 Mb)
      7. Isochromosome 9p10
      8. Trisomy 18
      9. Mosaicism ring 21/monosomy 21
   2. CNVp visible on karyotype and detected by CGH
      1. Del(3q) (15 Mb)
      2. Dup(8p8q) (98 Mb)
      3. Dup(8p8q) (45 Mb)
   3. CNVp not visible on karyotype and detected by FISH: Del(17p)
   4. CNVp not visible on karyotype and detected by CGH
      1. Del(14q) (2 Mb)
      2. Del(17q) (500 Kb)
      3. Dup(19p) (7 Mb)
      4. Dup(21q) (7 Mb)
      5. Mosaicism monosomy X
   5. VOUS (variant of unknown significance) not visible on karyotype and detected by CGH
      1. Del(10q) (2 Mb)
      2. Del(11p13.3) (384 Kb)
5. Molecular genetic diagnosis (Alby et al. 2016)
   1. Opitz syndrome: *MID1* mutation
   2. Zellweger syndrome: *PEX1* mutation
   3. PDH deficiency
   4. Tubulopathy: *TUBA1A* and *TUBB3* mutations
   5. Lissencephaly type 1: *PAFAH1B1* mutation
   6. Lissencephaly type 2: *POMT2*, *B3GALNT2*, and *ISPD* mutations
   7. Porencephaly type 2: *COL4A2* mutation
   8. Bicker-Adams syndrome: *LICAM* mutation
   9. Smith-Lemli-Opitz syndrome: *DHCR7* mutation
   10. Oral-facial-digital syndrome: *OFD1* mutation
   11. CHARGE syndrome: *CHD7* mutation
   12. Microcephaly 5: *ASPM* mutation

6. Prenatal counseling for ultrasonically diagnosed fetal agenesis of the corpus callosum remains very difficult, as giving precise information on outcome is impossible (Moutard et al. 2003). The following observation, however, may be of help in prenatal counseling: (Gupta and Lilford 1995)
    1. Isolated agenesis/dysgenesis of the corpus callosum (in the absence of other sonographically detectable anomalies) carrying apparent excellent prognosis
        1. 85% chance of a normal developmental outcome
        2. 15% risk of handicap
    2. Agenesis/dysgenesis of the corpus callosum with other associated anomalies: poor outcome
3. Management
    1. Identification of actual deficits resulting from the absence of such a major structure (corpus callosum): clearly an issue
    2. Multidisciplinary team approach to intervention programs
    3. Anticonvulsants for seizures
    4. Management based on the underlying etiology

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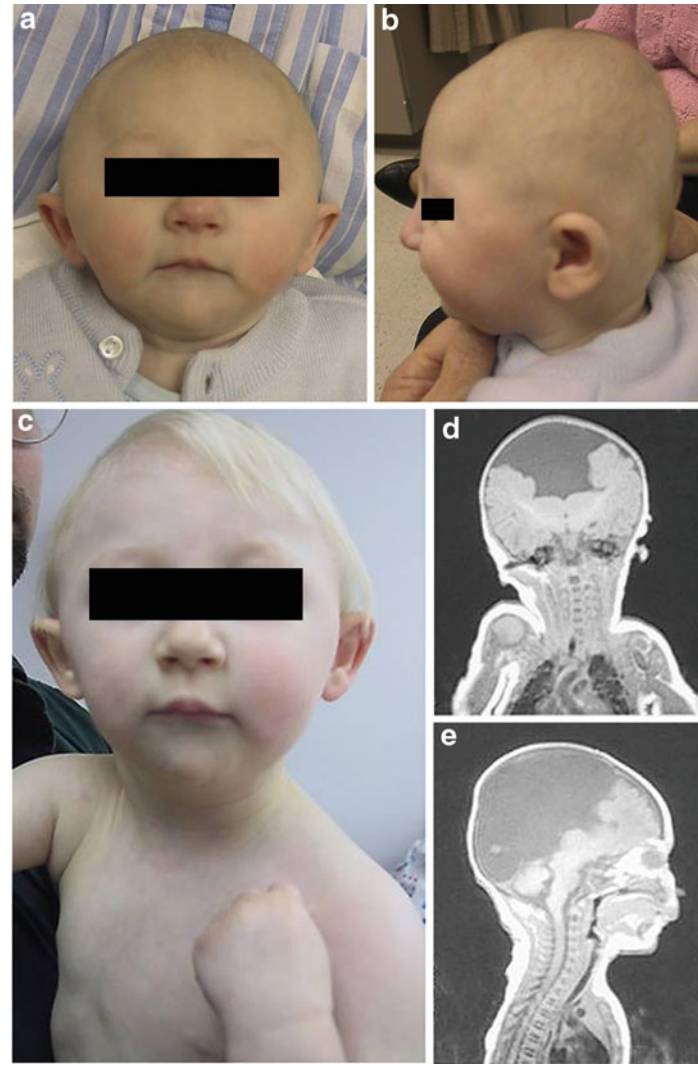

Fig. 1 (**a**–**e**) An infant (ages 3 months (**a**, **b**) and 16 months (**c**)) with agenesis of the corpus callosum and interhemispheric cyst, illustrated by MRI (**d**, **e**)

Craniometaphyseal Dysplasia

Contents

In 1954, Jackson et al. (1954) coined the term "craniometaphyseal dysplasia" for a hereditary bone disease with metaphyseal widening of the tubular bones and bony overgrowth of the facial and skull bones (leonteasis ossea).

Genetics/Basic Defects

1. Genetic heterogeneity (Beighton 1995)
    1. Autosomal dominant form [also called CMD, Jackson type (CMDJ)]:
        1. Variability of expression within a large family (Beighton et al. 1979; Carnevale et al. 1983)
        2. CMDJ locus mapped to 5p15.2-p14.1 (Nürnberg et al. 1997; Chandler et al. 2001) within a region harboring the human homolog (*ANKH*) of the mouse progressive ankylosis (*ank*) gene
        3. Mutations in ANKH have been associated in craniometaphyseal dysplasia in some families (Nürnberg et al. 2001; Reichenberger et al. 2001)
        4. ANKH mutations that cause CMD most likely entail a loss of function (Kornak et al. 2010) or a loss of ANKH protein expression and activity in the plasma membrane as a result of aberrant intracellular protein trafficking (Zajac et al. 2010)
    2. Autosomal dominant form cosegregating with chondrocalcinosis
        1. Mutations in ANKH have been associated with familial chondrocalcinosis (OCAL2) in some families (Pendleton et al. 2002; Williams et al. 2003)
        2. A family was reported with an *ANKH* mutations in which these conditions cosegregated in some affected family members (Baynam et al. 2009)
    3. Autosomal recessive form
        1. Rare
        2. Ill-defined
        3. Probably heterogeneous
        4. Often difficult to diagnose with precision
        5. Autosomal recessive CMD locus mapped to 6q21-22 (Iughetti et al. 2000)
        6. A report of a female patient with CMD phenotype, born from healthy first degree cousins and displaying homozygosity for polymorphic markers at the 6q21-22 locus, further support the existence of an autosomal recessive CMD, expanding its clinical spectrum to a more severe phenotype (Prontera et al. 2011)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_59

2. Basic defects
    1. Autosomal dominant form: caused by mutations in the human homolog of the mouse progressive ankylosis gene (*ANKH*) (Reichenberger et al. 2001)
    2. Autosomal recessive form (Beighton 1995)
        1. May involve dysfunctional osteoclasts because reported metabolic responses of affected children to therapy with calcitonin and calcitriol
        2. Osteoclast-like cells derived from the bone marrow shown to lack expression of the osteoclast vacuolar proton pump (Yamamoto et al. 1993)

Clinical Features

1. Autosomal dominant form
    1. General features
        1. Good general health
        2. Normal intelligence
        3. Normal stature
    2. Bony overgrowth of the facial bone resulting in the typical facies:
        1. Frontal bossing
        2. Hypertelorism
        3. Paranasal bossing (30% of cases in childhood)
            1. May be present during infancy
            2. Tends to regress with age
            3. Virtually absent by adolescence and early adulthood
            4. May be associated with some degree of nasal obstruction and frequent mouth breathing
        4. Mild to moderate mandibular prognathism
        5. An open mouth secondary to bony encroachment of the nasal passages
        6. Malalignment of the teeth
        7. Grotesque hyperostosis of the facial bones
        8. Decreased facial movement
    3. Bony overgrowth of the cranial foramina resulting in the following features:
        1. Cranial nerve paralysis
            2. Nystagmus
            3. Optic atrophy
            4. Facial palsy (30% of cases)
                1. Common but variable
                2. May be unilateral or bilateral
                3. May occur at any age
                4. The involvement often fluctuant in early childhood
                5. May be permanent in adulthood
            5. Deafness (50% of cases)
                1. Due to compromised auditory nerve and inner ear by bone overgrowth
                2. May be unilateral or bilateral
                3. Often "mixed" in type due to chronic otitis media and upper respiratory tract infection secondary to minor anatomical abnormalities of the airway and sinuses
                4. Usually partial and rarely profound
            6. Less commonly reported conditions (Kietzer and Paparella 1969)
                1. Compression of the cerebellar tonsils and medulla secondary to a narrowed foramen magnum
                2. Obstruction of Eustachian tube
                3. Obstruction of nasolacrimal duct
                4. Obstruction of nasal passages
                5. Raised intracranial pressure: rare instances of a potentially lethal rise in intracranial pressure due to hyperostosis of the calvarium
    4. Abnormal modeling of the metaphyses of the long bones
        1. Metaphyseal widening of the long and short tubular bones
        2. Thin cortical layer
        3. Coarse trabeculations
    5. Clinical and radiographic features improved in later childhood in the dominant form
2. Autosomal recessive form
    1. Similar to, but more severe than, those seen in the dominant form
    2. An increasing severity with age
    3. Progressive overgrowth and craniofacial deformity
        1. Very severe facial distortion
        2. A thick bony wedge over the bridge of the nose

3. Dystopia canthorum
4. Ocular hypertelorism
5. Enlarged malar prominences and mandible (marked prognathism)
6. Wide alveolar ridge
7. Narrowed nasal passages leading to mouth breathing
8. Dental abnormalities
9. Blindness
10. Facial palsy
11. Deafness

4. Cerebellomedullary compression in recessive craniometaphyseal dysplasia (Boltshauser et al. 1996)
5. Abnormal modeling of the metaphyses of the long bones
   1. Gradual, club-shaped widening of the metaphyses
   2. Thin cortex and undermineralized medullary bone

3. Differential diagnosis (Cole and Cohen 1988; Reichenberger and Chen 2015)
   1. Pyle disease (metaphyseal dysplasia) (Gorlin et al. 1970)
      1. Frequently confused with craniometaphyseal dysplasia. In Pyle disease, metaphyseal flaring occurs but there is minimal involvement of the skull
      2. Autosomal recessive inheritance
   2. Craniodiaphyseal dysplasia (Cole and Cohen 1988)
      1. Most severe thickening, distortion, and enlargement of the craniofacial region
      2. Characterized by diaphyseal endostosis
      3. Does not exhibit metaphyseal flaring
      4. Inheritance likely autosomal recessive
   3. Frontometaphyseal dysplasia (Cooper 1974)
      1. A pronounced bony supraorbital ridge
      2. Hirsutism
      3. Long-bone alterations
      4. Conductive deafness
   4. Camurati-Engelmann disease (progressive diaphyseal dysplasia) (Cooper 1974)
      1. Presence of excess subperiosteal bone in the diaphyses of the long bone
      2. Normal metaphyses
      3. Rare craniofacial involvement
   5. van Buchem disease (hyperostosis corticalis generalisata) (Cooper 1974)
      1. *SOST*-related sclerosing bone dysplasias: including van Buchem disease and sclerosteosis
      2. Autosomal recessive disorder
      3. Caused by pathogenic variants in *SOST*, the gene encoding sclerostin, the bone morphogenetic protein (BMP) antagonist
      4. Dense and thickened craniofacial skeleton
      5. Generalized cortical thickening of the long bones mainly due to endosteal bone apposition
   6. Osteopathia striata with cranial sclerosis
      1. Characteristic findings: longitudinal striations of sclerotic long bones in combination with osteosclerosis of cranial and facial bones
      2. Inheritance is X-linked dominant, with likely genetic heterogeneity
      3. Caused by pathogenic variants in *AMER1* (Jenkins et al. 2009)

Diagnostic Investigations

1. Normal serum calcium, phosphorous, and alkaline phosphatase
2. Radiographic features (Beighton 1995)
   1. Autosomal dominant form: age-related radiographic features
      1. Characteristic hyperostosis and sclerosis of the skull
      2. Paranasal bony bossing, most evident in early childhood
      3. May be present with prognathism and asymmetry
      4. Characteristic nonsclerotic widening of the metaphyses of the tubular bones: a major radiographic feature
         1. Most obvious at the lower end of the femur
         2. An “Erlenmeyer flask” configuration in childhood
         3. A “club” shape in adulthood

5. A "ground glass" pattern of the alveolar bone in some areas with an associated loss of the lamina dura around some of the teeth (Bricker et al. 1983)

2. Autosomal recessive form: severe radiographic manifestations (Penchaszadeh et al. 1980)
   1. Increasing severity with age
   2. Sclerosis and hyperostosis of the calvarium, the base of the skull, and the facial bones and mandible
   3. Increased bone deposition on the walls of the paranasal sinuses
   4. Underpneumatization of mastoid cells
   5. Gradual, club-shaped widening of the metaphyses
   6. Thin cortex and undermineralized medullary bone

3. Gross pathological features (Kietzer and Paparella 1969)
   1. Thickened "ivory-hard" facial and cranial bones
   2. Narrow cranial foramina
   3. Narrowing of the nasal chambers and posterior choanae (Cheung et al. 1997)
4. Histological features (Kietzer and Paparella 1969)
   1. Compact laminar cortical bone with dilated Haversian canals containing osteoblasts
   2. No osteoclasts identified in the periosteal or endosteal layers
   3. An increased amount of ground substance and excessive formation of subperiosteal and subendosteal bone
5. Molecular genetic analysis for human ankylosis gene (*ANKH*): Sequence analysis detects mutations in about 90% of individuals meeting the diagnostic criteria for CMD (Reichenberger and Chen 2015)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal dominant form: 50% risk if one parent is affected, otherwise risk not increased
      2. Autosomal recessive form: 25%
   2. Patient's offspring
      1. Autosomal dominant form: 50%
      2. Autosomal recessive form: not increased unless the spouse is also a carrier in which case there is 50% recurrence risk
   3. Possibility of the presence of a parental mosaicism in an *ANKH* mutation who had no apparent clinical or radiological features of CMD. Parental mosaicism may account for some apparently sporadic or new cases of CMD and has important implications in the genetic counseling of families affected by CMD (Kato et al. 2013)
2. Prenatal diagnosis and preimplantation genetic diagnosis for pregnancies at risk may be available through laboratories offering custom prenatal testing if the disease-causing mutations in the family is known (Reichenberger and Chen 2015)
3. Management
   1. Medical treatment attempted with the following two hormones
      1. Calcitonin: increases bone turnover and secondary hyperparathyroidism (Fanconi et al. 1988)
      2. Calcitriol (Key et al. 1988)
         1. Stimulates resorption of bone by promoting osteoclast formation
         2. Partial resolution of facial nerve paralysis, increased size of the cranial nerve foramina, and demineralization of the cranial base during treatment of one patient with high doses of calcitriol
   2. Hearing aids for hearing loss
   3. Most patients with CMD need orthodontic treatment (Chen et al. 2014)
   4. Psychological support for facial disfigurement
   5. Bony turbinoplasties along the whole length of the inferior turbinate may be required for nasal obstruction (Twigg et al. 2015).
   6. Surgical treatment with mixed results (Day et al. 1997)
      1. Resection of dysplastic bone arduous because it is highly mineralized with a consistency like thick ivory

2. Craniofacial reduction performed with some difficulty
3. Optic canal decompression for progressive visual loss
4. Facial nerve decompression
5. Middle ear exploration and implantation of total ossicular replacement prosthesis for conductive hearing loss
6. Foramen magnum decompression for cervicomedullary encroachment

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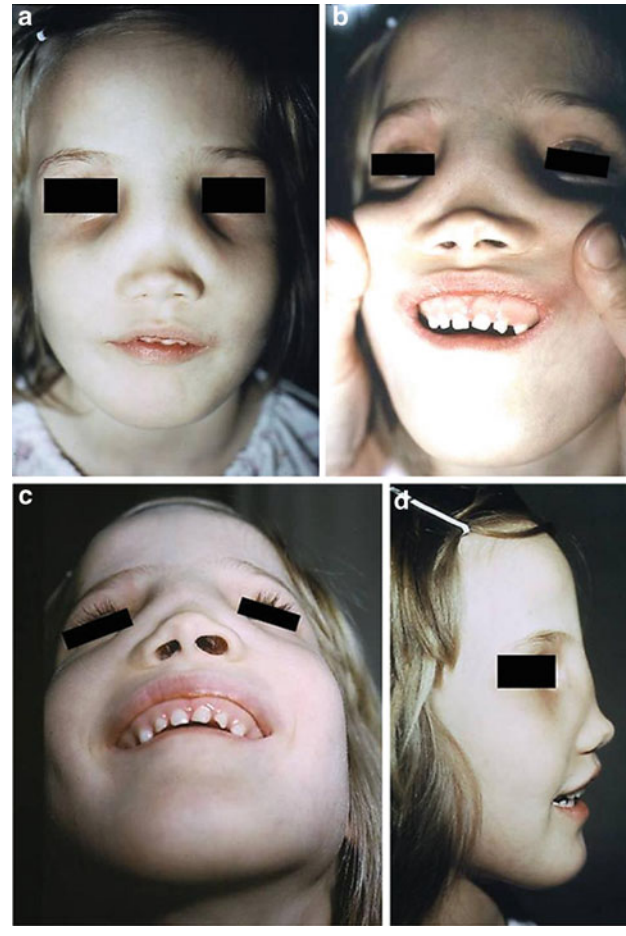

Fig. 1 (**a**–**d**) A girl with craniometaphyseal dysplasia showing characteristic craniofacial features consisting of hypertelorism, broadening nasal base with paranasal bossing, short nose, and prominent facial bones

Cri-Du-Chat Syndrome

Contents

Cri du chat syndrome is a chromosome 5p deletion syndrome first described by Lejeune et al. in 1963. The name of the syndrome refers to the most characteristic clinical feature, a high-pitched crying similar to the mewing of a cat, which usually disappears in the first years of life. The incidence is estimated to be approximately 1 in 15,000 (Higurashi et al. 1990) to 1 in 50,000 births (Niebuhr 1978). The prevalence among mentally retarded individuals is approximately 1.5 in 1,000.

Synonyms and Related Disorders

Cat cry syndrome; Chromosome 5p deletion syndrome

Genetics/Basic Defects

1. Cause:
   1. Caused by deletion of short arm of chromosome 5: The size of the deletion ranges from the entire short arm to the region 5p15 (Overhauser et al. 1994) and a deletion size ranging from 5 to 40 Mb (Simmons et al. 1995):
      1. De novo deletion (80%): paternally derived deletions in 80% of cases (Overhauser et al. 1990)
      2. Familial rearrangement (12%)
      3. Mosaicism (3%) (Perfumo et al. 2000)
      4. Rings (2.4%)
      5. De novo translocation (3%)
   2. A high-resolution physical and transcription map generated a 3.5-Mb region of 5p15.2 that is associated with the cri du chat syndrome region (Church et al. 1997).
   3. Mutations in the dynein axonemal heavy chain 5 gene (*DNAH5*) cause outer dynein arm ciliary defects and account for approximately 30% of cases of primary ciliary dyskinesia (Hornef et al. 2006). This gene resides in the same chromosome 5p region affected in cri du chat syndrome (Shapiro et al. 2014).
2. Genotype-phenotype correlation (Gersh et al. 1997; Mainardi et al. 2001):
   1. Deletion of 5p15.3 results in a catlike cry and speech delay (Gersh et al. 1995; Church et al. 1995).
   2. Deletion of 5p15.2 results in the distinct facial features associated with the syndrome as well as the severe mental and developmental delay.

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3. Progressive severity of clinical manifestation and psychomotor retardation related to the larger size of the deletion (Wilkins et al. 1983).
4. Analysis of seven patients with interstitial deletions and one with a small terminal deletion confirmed the existence of two critical regions:
    1. One for dysmorphism and mental retardation in p15.2
    2. Another for the cat cry in p15.3
3. Hemizygosity of δ-catenin (*CTNND2*, mapped to 5p15.2), reported to be associated with severe mental retardation in cri du chat syndrome (Medina et al. 2000).
4. Deletion of the *telomerase reverse transcriptase* (h *TERT*) gene (mapped at 5p15.33) and haploinsufficiency of telomere maintenance is probably a genetic element contributing to the phenotypic changes in cri du chat syndrome (Zhang et al. 2003).

Clinical Features

1. Characteristic mewing cry (Niebuhr 1978):
    1. A high-pitched monochromatic cry with subtle dysmorphism and neonatal complications: commonly observed in infants with this syndrome
    2. Observed in many infants with cri du chat syndrome
    3. Not associated with other aneuploidies
    4. Usually considered diagnostic
    5. Loss of the characteristic cry by age 2 years in one third of children
2. Clinical findings during infancy (Mainardi 2006; Chen 2015):
    1. Low birth weight
    2. Hypotonia
    3. Microcephaly
    4. Poor sucking/swallowing difficulties
    5. Need for incubator care
    6. Respiratory distress
    7. Jaundice
    8. Pneumonia
    9. Dehydration
    10. Failure to thrive/growth retardation
    11. Early ear infections
    12. Severe cognitive, speech, and motor delays
    13. Facial features:
        1. Round face with full cheek
        2. Hypertelorism
        3. Epicanthal folds
        4. Down-slanting palpebral fissures
        5. Strabismus
        6. Flat nasal bridge
        7. Down-turned mouth
        8. Micrognathia
        9. Low-set ears
    14. Cardiac defects:
        1. VSD
        2. ASD
        3. PDA
        4. Tetralogy of Fallot
    15. Short fingers
    16. Single palmar creases
    17. Less frequent features:
        1. Cleft lip and palate
        2. Preauricular tags and fistulas
        3. Thymic dysplasia
        4. Gut malrotation
        5. Megacolon
        6. Inguinal hernia
        7. Dislocated hips
        8. Cryptorchidism
        9. Hypospadias
        10. Rare renal malformations:
            1. Horseshoe kidneys
            2. Renal ectopia or agenesis
            3. Hydronephrosis
        11. Clinodactyly of the fifth fingers
        12. Talipes equinovarus
        13. Pes planus
        14. Syndactyly of the second and third fingers and toes
        15. Oligosyndactyly
        16. Hyperextensible joints
3. Clinical findings in childhood (Chen 2015):
    1. Severe mental retardation
    2. Developmental delay
    3. Microcephaly
    4. Hypertonicity
    5. Premature graying of the hair
    6. Small, narrow, and often asymmetric face

7. Dropped jaw
8. Open-mouth expression secondary to facial laxity
9. Short philtrum
10. Malocclusion of the teeth
11. Scoliosis
12. Short third–fifth metacarpals
13. Chronic medical problems:
    1. Upper respiratory tract infections
    2. Otitis media
    3. Severe constipation
    4. Hyperactivity

4. Clinical findings in late childhood and adolescence (Niebuhr 1971; Chen 2015):
    1. Coarsening of facial features
    2. Prominent supraorbital ridges
    3. Deep-set eyes
    4. Hypoplastic nasal bridge
    5. Affected females reaching puberty and developing secondary sex characteristics and menstruate at the usual time (Martinez et al. 1993)
    6. Small testis and normal spermatogenesis in males
    7. Changing phenotype in older patients (Van Buggenhout et al. 2000)
5. Dermatoglyphics:
    1. Transverse flexion creases
    2. Distal axial triradius
    3. Increased whorls and arches on digits
6. Behavioral profile (Cornish and Pigram 1996; Dykens and Clark 1997; Collins and Cornish 2002):
    1. Hyperactivity
    2. Aggression
    3. Tantrums
    4. Stereotypic and self-injurious behavior
    5. Repetitive movements
    6. Hypersensitivity to sound
    7. Clumsiness
    8. Obsessive attachments to objects
    9. Able to communicate needs and interact socially with others
    10. Autistic-like features and social withdrawal: more characteristic of individuals who have a 5p deletion as the result of an unbalanced segregation of a parental translocation
7. Prognosis (Wilkins et al. 1980):
    1. The ability of many children to develop some language and motor skills
    2. The ability of these children to attain developmental and social skills observed in 5–6-year-old children, although their linguistic abilities are seldom as advanced
    3. Older, home-reared children:
        1. Usually ambulatory
        2. Able to communicate verbally or through gestural sign language
        3. Independent in self-care skills

Diagnostic Investigations

1. Conventional cytogenetic studies once the suspected diagnosis is established. The size of the 5p deletion may vary from the entire short arm to only 5p15. A small deletion of 5p may be missed by a conventional cytogenetic technique.
2. High-resolution cytogenetic studies are required for a smaller 5p deletion.
3. Molecular cytogenetic studies using fluorescent in situ hybridization (FISH) (Marinescu et al. 1999; Dangare et al. 2012):
    1. Allow the diagnosis to be made in the patients with very small deletions.
    2. Use genetic markers that have been precisely localized to the area of interest.
    3. The absence of a fluorescent signal from either the maternal or paternal chromosome 5p regions: indicative of monosomy for that chromosomal region.
4. Comparative genomic hybridization (CGH) especially the CGH method based on DNA microarray and quantitative PCR (Mainardi et al. 2001; Rodriguez-Caballero et al. 2010).
5. Skeletal radiographs:
    1. Microcephaly
    2. Retromicrognathia
    3. Cranial base malformations:
        1. Reduced cranial base angle
        2. Malformed sella turcica and clivus
    4. Disproportionately short third, fourth, and fifth metacarpals and disproportionately

long second, third, fourth, and fifth proximal phalanges (frequent) (Fenger and Niebuhr 1978)
6. Echocardiography to rule out structural cardiac malformations.
7. MRI of the brain (Kjaer and Niebuhr 1999; Nandhagopal and Udayakumar 2014):
    1. Atrophic brainstem, middle cerebellar peduncles, and cerebellar white matter
    2. Possible hypoplasia of cerebellar vermis with enlargement of the cisterna magna and fourth ventricle
    3. Pontine hypoplasia (Mainardi 2006; Ninchoji and Takanashi 2010)
    4. Callosal agenesis
8. Swallowing study for feeding difficulty.
9. Comprehensive evaluation for receptive and expressive language (Cornish and Munir 1998): Most children have better receptive language than expressive language.
10. Developmental testing and referral to early intervention and appropriate school placement.

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib:
        1. Recurrence risk for a de novo case is 1% or less (possibility of gonadal mosaicism in one of the parents cannot be ruled out).
        2. Rare recurrences in chromosomally normal parents: most likely the result of gonadal mosaicism for the 5p deletion in one of the parents.
        3. The risk is substantially high if a parent is a balanced carrier of a structural rearrangement. Risk should be assessed based on the type of structural rearrangement and its pattern of segregation.
    2. Patient's offspring: Female patients are fertile and can deliver viable affected offspring, with an estimated recurrence risk of 50% (Martinez et al. 1993).
2. Prenatal diagnosis:
    1. Abnormal maternal serum testing: high hCG level (Fankhauser et al. 1998)
    2. Ultrasonography (Aoki et al. 1999; Chen et al. 2013):
        1. Hypoplastic cerebellum
        2. Ventricular septal defect
        3. Overriding aorta
        4. Cystic lesion within the nuchal skin edema
        5. Hypospadias
    3. Amniocentesis, CVS, and PUBS for chromosome analysis to detect 5p deletion (Tullu et al. 1998)
    4. aCGH characterization using uncultured amniocytes (Chen et al. 2013)
3. Fluorescent in situ hybridization-based preimplantation genetic diagnosis (Ye et al. 2011)
4. Management:
    1. Supportive care: No treatment exists for the underlying disorder.
    2. Family stress and sibling reactions (ignored and misunderstood) (Hodapp et al. 1997).
    3. Appropriate treatment for chronic medical problems:
        1. Upper respiratory tract infections
        2. Otitis media
        3. Severe constipation
    4. Using the relatively good receptive skills to encourage language and communicative development rather than relying on traditional verbal methods (Cornish and Munir 1998).
    5. Early intervention programs:
        1. Physical therapy
        2. Occupational therapy
        3. Speech therapy
    6. Introduction to sign language, an effective means of developing communication skills (>50% of children are able to use sign language to communicate) (Cornish and Munir 1998).
    7. Behavior modification programs to successfully manage hyperactivity, short attention span, low threshold for frustration, and self-stimulatory behaviors (e.g., head-banging, hand-waving).

8. Surgical interventions:
    1. Correction of congenital heart defects if indicated
    2. Medical problems involving minor malformations such as strabismus and clubfoot
    3. Gastrostomy in infancy to protect airway of patients with major feeding difficulties
    4. Orchiopexy for undescended testes
    5. Issues important to anesthetic plan (Brislin et al. 1995):
        1. Anatomical abnormalities of the airway
        2. Congenital heart disease
        3. Hypotonia
        4. Mental retardation
        5. Temperature maintenance

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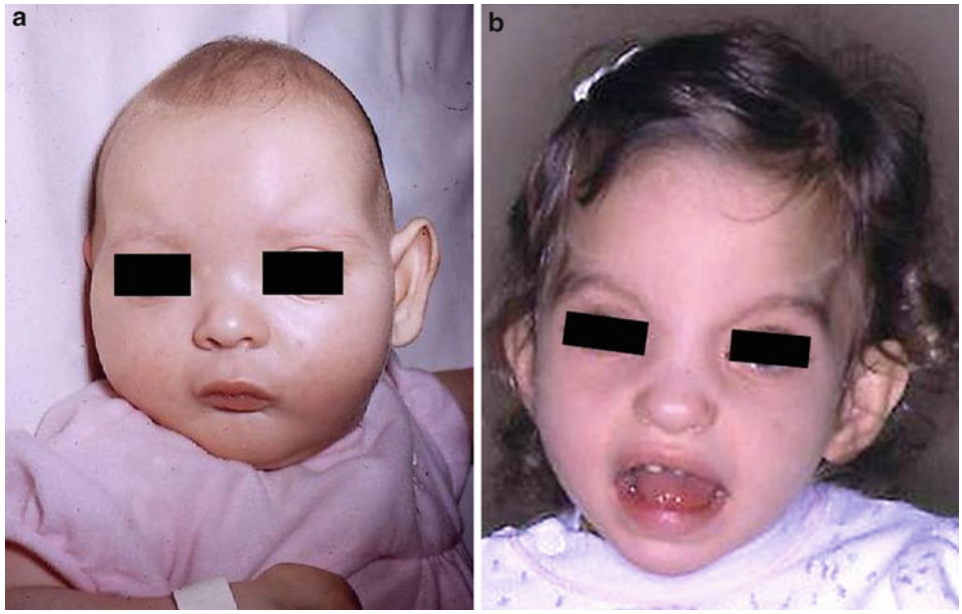

Fig. 1 (**a**, **b**) Two infants with cri du chat syndrome. Note a round face with full cheeks, hypertelorism, epicanthal folds, and apparently low-set ears

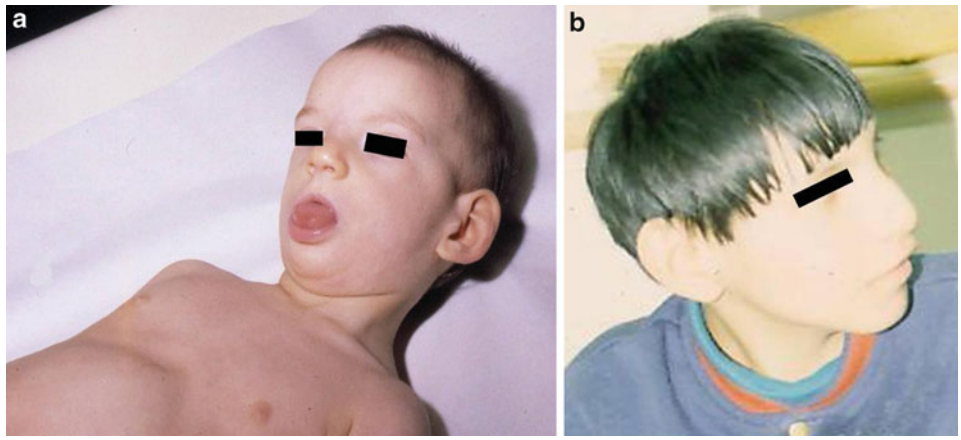

Fig. 2 (**a**, **b**) Cri du chat syndrome in an older child and a teenager showing a long and narrow face

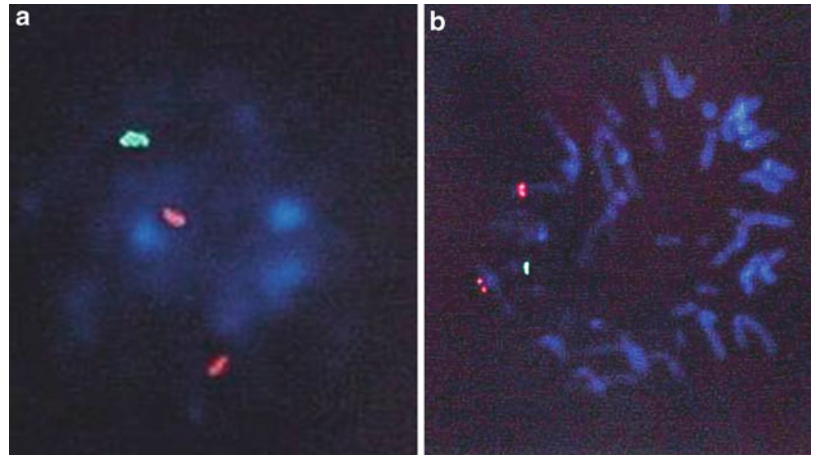

Fig. 3 (**a**, **b**) FISH of an interphase cell and a metaphase spread with two *orange* signals (LSI Spectrum *Orange*, D5S721) and one *green* signal (LSI Spectrum *Green*, D5S23 chromosome 5p15.2-specific probe) indicating deletion of 5p15.2

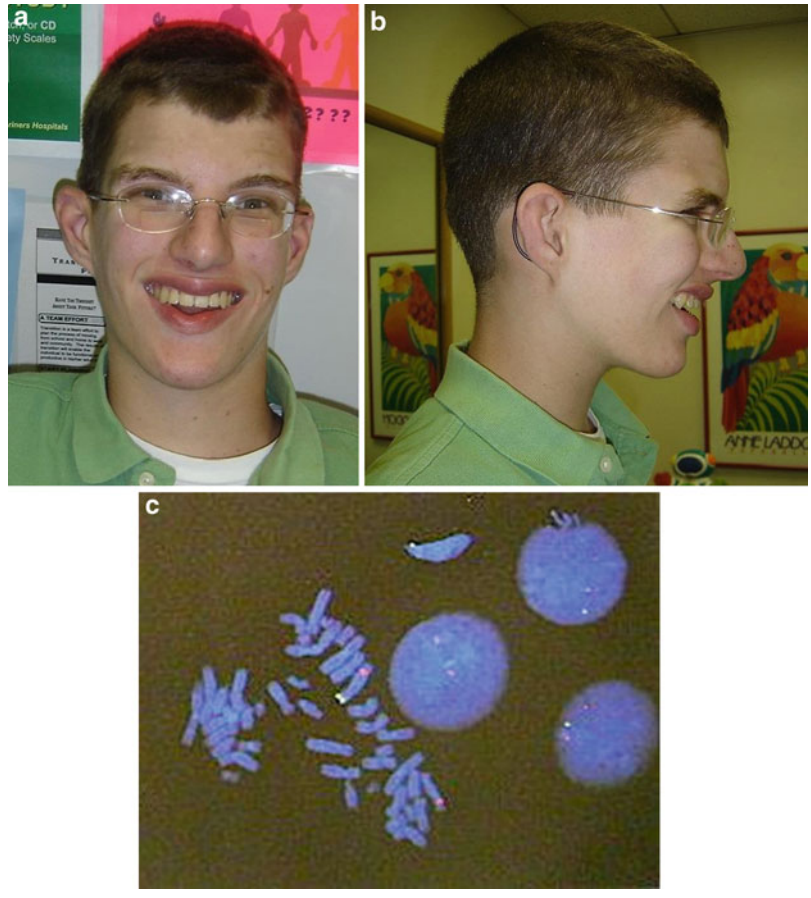

Fig. 4 (**a**–**c**) The 16-year-old boy was evaluated for developmental delay. He was noted to have unusual cry during early infancy, poor muscle control, and unable to hold his head up until 6 months of age. FISH using a locus specific for 5p11.2 cri du chat syndrome region showed 5p11.2 deletion (illustrated by a metaphase chromosome spread and interphase cells)

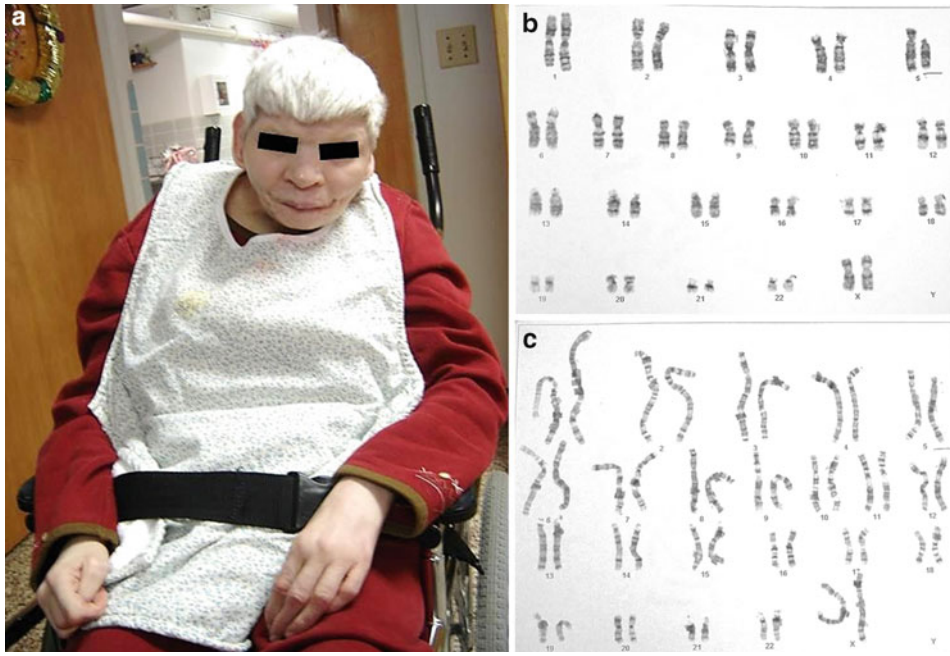

Fig. 5 (**a**–**c**) A blond-haired 60-year-old female with cri du chat syndrome, showing microcephaly with severe mental retardation. The karyotypes showed deletion of most of the short arm of a chromosome 4

Crouzon Syndrome

Contents

In *1912*, Crouzon described the hereditary syndrome of craniofacial dysostosis in a mother and son (Crouzon 1912). He described the triad of calvarial deformities, facial anomalies, and exophthalmos. Crouzon syndrome is characterized by premature closure of calvarial and cranial base sutures as well as those of the orbit and maxillary complex (craniosynostosis). Other clinical features include hypertelorism, exophthalmos, strabismus, beaked nose, short upper lip, hypoplastic maxilla, and relative mandibular prognathism. Prevalence is 1 per 60,000 (approximately 16.5 per 1,000,000) live births (Cohen and Kreiborg 1992). Crouzon syndrome makes up approximately 4.8% of all cases of craniosynostosis.

Synonyms and Related Disorders

Craniofacial dysostosis type I; Crouzon craniofacial dysostosis; Crouzon syndrome with acanthosis nigricans (Crouzonodermoskeletal syndrome)

Genetics/Basic Defects

1. Inheritance
   1. An autosomal dominant disorder with
      1. Complete penetrance
      2. Variable expressivity
   2. Sporadic in 50% of patients resulting from new mutations
   3. Paternal origin of FGFR2 mutation in sporadic cases of Crouzon syndrome (Glaser et al. 2000)
2. Cause
   1. Mutations in the fibroblast growth factor receptor-2 (*FGFR2*) gene which is mapped to 10q25-q26 (Preston et al. 1994; Reardon et al. 1994).
   2. Mutations reported in the third immunoglobulin-like domain (Oldridge et al. 1995; Meyers et al. 1996).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Different mutations detected in both exon IIIa and exon IIIc. Most of these mutations are missense, although several different mutations leading to alternative splicing have been recognized (Meyers et al. 1996).
4. Crouzon syndrome exhibits locus heterogeneity with causal mutations in *FGFR2* (Crouzon syndrome) and *FGFR3* (Crouzon syndrome with acanthosis nigricans) in different affected individuals (Chen 2015).
5. Crouzon syndrome with acanthosis nigricans (Crouzonodermoskeletal syndrome).
    1. Described as a separate entity from Crouzon syndrome (Cohen 1999)
    2. Caused by the GAG to GCG transversion mutation in the *FGFR3* gene, leading to Ala391Glu substitution (Meyers et al. 1995; Wilkes et al. 1996)
6. Germinal mosaicism: two affected brothers born to unrelated parents (Rollnick et al. 1988).

3. Pathophysiology
    1. Premature synostosis of the coronal, sagittal, and occasional lambdoidal sutures.
        1. Begins in the first year of life
        2. Completed by the second or third year
    2. Degree of deformity and disability determined by the order and rate of suture fusion.
    3. After fusion of a suture.
        1. Growth perpendicular to that suture becoming restricted
        2. Fused bones acting as a single bony structure.
    4. Compensatory growth occurring at the remaining open sutures to allow continued brain growth.
    5. Multiple sutural synostoses often extend to premature fusion of the skull base sutures causing the following effects:
        1. Midfacial hypoplasia
        2. Shallow orbit
        3. A foreshortened nasal dorsum
        4. Maxillary hypoplasia
        5. Occasional upper airway obstruction

Clinical Features

1. History
    1. The presence of mildly affected individuals in the family.
    2. Craniofacial abnormalities often present at birth and may progress with time.
    3. Decreased mental function in approximately 12% of the patients.
    4. Headaches (29%) and failing vision due to elevated intracranial pressure.
    5. Visual disturbance results from corneal injury due to exposed conjunctivitis and keratitis.
    6. Conductive deafness common due to ear canal stenosis or atresia.
    7. Causes of upper airway obstruction.
        1. Septal deviation
        2. Mid-nasal abnormalities
        3. Choanal abnormalities
        4. Nasopharyngeal narrowing
    8. Meniere disease.
    9. Seizures (12%).
2. The skull and face
    1. Craniosynostosis
        1. Onset: commonly seen during the first year
        2. Usually completing by the second or third year
        3. Coronal suture most commonly involved
        4. Acrocephaly
        5. Brachycephaly
        6. Turricephaly
        7. Oxycephaly
        8. Flat occiput
        9. A high prominent forehead with or without frontal bossing
        10. Ridging of the skull usually palpable
    2. A cloverleaf skull
        1. Rare
        2. Occurring in most severely affected individuals
        3. Flattened sphenoid bone
        4. Shallow orbits
        5. Hydrocephalus (progressive in 30%)
        6. Midface (maxillary) hypoplasia

3. Eyes (Chen 2015)
    1. Exophthalmos (proptosis) (100%) secondary to shallow orbits resulting in frequent exposure conjunctivitis or keratitis
    2. Ocular hypertelorism (100%)
    3. Divergent strabismus
    4. Rare occurrence
        1. Nystagmus
        2. Iris coloboma
        3. Aniridia
        4. Anisocoria
        5. Microcornea
        6. Megalocornea
        7. Cataract
        8. Ectopia lentis
        9. Blue sclera
        10. Glaucoma
        11. Luxation of the eye globes
        12. Blindness from optic atrophy
4. The nose
    1. Beaked appearance (parrot-like nose)
    2. Compressed nasal passage
    3. Choanal atresia or stenosis
    4. Deviated nasal septum
5. The mouth
    1. Mandibular prognathism
    2. Overcrowding of upper teeth
    3. Malocclusions
    4. V-shaped maxillary dental arch
    5. Narrow, high, or cleft palate and bifid uvula
    6. Oligodontia
    7. Macrodontia
    8. Peg-shaped
    9. Widely spaced teeth
6. Ears
    1. Narrow or absent ear canals
    2. Deformed middle ears
    3. Mild-to-moderate hearing losses
7. Other skeletal manifestations
    1. Cervical fusion (18%), C2–C3 and C5–C6 (Anderson et al. 1997a)
    2. Block fusions involving multiple vertebrae
    3. Subluxation of the radial heads
    4. Ankylosis of the elbows
8. Acanthosis nigricans (5%) (Di Rocco et al. 2011)
    1. Crouzon syndrome with acanthosis nigricans: a clinically and genetically distinct entity
    2. Associated with a craniofacial phenotype to anomalies of the skin and long bones
    3. Can be detected by genetic testing due to a specific mutation in *FGFR3* gene
    4. Cutaneous features of acanthosis nigricans (Mir et al. 2013)
        1. Velvety, light-brown to black darkened, thickened skin with accentuated markings that occur in areas including the face, neck, axillae, groin, and breasts
        2. Hypopigmented scars
        3. Other cutaneous findings: sacral pits associated with pink plaques, verrucae vulgaris, molluscum contagiosum, and seborrheic dermatitis
    5. Usual age of onset: first decade (80%)
    6. Only one case reported at birth (Koizumi et al. 1992), some will be patent only in the infancy or early childhood
    7. Typical presentation (Arnaud-Lopez et al. 2007; Sharda et al. 2010)
        1. Crouzonoid facies
        2. Acanthosis nigricans with atypical distribution
        3. Choanal atresia
        4. Hydrocephalus
        5. An abnormal posterior fossa with a hypoplastic foramen magnum and cerebellar tonsillar herniation
        6. Oral abnormalities
        7. Melanocytic nevi
        8. Less frequent findings: vertebral abnormalities and deafness
    8. Associated to several disorders including endocrinopathies mostly associated to hyperinsulinism, FGFR3-related skeletal dysplasias (such as SADDAN), and autoimmune disorders
9. CNS
    1. Chronic tonsillar herniation (approximately 73%). Of these, 47% have progressive hydrocephalus (Cinalli et al. 1995).
    2. Syringomyelia.
    3. Mental retardation (3%).

10. Cardiopulmonary abnormalities (Beck et al. 2002)
    1. Absent pulmonary valve syndrome
    2. Tracheobronchomalacia

Diagnostic Investigations

1. Skull radiographs (Kreiborg 1981; Chen 2015)
    1. Synostosis: The coronal, sagittal, lambdoidal, and metopic sutures may be involved.
    2. Craniofacial deformities.
    3. Digital markings of the skull.
    4. Basilar kyphosis.
    5. Widening of the hypophyseal fossa.
    6. Small paranasal sinuses.
    7. Maxillary hypoplasia with shallow orbits.
2. Cervical radiographs (Anderson et al. 1997a)
    1. Butterfly vertebrae
    2. Fusions of the vertebral bodies and the posterior elements
        1. Cervical fusions in approximately 18% of patients.
        2. C2–C3 and C5–C6 affected equally.
        3. Block fusions may involve multiple vertebrae.
3. Limb radiographs
    1. Metacarpophalangeal analysis
    2. Subluxation of the radial head
    3. Carpal fusion (Anderson 1997b)
4. 3D computed tomography (CT) scan (Nørgaard et al. 2012)
    1. Brachycephalic skull with protrusion of the forehead and flattened occiput
    2. Prematurely fused sutures
    3. A thin skull with extremely increased digital markings
    4. Depressed nasal root
    5. Short orbital roofs
    6. Ocular hypertelorism
    7. Hypoplastic maxilla
    8. Decreased choanal height with constricted nasopharyngeal airway
    9. Comparative 3D reconstruction analysis of the calvaria and cranial bases to precisely define the pathologic anatomy and to permit specific operative planning
5. Magnetic resonance imaging (MRI): used to demonstrate occasional corpus callosum agenesis and optic atrophy
6. Molecular analysis
    1. *FGFR2* mutations in more than 50% of patients (*FGFR2* mutations also observed in Apert syndrome, Pfeiffer syndrome, and Jackson-Weiss syndrome).
    2. *FGFR3* ala391-to-glu mutation in all patients with associated acanthosis nigricans: Finding of acanthosis nigricans in a young child with Crouzon syndrome should prompt testing for the Ala391Gln substitution in *FGFR3* before testing for *FGFR2* mutations (Sharda et al. 2010).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased unless a parent is affected or with germinal mosaicism (Navarrete et al. 1991)
    2. Patient's offspring: 50%
2. Prenatal diagnosis
    1. Prenatal ultrasonography
        1. Exophthalmos (Menashe et al. 1989)
        2. Ocular hypertelorism (Leo et al. 1991)
    2. 2D, 3D prenatal ultrasonography diagnosis of Crouzon syndrome with acanthosis nigricans (Nørgaard et al. 2012)
        1. Brachycephaly
        2. Hypertelorism
        3. Ocular proptosis
        4. A beaked nose
    3. Identification of the disease-causing *FGFR2* mutation using:
        1. CVS in the first trimester (Schwartz et al. 1996)
        2. Amniocentesis in the second trimester
        3. Preimplantation genetic diagnosis (Harper et al. 2002)
3. Management (Helman et al. 2014)
    1. Medical care

1. No specific medical therapy available
2. Nasal continuous positive airway pressure device to relieve airway obstruction
3. Management of speech
4. Evaluation of hearing deficits and obstructive sleep apnea
5. A combination of orthopedic and orthodontic treatment: effective for improving the appearance and occlusion of patients with mild Crouzon syndrome without surgery (Maspero et al. 2014)

2. Surgical care (David and Sheen 1990)
   1. Stage reconstruction to coincide with facial growth patterns, visceral function, and psychosocial development.
   2. Suture release: early craniectomy with frontal bone advancement most often indicated to prevent or treat increased intracranial pressure because newborns with Crouzon syndrome develop multiple suture synostosis and fused synchondrosis.
   3. Fronto-orbital and midfacial advancements to help in the cosmetic reconstruction of facial dysmorphisms.
   4. A new technique, craniofacial disjunction, followed by gradual bone distraction (Ilizarov procedure) has been reported to produce complete correction of exophthalmos and improvement in the functional and esthetic aspects of the middle third of the face without the need for bone graft in patients aged 6–11 years.
   5. Shunting procedures for hydrocephalus.
   6. Tracheostomy for airway compromise.
   7. Myringotomy to drain middle ear secretions secondary to distorted nasopharynx.
   8. Orthodontic management.

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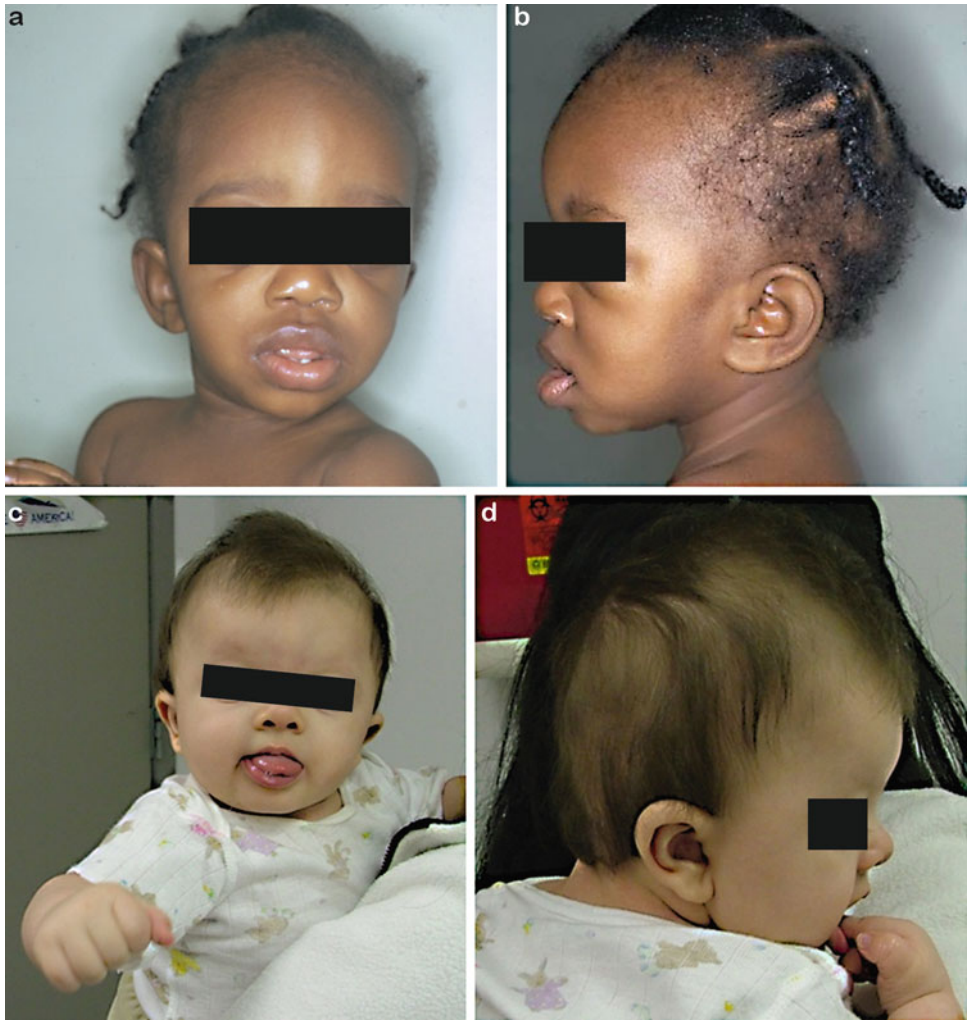

Fig. 1 (**a**–**d**) Two children with Crouzon syndrome showing proptosis secondary to shallow obits and hypertelorism

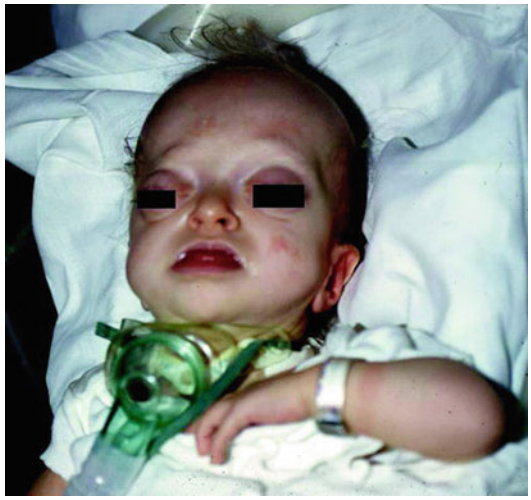

Fig. 2 A neonate with Crouzon syndrome showing typical craniofacial features with tracheostomy in place for the respiratory problem

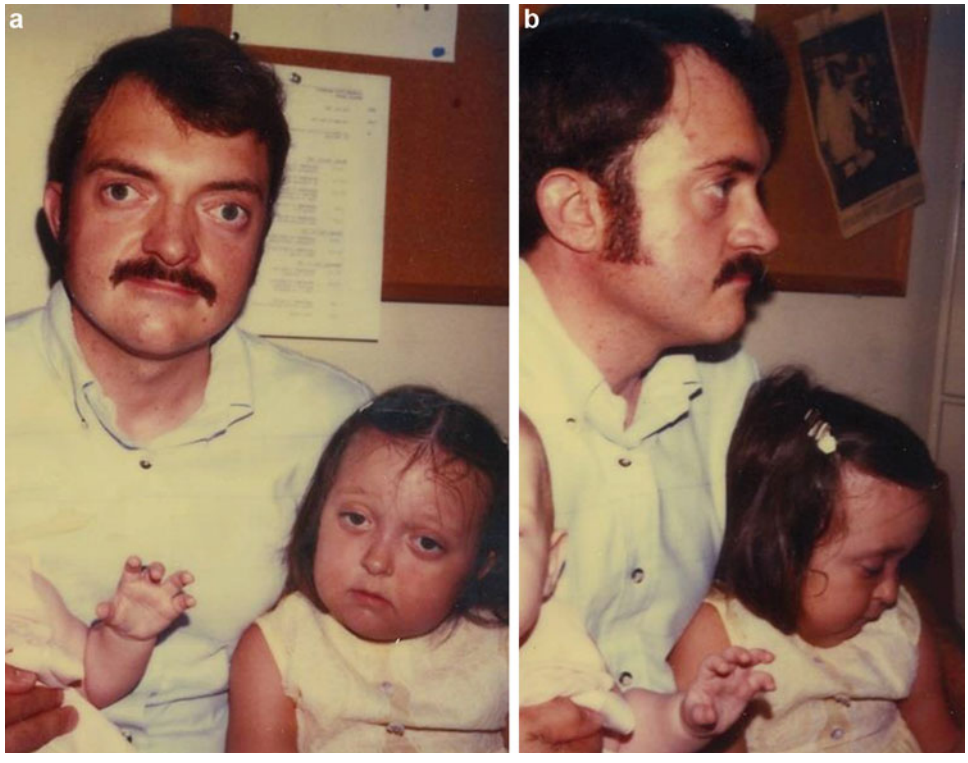

Fig. 3 (**a**, **b**) A father and a daughter with Crouzon syndrome showing characteristic craniofacial features

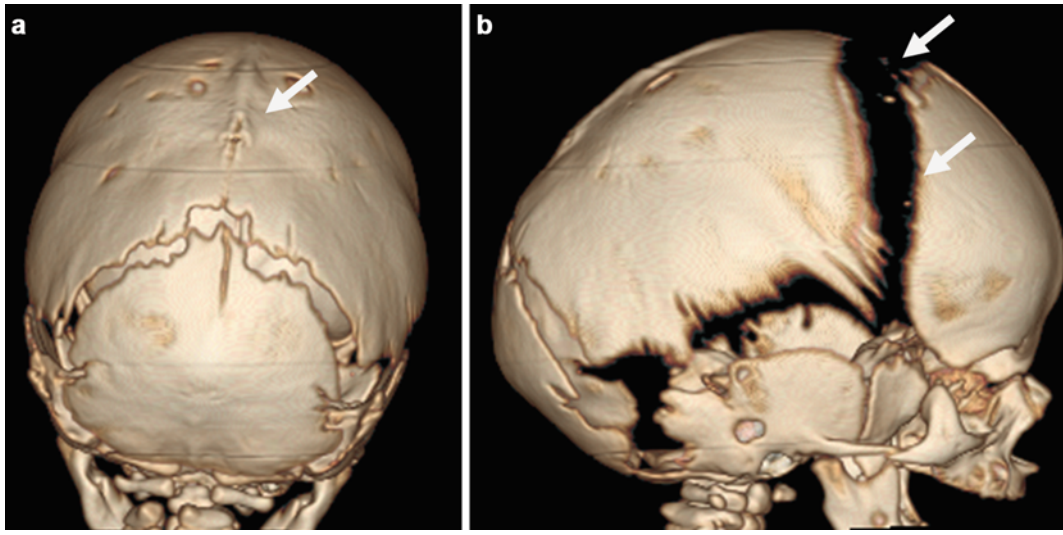

Fig. 4 (**a**, **b**) A 7-day-old boy was evaluated for Crouzon syndrome. CT scan showed complete sagittal synostosis (*arrow*) with consequent scaphocephaly (**a**). Partial fusion of the inferior aspect of the metopic suture was noted. The remainder of the sutures (*arrows*) is widened (**b**) (Courtesy of Dr. Grace Guo)

Cutaneous Vasculitis

Contents

Vasculitis, inflammation of the vessel wall, can result in mural destruction with hemorrhage, aneurysm formation, and infarction, or intimal-medial hyperplasia and subsequent stenosis leading to tissue ischemia and infarction. The skin, in part due to its large vascular bed, exposure to cold temperatures, and frequent presence of stasis, is involved in many distinct as well as unnamed vasculitic syndromes that vary from localized and self-limited to generalized and life-threatening with multi-organ disease. Cutaneous vasculitis comprises a wide spectrum of overlapping primary and secondary disease entities that are characterized by predominant skin involvement and varying degrees of systemic manifestations (Carlson et al. 2005).

Synonyms and Related Disorders

Cutaneous leukocytoclastic angiitis/vasculitis; Cutaneous small vessel vasculitis; Hypersensitivity angiitis/vasculitis; Leukocytoclastic vasculitis; Necrotizing vasculitis

Genetics/Basic Defects

1. Etiology:
    1. A primary process: no known cause or association
    2. A secondary process:
        1. Drug ingestion
        2. Infection
        3. Local factors such as trauma
        4. Systemic disease such as rheumatoid arthritis
2. Factors associated with vasculitis (Carlson et al. 2005):
    1. Gene polymorphisms:
        1. Major histocompatibility complex (MHC)
        2. Intercellular adhesion molecule 1 (ICAM1)
        3. Interleukin 1 receptor antagonist (IL1RA)
        4. Endothelial nitric oxide synthetase (eNOS)
    2. Chronic infections:
        1. Bacteria:
            1. *Neisseria* species
            2. *Staphylococcus aureus*

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. *Streptococcus* species
4. *Mycobacterium* species

2. *Rickettsia*: Rocky Mountain spotted fever
3. Virus:
   1. Hepatitis viruses A, B, and C
   2. *Hantavirus*
   3. *Herpesviridae*
   4. Parvovirus B19
   5. Human immunodeficiency virus
4. Fungus
5. Protozoa: malaria
6. Helminthic infections:
   1. Gnathostomiasis
   2. Schistosomiasis

3. Drugs:
   1. Insulin
   2. Antibiotics (penicillin, sulfonamides, chloramphenicol, streptomycin)
   3. Anticonvulsants (hydantoin)
   4. Diuretics (thiazides, furosemide)
   5. Analgesics (aminosalicylic acid, phenylbutazone)
   6. Phenothiazine
   7. Vitamins
   8. Quinine
   9. Streptokinase
   10. Tamoxifen
   11. Oral contraceptives
   12. Serum (sickness)
   13. Propylthiouracil
   14. Potassium iodide
   15. Granulocyte colony-stimulating factor (GCSF)
   16. Leukotriene inhibitors (montelukast)
   17. Interferons (IFN-γ/α)
   18. Nicotine patches
   19. TNF inhibitors
4. Vaccines:
   1. Anti-influenza
   2. Anthrax
   3. Hepatitis B
5. Chemicals, environmental agents, and external factors:
   1. Insecticides
   2. Petroleum products
   3. Particulate silica (quartz, granite, sandstone, and grain dust)
   4. Solvents
   5. Farm work
   6. Drug abuse (cocaine)
   7. Radiocontrast media
   8. Protein A column pheresis
   9. Arthropod assaults
   10. Prolonged exercise
   11. Coronary artery bypass surgery
   12. Coral ulcers
6. Allergy:
   1. Food allergens (milk proteins, gluten)
   2. Drug allergy
   3. Atopy
   4. Hyposensitization antigen
7. Connective tissue diseases:
   1. Systemic lupus erythematosus
   2. Rheumatoid arthritis
   3. Sjogren syndrome
   4. Mixed connective tissue disease
   5. Scleroderma
   6. Dermatomyositis/myositis
   7. Relapsing polychondritis
   8. Ankylosing spondylitis
   9. Primary biliary cirrhosis
   10. Adult Still disease
8. Other systemic inflammatory diseases:
   1. Behcet disease
   2. Sarcoidosis
   3. Inflammatory bowel disease
9. Chronic disease:
   1. Cryoglobulinemia
   2. Hyperglobulinemic states
   3. Cystic fibrosis
   4. Bowel-bypass syndrome
   5. Alpha-1 antitrypsin deficiency
   6. St. Jude aortic valve replacement
   7. Diabetes mellitus
   8. Chronic hepatitis (viral, alcoholic)
   9. Endocarditis
   10. Wiskott-Aldrich syndrome
   11. Hemolytic anemia
10. Immunodeficiency states:
    1. Primary combined immunodeficiency
    2. Acquired immunodeficiency syndrome (AIDS)
11. Cancer, lymphoproliferative disorders:
    1. Hodgkin disease
    2. Mycosis fungoides

3. Chronic lymphocytic leukemia
4. B- and T-cell lymphomas
5. Myeloma
6. Adult T-cell lymphoma/leukemia
7. Waldenstrom macroglobulinemia
8. Angioimmunoblastic lymphadenopathy
9. Hairy cell leukemia

12. Cancer, solid tumors/carcinomas:
    1. Lung, colon, renal, breast, prostate, head, and neck squamous cell carcinoma
    2. Nasopharyngeal carcinoma
    3. Barrett esophagus

Clinical Features

1. Physical signs of cutaneous vasculitis affecting the skin with varying intensity, depth, and distribution (Carlson et al. 2005):
    1. Urticaria
    2. Purpura
    3. Purpuric papules
    4. Infiltrated erythema
    5. Ulcer
    6. Infarct
    7. Livedo reticularis
    8. Nodules
2. Clinical assessment for extracutaneous (systemic) vasculitis (Carlson et al. 2005):
    1. Systemic (generalized) disease:
        1. Malaise
        2. Myalgia
        3. Arthralgia/arthritis
        4. Headache
        5. Fever
        6. Weight loss
    2. Mucous membranes and eyes:
        1. Oral or genital ulcers
        2. Proptosis
        3. Conjunctivitis
        4. Episcleritis
        5. Visual disturbances
        6. Uveitis
        7. Retinal exudates/hemorrhages
    3. Ear, nose, and throat disease:
        1. Nasal obstruction
        2. Bloody nasal discharge
        3. Crusting
        4. Sinus involvement
        5. New deafness
        6. Hoarseness/stridor
        7. Subglottic stenosis
    4. Respiratory disease:
        1. Persistent cough
        2. Dyspnea
        3. Wheeze
        4. Hemoptysis
        5. Pulmonary
        6. Hemorrhage
        7. Nodules
        8. Cavities
        9. Infiltrates
        10. Pleurisy/pleural effusion
        11. Respiratory failure
    5. Genitourinary disease:
        1. Hypertension >95 mg Hg diastolic
        2. Proteinuria >0.2 g/24 h
        3. Hematuria >10 red blood cells/ml
        4. Renal impairment/failure
        5. Rise in creatinine >30% or fall in creatinine clearance >25%
    6. Neurologic disease:
        1. Organic confusion/dementia
        2. Seizures (not hypertensive)
        3. Stroke
        4. Cord lesion
        5. Sensory peripheral neuropathy
        6. Cranial nerve palsy
        7. Motor mononeuritis multiplex
    7. Gastrointestinal disease:
        1. Severe abdominal pain
        2. Bloody diarrhea
        3. Intestinal perforation/infarction
        4. Acute pancreatitis
3. A constellation of morphologic signs overlapping with another clinical entity preventing confident clinical diagnosis (Guillevin et al. 1996; Sorensen et al. 2000).
4. Names of vasculitides adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis (CHCC1994): the goals were to reach consensus on names of the

most common forms of vasculitis and to construct a specific definition for each (Jennette et al. 1994). For American College of Rheumatology (ACR) criteria, please refer to Carlson et al. (2005).

1. Large vessel vasculitis:
    1. Giant cell (temporal) arteritis:
        1. Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery
        2. Often involves the temporal artery
        3. Usually occurs in patients older than 50 and often associated with polymyalgia rheumatica
    2. Takayasu arteritis:
        1. Granulomatous inflammation of the aorta and its major branches
        2. Usually occurs in patients younger than 50
2. Medium-sized vessel vasculitis:
    1. Polyarteritis nodosa: necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
    2. Kawasaki disease:
        1. Arteritis involving large, medium-sized, and small arteries and associated with mucocutaneous lymph node syndrome.
        2. Coronary arteries are often involved.
        3. Aorta and veins may be involved.
        4. Usually occurs in children.
3. Small vessel vasculitis:
    1. Wegener granulomatosis:
        1. Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries).
        2. Necrotizing glomerulonephritis is common.
    2. Churg-Strauss syndrome: eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and eosinophilia
    3. Microscopic polyangiitis:
        1. Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (capillaries, venules, and arterioles).
        2. Necrotizing arteritis involving small- and medium-sized vessels may be present.
        3. Necrotizing glomerulonephritis: very common.
        4. Pulmonary capillaritis often occurs.
    4. Henoch-Schonlein purpura:
        1. Vasculitis, with IgA-dominant immune deposits, affecting small vessels (capillaries, venules, and arterioles)
        2. Typically involves the skin, gut, and glomeruli and is associated with arthralgias or arthritis
    5. Cryoglobulinemic vasculitis (essential):
        1. Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with cryoglobulins in the serum.
        2. The skin and glomeruli are often involved.
    6. Cutaneous leukocytoclastic vasculitis: isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis
5. Because of our understanding of vasculitis, another (Revised) International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides (CHCC2012) was convened to improve CHCC1994 nomenclature, change names and definitions as appropriate, and add important categories of vasculitis that were not included in CHCC1994 (Jennette et al. 2013). Names for vasculitides adopted by CHCC2012 are:
    1. Large vessel vasculitis:
        1. Takayasu arteritis
        2. Giant cell arteritis
    2. Medium vessel vasculitis:
        1. Polyarteritis nodosa
        2. Kawasaki disease

3. Small vessel vasculitis (SVV):
   1. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis:
      1. Microscopic polyangiitis
      2. Granulomatosis with polyangiitis (Wegener)
      3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
   2. Immune complex SVV:
      1. Anti-glomerular basement membrane disease
      2. Cryoglobulinemic vasculitis
      3. IgA vasculitis (Henoch-Schonlein)
      4. Hypocomplementemic urticarial vasculitis
4. Variable vessel vasculitis:
   1. Behcet disease
   2. Cogan syndrome
5. Single-organ vasculitis:
   1. Cutis leukocytoclastic angiitis
   2. Cutaneous arteritis
   3. Primary central nervous system vasculitis
   4. Isolated aortitis
   5. Others
6. Vasculitis associated with systemic disease:
   1. Lupus vasculitis
   2. Rheumatoid vasculitis
   3. Sarcoid vasculitis
   4. Others
7. Vasculitis associated with probable etiology:
   1. Hepatitis C virus-associated cryoglobulinemic vasculitis
   2. Hepatitis B virus-associated vasculitis
   3. Syphilis-associated aortitis
   4. Drug-associated immune complex vasculitis
   5. Drug-associated ANCA-associated vasculitis
   6. Cancer-associated vasculitis
   7. Others

6. Prognosis:
   1. Cutaneous vasculitis should be considered a cutaneous disease with potential to progress to life-threatening systemic disorder (Figs. 1–3) as a minority of these patients will have internal organ involvement and a few of these patients will die of vasculitis.
   2. Mean mortality: 4%.

Diagnostic Investigations

1. Skin biopsy for routine histologic examination, direct immunofluorescence, and tissue culture and sensitivity:
   1. Acute signs: fibrinoid necrosis.
   2. Chronic signs: endarteritis obliterans.
   3. Past signs: acellular scar of healed arteritis.
   4. Presence of extravascular findings such as patterned fibrosis or collagenolytic granulomas.
   5. Most biopsies of cutaneous vasculitis will exhibit a small vessel neutrophilic vasculitis (leukocytoclastic vasculitis) that is associated with immune complexes on direct immunofluorescence examination or, less commonly, antineutrophil cytoplasmic antibodies by indirect immunofluorescence testing (Carlson and Chen 2007).
2. Laboratory studies (Carlson et al. 2005):
   1. Routine blood tests for full blood count, erythrocyte sedimentation rate, aminotransferases, alkaline phosphatase, albumin, bilirubin, creatinine, blood urea nitrogen, serum electrolytes, and urine analysis
   2. Tests for antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), rheumatoid factor, antidouble-stranded DNA, cryoglobulins, precipitins (Ro, La, RNP, Sm), and complement studies (CH50, C3, C4)
   3. Thrombophilia tests for anticardiolipin antibody, lupus anticoagulant (activated partial thromboplastin time, Russell viper venom test), thrombin time, prothrombin time, antigenic and functional antithrombin III, protein C, protein S, factor V Leiden mutation, and serum homocysteine levels
   4. Paraproteinemia screens including serum protein electrophoresis, serum protein immunofixation, serum immunoglobulins, and random urine protein immunofixation

5. Viral serologic screens for human immunodeficiency virus and hepatitis B and C
6. ECG

3. Radiology:
   1. Chest X-ray.
   2. Skeletal survey (Fig. 4).
      1. Bone age: may be retarded.
      2. Joints: contractures.
      3. Tubular bones: infarcts.
      4. Subcutaneous tissue: calcifications may be present.
      5. Fractures of tubular bones and spines.

Genetic Counseling

1. Recurrence risk: depends on underlying etiology
2. Prenatal diagnosis: not reported to date
3. Management (Carlson et al. 2005; Chen and Carlson 2008):
   1. By and large empiric in nature and defined by the principal of do no harm.
   2. The foremost reason to treat: to comfort the patient.
   3. In most instances, cutaneous vasculitis represents a self-limited condition and will be relieved by leg elevation, avoidance of standing, and therapy with NSAIDs.
   4. For mild recurrent or persistent disease, colchicine and dapsone are first-choice agents.
   5. Severe cutaneous disease requires treatment with systemic corticosteroids or more potent immunosuppression (azathioprine, methotrexate, and cyclophosphamide).
   6. A combination of corticosteroids and cyclophosphamide is required therapy for systemic vasculitis, which is associated with a high risk of permanent organ damage or death.
   7. In cases of refractory vasculitis, plasmapheresis and intravenous immunoglobulin are viable considerations.
   8. The new biologic therapies that act via cytokine blockade or lymphocyte depletion, such as the tumor necrosis factor-α inhibitor infliximab (Booth et al. 2004) and the anti-B-cell antibody rituximab, respectively, are showing benefit in certain settings such as connective tissue disease (CTD) and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.
   9. Goal of treatment for more severe vasculitis: to prevent extensive ulceration and infarction (permanent damage of the skin and other tissues).
   10. Treatment of small vessel neutrophilic vasculitis: follow a therapeutic ladder from safe and cheap (e.g., support hose and antihistamines) for nonulcerative, purpuric lesions to expensive and dangerous (e.g., daily pulses of cyclophosphamide) for severe systemic disease with ulcers and infarcts (Sais et al. 1998; Lotti et al. 1998; Garcia-Porrua et al. 2001).
   11. In cases not associated with systemic involvement or neuropathy, conservative treatment usually leads to good results.
   12. If an associated disorder can be identified, management of this disorder may result in abatement or clearing of the vasculitis. For example, hepatitis C-induced mixed cryoglobulinemia treated with IFN-α and antiviral medication (ribavirin) leads to decreased liver inflammation and resolution of the hepatitis C-associated vasculitis.
   13. Suppression of inflammation due to systemic inflammatory disorders such as CTD may reduce both acute and long-term vascular damage (Raza et al. 2000).
   14. Basic instructions on self-care, including diminishing factors known to exacerbate vasculitis such as excessive stress or heat or cold exposure (in vasculitis caused by cryoglobulins).
   15. The bottom line in caring for patients with cutaneous vasculitis is to tailor treatment to disease severity (Willcocks et al. 2003).

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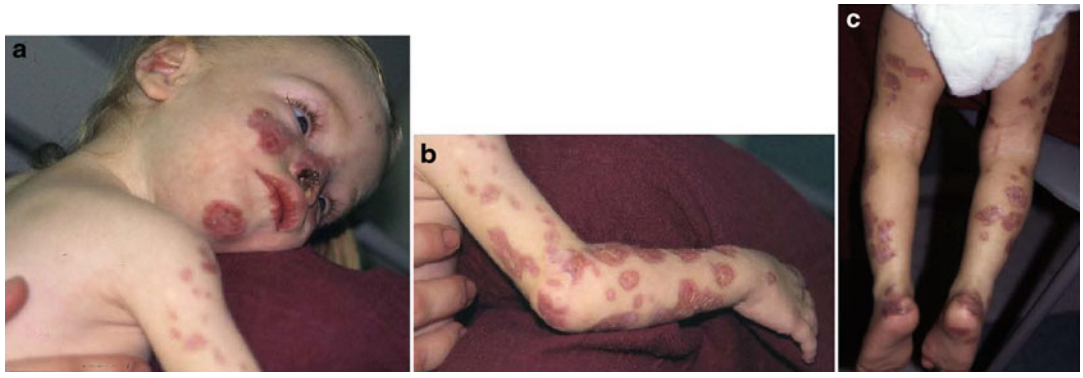

Fig. 1 (**a**–**c**) A 6-year-old Caucasian female was seen for leukocytoclastic vasculitis of unknown etiology, possibly due to autoimmune etiology. She was born 2 weeks early with birth weight of 5 lb 14 oz. She appeared developing normally until around 2 months of age when she was noticed to have small *red dots* on her soles, associated with fever. The rash started as small papules and then ulcerated, spreading to the body and face and leaving extensive scarring. She was also noted to have failure to thrive, growth retardation, developmental delay, and aspiration pneumonia. Throughout the course of her history, the patient has seen rheumatologists, allergists, immunologists, infectious disease experts, dermatologists, and geneticists. Antibiotics, steroids, and methotrexate were tried without success. The biopsy was performed around 3 months of age and was interpreted to be leukocytoclastic vasculitis. A second biopsy around 1 year of age was interpreted to be lupus erythematosus. She had bilateral cataracts and severe growth retardation (severe short stature). She auto-amputated her nasal cartilage and right fifth digit and had multiple contractures at the elbows, knees, ankles, and wrists. She also had chronic hypertension, limb spasticity, chronic infections, and chronic osteomyelitis of multiple joints

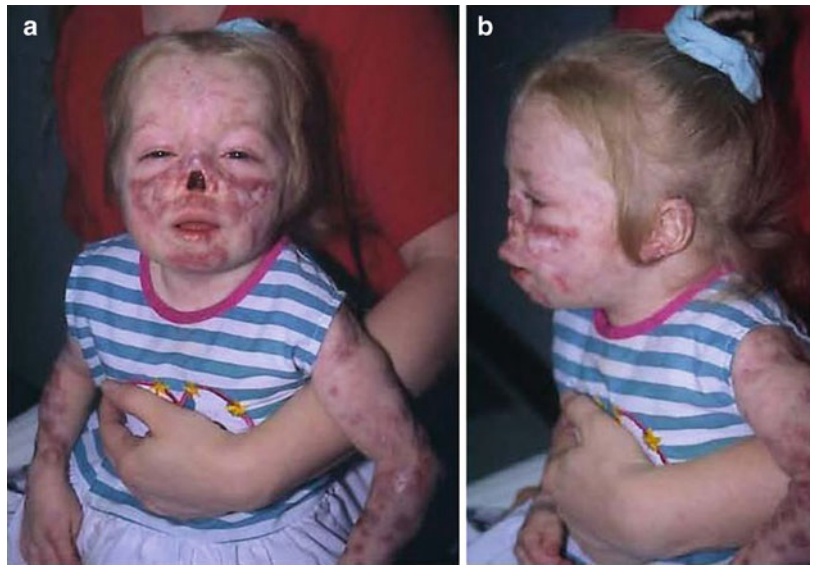

Fig. 2 (**a**, **b**) Patient at 7 years of age

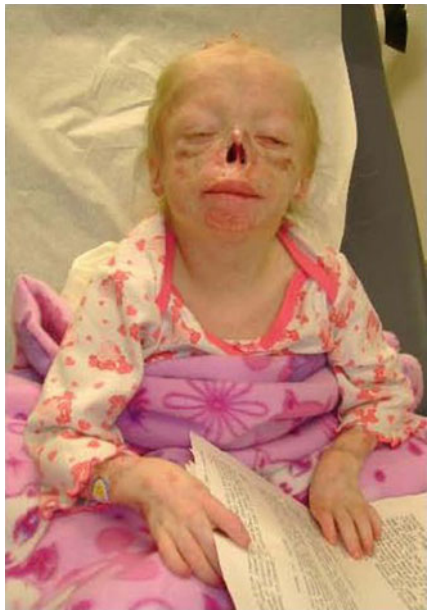

Fig. 3 Patient at 12 years of age. Her height was 34½ in. (height age of approximately 2 years and 3 months). Her weight was 22 lb (weight age of approximately 2 years of age). She had extensive skin lesions affecting mostly the nose, face, cheeks, mouth, ears, and upper and lower extremities. Her trunk, chest, and abdomen were mostly spared. The cartilage portion (nose tip) of her nose was gone. The skin lesions were dry and irregularly shaped with healed ulcerations (*reddened color*). She was admitted to NIH under the undiagnosed diseases program protocol at 17 years of age with chief complaints of leukocytoclastic vasculitis, lupus profundus, bilateral cataracts, multiple joint contractures, hypertension, and severe growth retardation, Raynaud phenomenon with auto-amputation, spasticity, chronic elevated CRP, and wounds with a history of *Pseudomonas* infection with sensitivity to amikacin and gentamicin. She was diagnosed to have a rheumatologic process involving either a vasculitis or vasculopathy with a destructive panniculitis, severe ichthyosis with autoimmune process of unclear etiology, poor wound healing, primordial dwarfism, chronic osteomyelitis versus primary bone disease of unclear etiology, severe generalized osteopenia, multiple contractures, intellectual disability, iron-deficiency anemia, vitamin D toxicity, left renal stones, and vitamin A and zinc deficiencies. This patient may represent a unique syndrome (Collaboration with Dr. Vidya Raman)

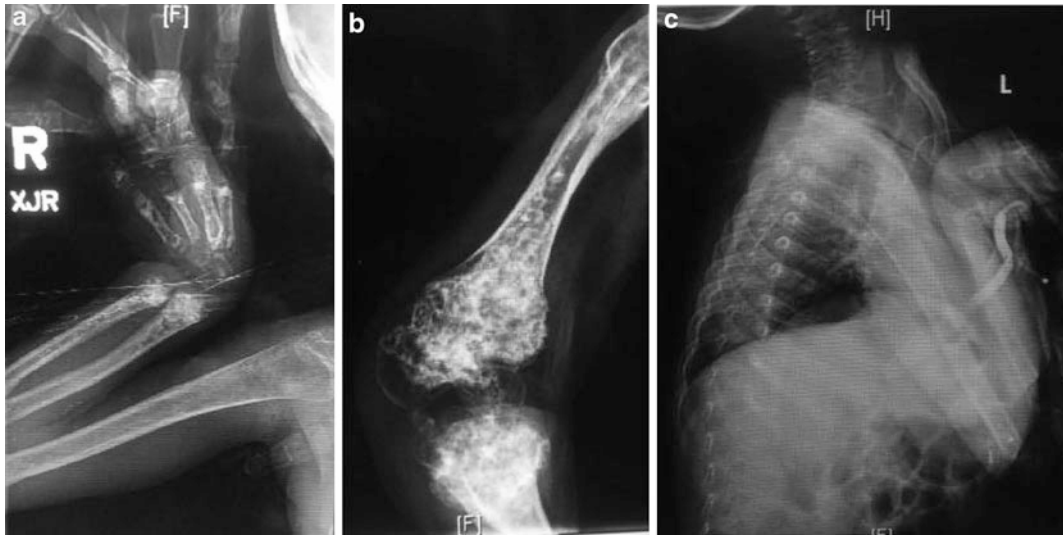

Fig. 4 (**a**–**c**) The radiographs at 18 years of age showed widespread blastic lesions (bone marrow calcifications) involving the dia-metaphyseal portions of the distal radius and ulna as well as the metacarpals and phalanges. There were also subcutaneous calcifications in her forearms and elbows. The extremities appeared to be held in a flexion contracture. There was widespread disuse osteoporosis with multiple chronic-appearing compression fractures throughout the thoracic and lumbar spine. Appearance is consistent with widespread chronic-appearing bony infarcts

Cutis Marmorata Telangiectatica Congenita

Contents

In 1922, Van Lohuizen (Van Lohuizen 1922) first described cutis marmorata telangiectatica congenita (CMTC) as a pattern of reticulate erythema and telangiectasia, skin atrophy, and/or ulceration.

Synonyms and Related Disorders

Adams-Oliver syndrome; CMTC phakomatosis pigmentovascularis; Macrocephaly-CMTC syndrome

Genetics/Basic Defects

1. Pathogenesis
    1. Unknown
    2. Most cases are sporadic
2. Hypothesis
    1. Environmental factors
    2. Multifactorial cause
    3. A nerve conduction defect (Bormann et al. 2001)
    4. A lethal gene surviving by mosaicism suggested by segmental distribution often with a sharp midline separation (Rogers and Poyzer 1982)
    5. Autosomal dominant inheritance with low or variable penetrance
        1. An affected parent showing more limited involvement than his offspring (Kurczynski 1982)
        2. Two siblings with one having CMTC alone and the other showing associated anomalies (hypertension and acrocyanosis) (Andreev and Pramatarov 1979)

Clinical Features

1. Onset (Garzon and Schweiger 2004):
    1. Congenital: common
    2. Later onset (Way et al. 1974)
2. Reticulated vascular pattern
    1. Finely reticular or coarse pattern: will not resolve completely with warming of the skin
    2. Broad streaks of discolored skin in a "train-track-like" pattern
    3. Relatively fixed and discernable at rest
    4. Pallor of the skin between the vascular network pattern: often reported (Ben-Amitai et al. 2000)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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5. Often accompanied by:
    1. Phlebectasia (prominent veins)
    2. Telangiectasias
    3. Cutaneous and subcutaneous tissue atrophy: may manifest as hypoplasia of the affected limb (an inconsistent feature) (South and Jacobs 1978)
    4. Ulceration of the affected skin, particularly involving the skin overlying the elbows and knees (Picascia and Esterly 1989)
    5. Hyperkeratosis
6. The presence of atrophy and ulceration helps to differentiate CMTC from physiologic cutis marmorata
7. Localized lesions
    1. Most commonly affecting the trunk and extremities
    2. Sharp segmental pattern: easy to differentiate from physiologic cutis marmorata
8. Generalized lesions
    1. Often unilateral
    2. May involve face but mucosal involvement uncommon (Ben-Amitai et al. 2000)
    3. Do not occur on the entire body surface (Devillers et al. 1999)

3. Associated anomalies (27–80%) (Picascia and Esterly 1989; Devillers et al. 1999; Gerritsen et al. 2000)
    1. Relatively high associated defects
        1. May represent true associations or coincidental
        2. May represent a bias toward reporting cases with more severe anomalies
        3. Inconsistency among authors regarding diagnostic criteria
    2. Asymmetry
        1. Limb asymmetry (hyperplasia or hypoplasia of a limb)
            1. The most common associated anomaly
            2. Cutaneous atrophy may be noted concomitantly with asymmetry
        2. Facial asymmetry may occur
    3. Skeletal defects
        1. Syndactyly
        2. Tendonitis stenosans
        3. Hip dysplasia
        4. Clubfoot
        5. Scoliosis
        6. Macrocephaly
        7. Skull asymmetry
        8. Scaphoid scapula
        9. Micrognathia
        10. Generalized osteoporosis
        11. Consider Adams-Oliver syndrome and macrocephaly-CMTC if limb defects are present
4. Other vascular anomalies:
    1. May occur distant to the area of CMTC or within the same affected area (Picascia and Esterly 1989)
    2. Capillary malformations (port-wine stains): the most commonly associated vascular birthmark occurring in 20% of patient (Ben-Amitai et al. 2000)
    3. Sturge-Weber syndrome (Petrozzi et al. 1970)
    4. Hemangiomas of infancy
    5. Multiple angiokeratomas
5. Ocular anomalies:
    1. Glaucoma
    2. Infrequent anomalies:
        1. Persistent arterial hyaloidia (an embryonic vessel that typically regresses)
        2. Granular retinal pigmentation
        3. Small optic disks
        4. Optic nerve atrophy
6. Macrocephaly-CMTC syndrome (Moore et al. 1997; Robertson et al. 2000; Lapunzina et al. 2004; Katugampola et al. 2008):
    1. Macrocephaly and cutis marmorata: diagnostic features
    2. Hypotonia
    3. Psychomotor retardation
    4. Seizures
    5. Hydrocephaly
    6. Cerebral atrophy
    7. Agenesis of the corpus callosum
    8. Dilated ventricles
    9. Hemangioma of the lip and philtrum
    10. Syndactyly of the second and third toes

11. Segmental overgrowth
12. Connective tissue abnormalities: features similar to Ehlers-Danlos syndrome

7. Other cutaneous anomalies (may be coincidental) (Ben-Amitai et al. 2000):
   1. Congenital melanocytic nevi
   2. Café au lait macules
   3. Mongolian spots
8. Other systemic anomalies (uncommon):
   1. Hypothyroidism
   2. Cardiac defects
   3. Genitourinary tract anomalies (Del Guidice and Nydorf 1986; Ben-Amitai et al. 2001; Sills et al. 2002; Fujita et al. 2003):
      1. Hypospadias
      2. Renal cysts
      3. Duplication of the renal collecting system
      4. Rectovaginal and ureterovaginal fistulae
      5. Absent clitoris
      6. Imperforate anus
      7. Unilateral ovarian agenesis
      8. Septate uterus
      9. Premature gonadal failure associated with de novo balance translocation affecting chromosomes 8 and 9

4. Suggested diagnostic criteria for cutis marmorata telangiectatica congenita (Kienast and Hoeger 2009): The presence of all three major criteria and two minor criteria is sufficient for diagnosis:
   1. Major criteria
      1. Congenital reticulate (marmorated) erythema (27%)
      2. The absence of venectasia (27%)
      3. Unresponsiveness to local warming (27%)
   2. Minor criteria
      1. Fading of erythema within 2 years (18%)
      2. Telangiectasia (5%)
      3. Port-wine stain outside the area affected by CMTC (2%)
      4. Ulceration (2%)
      5. Atrophy (2%)
5. Differential diagnosis
   1. Cutis marmorata (physiologic)
   2. Cutis marmorata (associated with genetic syndrome)
      1. Cornelia de Lange syndrome
      2. Down syndrome
      3. Homocystinuria
      4. Divry and Van Bogaert syndrome
         1. A rare disorder
         2. Corticomeningeal angiomatosis
         3. Visual field defects
         4. Seizures
         5. "Marble" skin
   3. Reticulated capillary malformations
      1. A diffuse, generalized form of a "livedoid" capillary malformation involving the entire skin
      2. Not associated with atrophy, ulceration, or limb hypoplasia
      3. Associated with a significant risk of associated visceral vascular anomalies (eye, brain, kidneys, and heart) and requires evaluation and follow-up (Enjolras and Garzon 2001)
   4. Bockenheimer syndrome (diffuse phlebectasia):
      1. A very rare disorder
      2. Onset in infancy
      3. Characterized by progressive venous varicosity
   5. Neonatal lupus erythematosus
   6. CMTC "syndrome"
      1. Macrocephaly-CMTC syndrome
      2. Adams-Oliver syndrome
      3. CMTC phakomatosis pigmentovascularis

Diagnostic Investigations

1. Physical evaluation (Garzon and Schweiger 2004)
   1. Reticulated vascular pattern
   2. Limb length and girth
   3. Limb defects
   4. Scalp defects
   5. Head circumference
   6. Other associated anomalies
   7. Facial lesions
2. Ophthalmologic evaluation

3. Brain MRI in macrocephaly-CMTC (Akcar et al. 2004; Giuliano et al. 2004; Garavelli et al. 2005)
    1. Megalencephaly
    2. Asymmetry of the cerebral hemispheres
    3. Abnormally increased signal of white matter
    4. Chiari type I malformation
    5. Bilateral prominent lateral ventricles
    6. Generalized cortical dysplasia
    7. Cavum septi pellucidum cyst
    8. Calvarial hemangioma.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Sporadic cases: a low recurrence risk
        2. A 50% risk if one of the parents is affected
    2. Patient's offspring: a 50% risk in autosomal dominant transmission, otherwise a low recurrence risk
2. Prenatal diagnosis: not reported
3. Management
    1. Careful physical examination to assess for other congenital anomalies
    2. Measurement of limb length and girth at the time of evaluation
    3. Baseline and follow-up ophthalmologic examinations should be performed when the vascular lesions affect the periocular skin
    4. Local supportive care including application of hydrocolloid dressings for ulcerations

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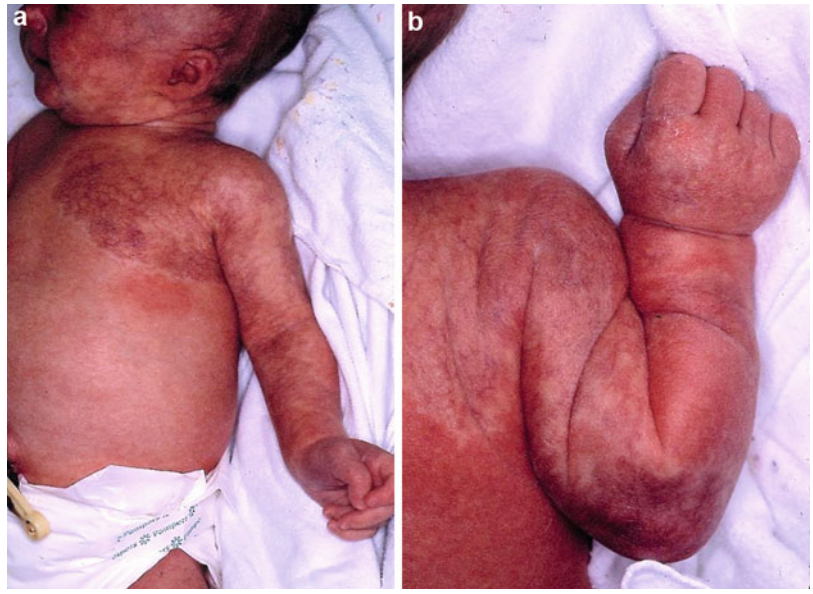

Fig. 1 (**a**, **b**) A 2-month-old infant with cutis marmorata telangiectatica congenita showing a reticular vascular pattern which was present from birth

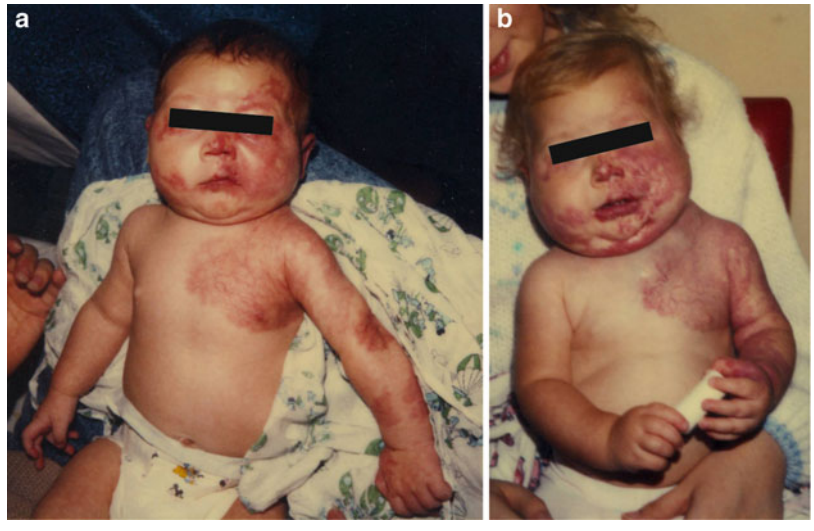

Fig. 2 (**a**, **b**) The same infant at 14 months of age

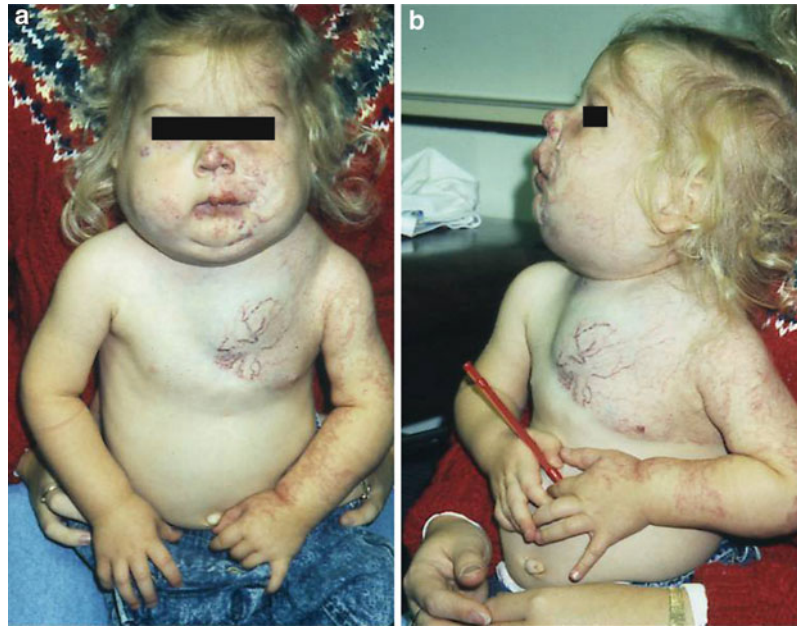

Fig. 3 (**a**, **b**) The same patient at 26 months of age showing development of a large diffuse vascular lesion extending from the whole *left* anterior chest to the *left* neck

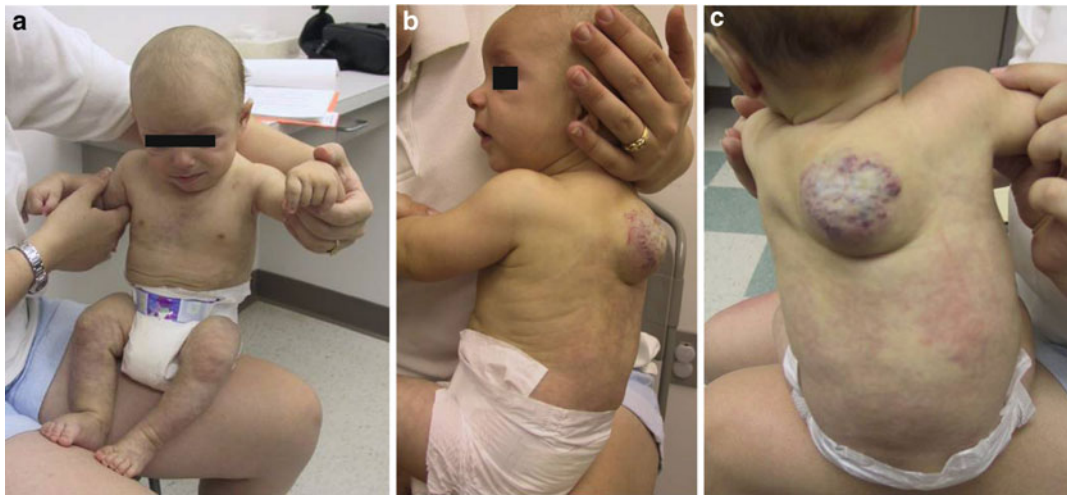

Fig. 4 (**a**–**c**) A 3-month-old infant boy with cutis marmorata telangiectatica congenita. Cutaneous vascular lesions consist of a 4 × 4 × 2 cm soft vascular lesion of the upper posterior back and diffuse *bluish* vascular lesions on the front chest, shoulders, arms, trunk, buttock, and legs. The right leg is larger than the left

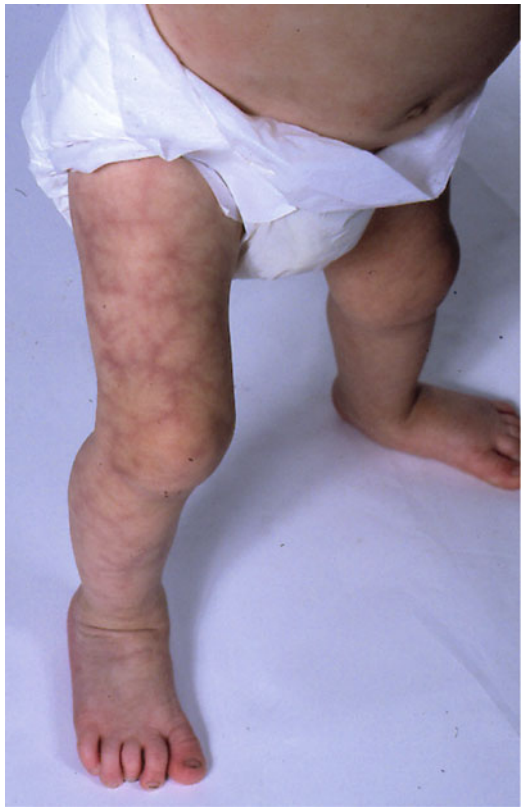

Fig. 5 Another infant with a reticular vascular pattern on the *right* leg

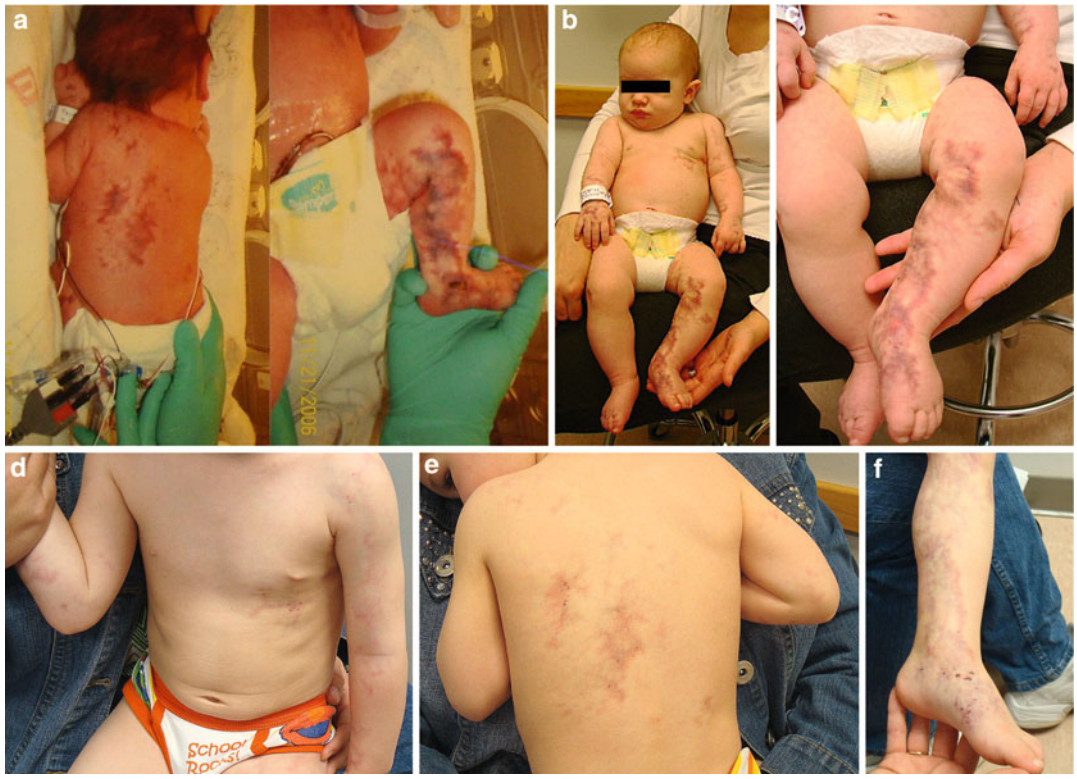

Fig. 6 (**a**–**f**) A child with cutis marmorata telangiectatica congenita at different ages (newborn, 4 months, and 4 years of age)

Cystic Fibrosis

Contents

Cystic fibrosis (CF) is the most common Caucasian lethal genetic disorder (with gene frequency of 1 in 25) in the USA, where 4–5% of population have at least one CF allele. CF affects approximately 1 in 2,500 live births among Caucasians, 1 in 17,000 among African-Americans, and 1 in 90,000 among Asians (Ruzal-Shapiro 1998).

Synonyms and Related Disorders

CFTR-related disorders; Congenital absence of vas deferens; Mucoviscidosis

Genetics/Basic Defects

1. Inheritance
    1. Autosomal recessive
    2. CF gene mapped to chromosome 7q31.2
2. Molecular defect (Moskowitz et al. 2008)
    1. Caused by a single gene defect on chromosome 7 that encodes a cAMP-regulated chloride channel (Davis et al. 1996) known as the cystic fibrosis transmembrane conductance regulator (CFTR)
        1. CFTR usually resides in the apical membrane of epithelial cells lining the airway, biliary tree, intestines, vas deferens, sweat ducts, and pancreatic ducts.
        2. Insufficient fluid secretion secondary to inability of CFTR to transport chloride ion at the above sites causes higher viscidity of the protein portions of the secretions and obstructing the ducts, leading to plugging and dysfunction at the organ level.
        3. CFTR also regulates the activity of other proteins that conduct ions and affects intracellular regulatory processes at the cellular level.
    2. Presence of close to 1,500 different disease-causing mutations of the *CFTR* gene (Ruzal-Shapiro 1998; O'Sullivan and Freedman 2009)
        1. Presence of a striking difference in the distribution of CFTR mutations in different populations (Cystic Fibrosis Genetic Analysis consortium 1994)
        2. Deletion mutations including delta F508 which, observed in over 70% of

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patients with CF, have a deletion of three contiguous base pairs resulting in the loss of a single amino acid, phenylalanine at codon 508
3. Missense mutation (single base pair exchange within a normal length CFTR protein)
4. Nonsense mutations (exchange of a single base pair resulting in premature termination of the protein)
5. Frameshift mutations (the deletions or insertion of a single base pair)

3. Classification of CFTR mutations (Culling and Ogle 2010)
   1. Class I mutations
      1. Introduce a stop codon prematurely
      2. Produce either an unstable mRNA with no detectable protein being made or an unstable protein that is rapidly degraded or has no functional capability
      3. No CFTR protein in the cell membrane
      4. For example, G542X, 394delTT, 1717-1 G → A
   2. Class II mutations
      1. Block the processing of the protein due to aberrant folding and subsequent degradation when recognized as abnormal by cellular "quality control" mechanisms
      2. No CFTR protein at the apical cell membrane
      3. For example, N1303K, ΔF508, 3905insT
   3. Class III mutations:
      1. Produce a CFTR protein that does not function as a chloride channel due to a block in regulation, despite being fully processed and correctly located.
      2. Within this class there are mutations that have very little function (G551D), those where ATP is less potent at stimulating activity (S1255P) and those with reduced absolute activity (G551S, G1244E, and G1349D).
   4. Class IV mutations
      1. Produce a fully processed and correctly located CFTR protein
      2. However, the conductance and/or gating properties of the channel have been altered by mutations in the membrane spanning domains
      3. Extent to which conduction is affected varies between mutations
      4. For example, R117H, R347P
   5. Class V mutations
      1. Result in a reduction in the synthesis of CFTR protein
      2. Include promoter mutations, the promotion of alternative splicing, and inefficient protein maturation
      3. For example, A455E, 2789 + 5G → A, IVS8-5 T
   6. Class VI mutations
      1. Presence of functional but unstable CFTR protein at the apical membrane
      2. Decreased stability on CFTR protein
      3. For example, Q1412X, 4326delTC, 4279insA
4. Genotype-phenotype correlations (Zielenski and Tsui 1995; Kerem and Kerem 1996a, 1996b; Ruzal-Shapiro 1998)
   1. CF phenotype: highly variable and hundreds of different genotypes are responsible for the varied clinical presentations of the disease (Fiel 1998).
   2. Patients with homozygous delta F508 typically have respiratory distress and malabsorption.
   3. A CF mutation associated with mild lung disease: Patients with the *A455E* mutation have a better prognosis than patients who are homozygous for the delta F508 mutation (Gan et al. 1995).

4. A good correlation between CFTR genotype and one of the clinical variables – pancreatic function status.
5. Documentation of CFTR mutations in patients with atypical CF disease presentations, including congenital absence of vas deferens and several pulmonary diseases.
6. Patients with less severe variations of the disease or typical CF with borderline normal sweat tests may have other haplotypes.

Clinical Features

1. Criteria for the diagnosis of CF (Rosenstein and Cutting 1998)
    1. One or more characteristic phenotypic features:
        1. Or a history of CF in a sibling
        2. Or a positive newborn screening test result
    2. And an increased sweat chloride concentration by pilocarpine iontophoresis on two or more occasions:
        1. Or identification of two CF mutations
        2. Or demonstration of abnormal nasal epithelial ion transport
2. Signs and symptoms of cystic fibrosis (Davies et al. 2007; O'Sullivan and Freedman 2009)
    1. General (any age)
        1. Family history of cystic fibrosis
        2. Salty-tasting skin
        3. Clubbing fingers and toes
        4. Cough with sputum production
        5. Mucoid *Pseudomonas aeruginosa* isolated from airway secretions
        6. Hypochloremic metabolic alkalosis
    2. Prenatal
        1. Echogenic bowel on ultrasound
        2. Perforated meconium ileus
    3. Neonatal
        1. Meconium ileus
        2. Protracted jaundice
        3. Abdominal or scrotal calcifications
        4. Intestinal atresia
    4. Infancy
        1. Persistent infiltrates on chest radiographs
        2. Failure to thrive
        3. Anasarca or hypoproteinemia
        4. Chronic diarrhea
        5. Abdominal distention
        6. Cholestasis
        7. *Staphylococcus aureus* pneumonia
        8. Idiopathic intracranial hypertension (vitamin A deficiency)
        9. Hemolytic anemia (vitamin E deficiency causes anemia by increasing fragility and reducing lifespan of red blood cells)
    5. Childhood
        1. Chronic pansinusitis or nasal polyposis
        2. Steatorrhea
        3. Rectal prolapse
        4. Distal intestinal obstruction syndrome or intussusceptions
        5. Idiopathic recurrent or chronic pancreatitis
        6. Liver disease
    6. Adolescence and adulthood
        1. Allergic bronchopulmonary aspergillosis
        2. Chronic pansinusitis or nasal polyposis
        3. Bronchiectasis
        4. Hemoptysis
        5. Idiopathic recurrent pancreatitis
        6. Portal hypertension
        7. Delayed puberty
        8. Azoospermia (male infertility) secondary to congenital bilateral absence of the vas deferens
        9. Malabsorption
        10. Liver disease
        11. Dehydration and electrolyte disturbance (pseudo-Barter syndrome)
3. Classic clinical triad
    1. Exocrine pancreatic insufficiency

2. Chronic obstructive pulmonary disease
3. Elevation of sodium and chloride concentration in sweat

4. Chronic sinopulmonary disease
   1. Varying widely in age of onset and rate of progression
   2. Clinical course
      1. Newborn with CF with histologically normal respiratory systems
      2. First few months of age
         1. Epithelial chloride channel defect, leading to abnormal respiratory secretions, bronchopulmonary infections, and airway obstruction
         2. Clinical manifestations including cough, wheezing, retractions, and tachypnea
   3. Persistent endobronchial infection and inflammation with typical CF pathogens (Ruzal-Shapiro 1998)
      1. *Staphylococcus aureus*
         1. Responsible for the majority of lung disease when CF was first described
         2. Commonly isolated in the first year of life from the sputum of patients with CF
         3. Typically controlled by antibiotic therapy
         4. Currently only 10% of adult patients with CF are chronically colonized by the pathogen.
      2. Mucoid and nonmucoid *Pseudomonas aeruginosa*
         1. The most prevalent of the pathogens in CF, causing chronic infection in up to 90% of adults and 80% of children
         2. Initial colonization with nonmucoid forms
         3. Subsequent conversion to mucoid variants
      3. *Hemophilus influenzae*
         1. Commonly seen in babies
         2. Rarely encountered in the adults
      4. Other pulmonary pathogens
         1. *Burkholderia cepacia*
         2. Aspergillus
         3. Mycobacteria
         4. Respiratory viruses
   4. Upper airway disease
      1. Opacified or maldeveloped sinuses
      2. Nasal polyps (up to 26% of patients)
      3. Sinusitis
         1. Facial pain
         2. Swelling
         3. Tenderness
         4. Air-fluid levels on radiograph
   5. Pulmonary exacerbations
      1. Persistent cough and sputum production
      2. Increased dyspnea
      3. Reduction in pulmonary function
      4. Increased hemoptysis: a life-threatening complication but fatal hemoptysis is rare
      5. Digital clubbing
      6. Changes in chest radiographic findings
      7. Bronchiolitis
      8. Increased rales or rhonchi
      9. Decreased air exchange
      10. Increased use of accessory muscles of respiration
      11. Spontaneous pneumothorax (5–8%), a life-threatening complication
      12. Obstructive airway disease, leading to respiratory insufficiency associated with bronchiectasis
5. Gastrointestinal abnormalities (Shalon and Adelson 1996; Haller et al. 2014)
   1. Intestine
      1. Meconium ileus at birth
         1. An obstruction of the distal ileum or proximal colon with thickened, viscous meconium in 15–20% of CF patients developed in utero in the second trimester
         2. Virtually diagnostic of CF
      2. Meconium peritonitis (rupture of the intestine secondary to complete obstruction)
      3. Meconium plug syndrome in the newborn infants, a more benign

condition characterized by blockage of the colon
4. Distal intestinal obstruction syndrome later in childhood, adolescence, or adulthood (10%), presenting as crampy abdominal pain, usually with decreased stooling
5. Rectal prolapse occurring in less than 1% of patients but may be the presenting symptom, particularly in infants
6. Occasional intussusception
7. Disorders of motility
    1. Gastroesophageal reflux (GER)
    2. Gastroparesis: previously described as a common phenomenon in the group of lung-transplanted patients and may be associated with the increased incidence of GER and its pulmonary complications
8. Disorders related to intestinal dysbiosis, infection, and inflammation
    1. Small bowel bacterial overgrowth
    2. Colonic dysbiosis
    3. *Clostridium difficile* infection
    4. Intestinal inflammation and associated gastrointestinal disorders
9. Disorders of intestinal obstruction
    1. Meconium ileus
    2. Constipation
    3. Intussusception
    4. Appendicitis
10. Gastrointestinal cancer

2. Pancreas
    1. Pancreatic exocrine insufficiency
        1. Failure of the pancreas to produce sufficient digestive enzymes to allow breakdown and absorption of fats and protein
        2. Obstruction of the pancreatic duct in utero with resultant progressive loss of exocrine pancreatic acini and their function
        3. A hallmark of the disease, occurring in 90% of patients by 1 year of age
        4. Leads to frequent, bulky, foul-smelling, oily stools
        5. Steatorrhea (presence of excessive undigested fat in the stool)
        6. Failure to thrive is common in the patients with CF
    2. Recurrent pancreatitis in few patients
    3. CF-related diabetes mellitus (Nathan et al. 2010)
        1. Affect approximately one third of all CF patients
        2. Rare before 10 years of age
        3. Resulting from a loss of functional pancreatic β cells and a state of relative insulin deficiency
        4. Oral glucose tolerance test as a screening tool
        5. HbA1c, an accepted diagnostic test for diabetes in the general population (International Expert Committee 2009), cannot be used as screening tool because levels are often falsely low (Holl et al. 2000).
3. Liver
    1. Prolonged obstructive jaundice in a few affected infants, presumably secondary to obstruction of extrahepatic bile ducts by thick bile along with intrahepatic bile stasis
    2. Chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis or multilobular cirrhosis

6. Genitourinary manifestations (Ruzal-Shapiro 1998)
    1. Congenital bilateral absence of the vas deferens in most males
        1. Leading to azoospermia
        2. A significant cause of infertility
    2. Infertility common in women
        1. Due to increased amounts of thick mucus in the cervical canal
        2. An increased incidence of amenorrhea
        3. Occasional patients carrying pregnancies to term without significant respiratory deterioration

7. Skeletal manifestations (Ruzal-Shapiro 1998)
    1. Hypertrophic pulmonary osteoarthropathy
        1. Rarely seen in children with CF
        2. Increasing frequency with increasing age and severity of disease
    2. Triad of skeletal manifestations
        1. Clubbing of fingers and toes
        2. Arthritis
        3. Periosteal new bone formation
8. Nutritional abnormalities
    1. Failure to thrive, a common manifestation during infancy and beyond
    2. Poor appetite
    3. Weight loss
    4. Fatigue
    5. Prone to heat prostration
    6. Hypoproteinemia with or without edema, anemia, and deficient fat-soluble vitamins A, D, E, and K
    7. Peripheral neuropathy secondary to deficient vitamin E
    8. Delayed puberty largely due to nutritional factors
    9. Potentially lethal protein-energy malnutrition in some infants
    10. Development of some degree of malabsorption by 4 years of age in roughly 85% of patients
9. Salt losing syndromes
    1. Acute salt depletion
    2. Chronic hypochloremic or hyponatremic alkalosis
    3. Excessive salt loss in the sweat potentially fatal for patients exposed to moderate heat or during prolonged hot weather
10. Prognosis
    1. Respiratory failure: the leading cause of death in CF and occurs eventually in nearly all patients
    2. Current median survival: approximately 35 years in the USA
    3. Current data suggesting a lifespan exceeding 50 years for those diagnosed and treated early

Diagnostic Investigations

1. Newborn screening (Farrell and Mischler 1992; Pollitt 1998; Farrell 2000; Farrell and Farrell 2003)
    1. Potential benefits
        1. Reductions in mortality (patients dying with undiagnosed CF estimated at 5%)
        2. Improved nutrition
        3. Informed reproductive decisions
        4. Creation of the opportunity for early pulmonary intervention before irreversible lung disease develops
    2. Measuring blood immunoreactive trypsinogen in dried blood spots (Hammond et al. 1991)
        1. Elevated levels in most CF infants (85–90% sensitive)
        2. Associated with a relatively large number of false-positive results
        3. Diagnosis must be confirmed by sweat tests or genotyping (CF multimutational analysis)
    3. Use DNA-based testing on dried blood spots by CFTR multimutational analysis
2. Population screening (Grody 1999)
    1. Target population to be offered testing (the entire population vs. high-risk ethnic groups)
    2. Size and nature of the mutation test panel (universal vs. ethnic specific)
    3. Inclusion or exclusion of CFTR variants that do not cause classical CF
    4. Optimal testing technology
    5. Appropriate standards for laboratory quality assurance
    6. Development of sufficient educational materials
    7. Genetic counseling resources for test delivery
    8. Reporting and interpretation
3. Sweat test (Bye et al. 1994; LeGrys 1996; LeGrys et al. 2007)
    1. The traditional method (gold standard) of CF diagnosis

2. Remains the most readily available and clinically useful way of making the diagnosis of CF, provided it is done according to strict guidelines with pilocarpine iontophoresis and a quantitative determination of chloride concentration (LeGrys et al. 2007)
3. Reliably identifies the vast majority of patients with CF who have multiorgan involvement including the lungs and pancreas
4. Using pilocarpine iontophoresis technique to produce sweat for chloride analysis
5. Sweat chloride concentrations
    1. >60 mEq/L, observed in:
        1. CF patients with clinical manifestation of chronic pulmonary disease and/or pancreatic insufficiency
        2. CF patients with positive family history
        3. Untreated Addison disease
        4. Ectodermal dysplasia
        5. Certain types of glycogen storage diseases
        6. Untreated hypothyroidism
        7. A few normal adults
    2. <60 mEq/L, observed in:
        1. Very few patients with CF (fewer than 1% of CF patients when they are well)
        2. CF patients with malnutrition and edema

4. Indications for sweat testing (Davis 2001)
    1. Meconium ileus or peritonitis (neonate)
    2. Jaundice (infancy)
    3. Hypochloremic alkalosis (infancy)
    4. Heat prostration (infancy or adulthood in males)
    5. Failure to thrive (infancy to childhood)
    6. Rectal prolapse (childhood)
    7. Nasal polyposis (childhood to adulthood)
    8. Panopacification of sinuses or pansinusitis (childhood)
    9. Pancreatitis (late childhood to early adulthood)
    10. Unexplained cirrhosis (childhood to adolescence)
    11. Gallstones (late childhood to early adulthood)
    12. Congenital bilateral absence of the vas deferens or azoospermia (any age but more obvious in adults)
    13. Recurrent or persistent pneumonia (any age)
    14. Staphylococcal pneumonia (any age but especially infants)
    15. Mucoid *Pseudomonas* in lung (any age)
    16. Bronchiectasis (any age)
    17. Positive family history in siblings or first cousins (any age)
5. Causes of false-positive or false-negative sweat test results (O'Sullivan and Freedman 2009)
    1. False-positive result
        1. Atopic dermatitis (eczema)
        2. Malnutrition
        3. Congenital adrenal hyperplasia
        4. Mauriac syndrome
        5. Fucosidosis
        6. Ectodermal dysplasia
        7. Klinefelter syndrome
        8. Nephrogenic diabetes insipidus
        9. Adrenal insufficiency
        10. Hypothyroidism
        11. Autonomic dysfunction
        12. Environmental deprivation
        13. Munchausen syndrome by proxy
    2. False-negative result
        1. Dilution of sample
        2. Malnutrition
        3. Peripheral edema
        4. Low sweat rate (quantity not sufficient)
        5. Hypoproteinemia
        6. Dehydration
        7. CFTR mutations with preserved sweat duct function (e.g., 3,849 + 10 kb C → T; Arg117His-7 T)

6. Other clinical laboratory tests
    1. Prolonged prothrombin time secondary to deficient vitamin K
    2. Shortened red blood cell survival time secondary to deficient vitamin E
    3. Hypochloremic alkalosis secondary to high salt loss
    4. Isolation of organisms from the respiratory tract
        1. *Pseudomonas aeruginosa*
        2. *Burkholderia cepacia*
        3. *Staphylococcus aureus*
    5. Oxygen saturation
7. Radiographic findings
    1. Chest X-ray
        1. Earliest finding: hyperinflation often with right upper lobe mucus retention
        2. Progression to widespread bronchial dilatation, cysts, linear shadows, and infiltrates
    2. Sinuses X-ray: nearly universal presence of pansinusitis
    3. Abdominal X-ray
        1. Uncomplicated meconium ileus: multiple loops of dilated small bowel
        2. Meconium peritonitis
            1. Calcifications within the abdominal cavity or even within the scrotum
            2. Resulting from an in utero perforation or complicated meconium ileus associated with volvulus
    4. Skeletal X-ray
        1. Arthritis
        2. Periostitis in the diaphysis of the tubular bones
8. CT scan, especially high-resolution CT scan (Ruzal-Shapiro 1998)
    1. Readily identify air trapping in the expiratory phase
    2. Mosaic perfusion, a secondary sign of small airway abnormality
    3. Centilobular nodule characterized by a cluster of ill-defined nodules corresponding to branching terminal airways filled with secretions
    4. Classic findings of CF of progressive bronchiectasis involving the large airways
        1. Thick parallel bronchial walls seen as linear shadows or tram-line tracts
        2. Ring shadows representing dilated thick-walled bronchi
        3. Multiple nodular densities representing mucus plugging
9. Pulmonary function test
10. Molecular testing
    1. More than 1,000 different mutations described to date
    2. ΔF508 mutation (deletion of a phenylalanine residue at position 508 in the 1,480 amino acid protein)
        1. Present in about 70% of CF alleles in the USA
        2. Homozygous ΔF508 mutation in about 50% of American CF patients
    3. Higher frequencies of certain mutations in different ethnic groups
        1. A455E mutation in Dutch CF patients
        2. W1282X mutation in Ashkenazi Jewish CF patients
    4. Presence of two alleles with CF causing mutations confirms the diagnosis
    5. Conventional commercial genotyping testing for about 80 specific mutations in CFTR (including ΔF508 mutation) identifies about 95% of all CF alleles
11. Carrier testing: available for family members of known patients (Wilson et al. 2002) or for couples without a family history
12. In general, a diagnosis of cystic fibrosis can be made in a patient with clinical features of the disease if the concentration of chloride in sweat is greater than 60 mmol/L or if it is in the intermediate range (30–59 mmol/L for infants less than 6 months of age, 40–59 mmol/L for older individuals), and two disease-causing CFTR mutations are identified (Farrell et al. 2008)

Genetic Counseling

1. Recurrence risk
    1. Both parents carrying at least one abnormal copy of the CF gene
    2. Patient's siblings
        1. 25 % with CF disease
        2. 50 % with CF carrier
    3. Patient's offspring: low recurrence risk unless the spouse is affected or a carrier of CF mutation
2. Prenatal diagnosis (Rosenstein 1998)
    1. Prenatal screening programs: ensuring more good than harm, the ultimate objective and duty (Farrell and Fost 2002)
    2. Ultrasonography
        1. Bowel abnormalities in the fetus (Corteville et al. 1996)
            1. Dilated bowel with hyperechoic bowel (33% with cystic fibrosis) (Estroff et al. 1992): outcome (no bowel obstruction, meconium ileus, malrotation, jejunal obstruction/atresia, choledochal cyst)
            2. Ascites: most commonly associated with hydrops of diverse causes
            3. Cystic abdominal masses: outcome (gastrointestinal duplications, meconium pseudocyst, ovarian cyst, choledochal cyst, omental cyst, and biliary atresia)
            4. Fetal bowel anomalies by ultrasonography: indicate a risk of severe cystic fibrosis and justify careful *CFTR* molecular analysis (Muller et al. 2002)
        2. Hyperechogenic fetal bowel suggestive of intestinal obstruction: perform carrier testing for CF gene mutations in the parents
            1. Diagnosis of CF highly likely in the fetus if both parents are carriers of a CF mutation
            2. Confirmed CF diagnosis by direct mutation analysis of amniotic fluid cells
        3. Meconium peritonitis secondary to small bowel perforation in utero
            1. Associated with CF in only 7% of cases
            2. Presence of abdominal calcification usually associated with causes of meconium peritonitis other than CF
            3. Absence of abdominal calcifications favors the diagnosis of CF, to be confirmed by parental CF carrier testing and mutation analysis of fetal cells in at-risk couples
    3. Molecular genetic analysis
        1. Prenatal diagnosis accomplished in most families with an affected member by mutation analysis from fetal cells obtained from CVS (10 weeks) or amniocentesis (15–18 weeks)
        2. Preimplantation genetic diagnosis to screen embryos before implantation, an alternative for at-risk couples
            1. A cleavage stage biopsy of embryo on day 2 or 3 after in vitro fertili-zation
            2. Removal of one or two cells for genetic analysis by nested polymerase chain reaction and heteroduplex formation
            3. Transfer of normal or carrier embryos to establish pregnancy
            4. Followed by CVS or amniocentesis to confirm the original diagnosis
    4. Postnatal sweat testing mandatory in all cases in which the diagnosis of CF has been made or excluded on the basis of prenatal DNA analysis
3. Management (Davis et al. 1996; Orenstein et al. 2002)
    1. Antibiotic treatment of acute respiratory infections and exacerbations of chronic endobronchial infections
        1. Purpose
            1. To improve pulmonary function
            2. To improve exercise tolerance
            3. To improve quality of life

2. Short-term oral ciprofloxacin for mild exacerbations by pseudomonas agent with caution in the younger pediatric age patients
3. Intravenous antibiotics, a mainstay of treatment of acute exacerbations of pulmonary disease
    1. Aminoglycoside (usually tobramycin) and β-lactam antibiotics
    2. Implanted central lines or peripheral vein catheters to maintain IV access
4. Aerosol (inhaled) antibiotics such as tobramycin
5. Other aerosol antibiotics such as colistin

2. Airway clearance and exercise (Marshall and Samuelson 1998)
    1. Percussion and postural drainage in an attempt to keep the airways free of infected and obstructive secretions
    2. Positive expiratory pressure (PEP) devices to promote mucous clearance by preventing airway closure and increase collateral ventilation
    3. ThAIRapy Vest, a chest wall compression and oscillation system comprising a fitted vest coupled to a pneumatic compressor
    4. Flutter valve vibrating devices
    5. Directed exhalation techniques
3. Sodium cromolyn (Intal™) or nedocromil (Tilade™) beneficial in some patients
4. Use of inhaled (aerosolized) bronchodilators such as β-adrenergics
5. Use of inhaled alpha dornase (DNase) (Pulmozyme™) to reduce sputum viscosity by cleaving extracellular neutrophil-derived DNA and brings about sustained improvement in pulmonary function in many patients with CF
6. Avoid cough depressants
7. Oxygen therapy if indicated
8. Anti-inflammatory therapies
    1. Glucocorticoids: useful in selected patients
    2. Ibuprofen
9. Nutritional support to prevent malnutrition
    1. Provide pancreatic enzyme supplements and vitamins to correct malabsorption
    2. Provide normal or high-fat diets with essential fatty acids necessary for growth and development
    3. Provide fat-soluble vitamin supplements
10. Management of gastrointestinal obstructive complications
    1. Gastrografin enema for treatment of fecal impaction with distal intestinal obstruction syndrome
    2. Surgery for intussusception if indicated
    3. Surgery necessary to correct obstruction due to meconium ileus in most newborns
11. Management of biliary tract disease
    1. Treatment of severe focal or multilobular biliary cirrhosis, portal hypertension, and hypersplenism
        1. Sclerosing of esophageal varices
        2. Hepatic shunt procedures
        3. Liver transplantation
    2. Cholecystectomy for gallstones
    3. Urodeoxycholic acid for selected cases of liver dysfunction
12. Management of CF-related diabetes mellitus
    1. Dietary management
    2. Insulin often required
    3. Complementary diabetes pharmaceutical agents: no current place in management of CF-related diabetes (Nathan et al. 2010)
13. Management of pneumothorax
    1. Chest tube drainage
    2. Followed by simple surgical oversewing of blebs if the initial air leak does not resolve

3. Followed by definitive pleural ablation if necessary

14. Management of hemoptysis
    1. Reassurance in most cases
    2. Additional vitamin K
    3. Discontinue drugs that may interfere clotting
    4. Bronchial artery embolization by interventional radiologic techniques in unusual cases
15. Management of respiratory failure
    1. Oxygen administration
    2. Tracheal intubation and mechanical ventilation in terminally ill patients on the lung transplant waiting list
    3. Lung transplantation (Yankaskas and Mallory 1998): now an accepted therapy in patients with end-stage lung disease (Rosenblatt 2009)
        1. Acceptable survival rate
        2. Good quality of life
        3. Overall survival, however, still lags behind other solid-organ transplants
        4. Despite the higher incidence of diabetes mellitus, poor nutrition, and colonization with both multiresistant and panresistant Gram-negative organisms, the patients with CF clearly benefit from lung transplantation
    4. Heart-lung and lung transplantation successfully applied to patients with end-stage CF patients (Zuckerman and Kotloff 1998)
16. Management goals in CF (Martiniano et al. 2014)
    1. Nutritional
        1. Maintain normal growth patterns in children: goal weight for length $\geq$50th percentile for infants $<$2-year old; goal BMI $\geq$50th percentile for children $\geq$2-year old
        2. Maintain normal blood levels of fat-soluble vitamins
        3. Prevent hyponatremia and hypochloremia
    2. Lung health
        1. Minimize lung damage caused by infection, mucus plugging, and inflammation
        2. Maintain lung function (age $\geq$6 year)
        3. Prevent onset of new lung infections
        4. Detect and treat chronic lung infections
        5. Prevent and treat pulmonary exacerbations
    3. Comorbidities: detect and treat complications of CF including:
        1. CF liver disease
        2. CF-related diabetes
        3. Nasal polyposis
        4. Gastrointestinal complications
        5. Allergic bronchopulmonary aspergillosis
        6. CF-related osteoporosis
        7. Depression
        8. Anxiety
17. Cystic fibrosis in pregnancy (Whitty 2010)
    1. Women with cystic fibrosis (CF): now living to childbearing age and many have successful pregnancies
    2. Improvement of fertility and pregnancy outcome:
        1. Preconception care with optimization of pulmonary function
        2. Eradication of pulmonary infection
        3. Improved nutritional status
        4. Improved diabetes
    3. Women with CF with poor pulmonary function and nutrition, and less than ideal body weight: more likely to suffer adverse outcomes
    4. Women with CF with pulmonary hypertension, cor pulmonale, and forced expiratory volume $<$50% predicted: adversely affect mild and moderate lung disease due to cystic fibrosis and should avoid pregnancy (Edenborough et al. 2000)

5. Women with lung transplants can have successful pregnancy, but the risk of organ rejection and death are high

18. Fertility in men with cystic fibrosis (Smith 2010)
    1. Men with CF, now surviving longer, may wish to be fertile and want to have children regardless of the disease severity (Sawyer et al. 2005)
    2. Obstructive azoospermia in men with CF are due to (Kaplan et al. 1968; Holsclaw et al. 1971):
        1. Congenital bilateral absence of the vas deferens, or
        2. Atrophy or complete absence of the epididymis or seminal vesicles
    3. Sperm capable of fertilizing mature oocytes by intracytoplasmic sperm injection in vitro can be extracted from the majority of men with cystic fibrosis
    4. Sperm may be retrieved either by aspiration from the caput of the epididymis or directly from the testis or other alternative procedures
19. Recently, a first-in-class disease-modifying CF treatment was approved in the USA and Europe for patients with a specific mutation in their *CFTR* gene. The clinical development of this small molecule CFTR modulator (ivacaftor) serves as a promising example of how personalized therapies can transform the therapeutic landscape (Elborn 2013)
20. The UK CF Gene Therapy Multidose trial, along with continuing work on viral vectors, will shape the role of this exciting therapy as a potential treatment for all CF patients in the years ahead (Armstrong et al. 2014; Davies et al. 2014)

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Fig. 1 This 5-month-old infant has history of failure to thrive, foul-smelling stools, and excessive spitting. The patient is positive for two copies of the ΔF508 mutation

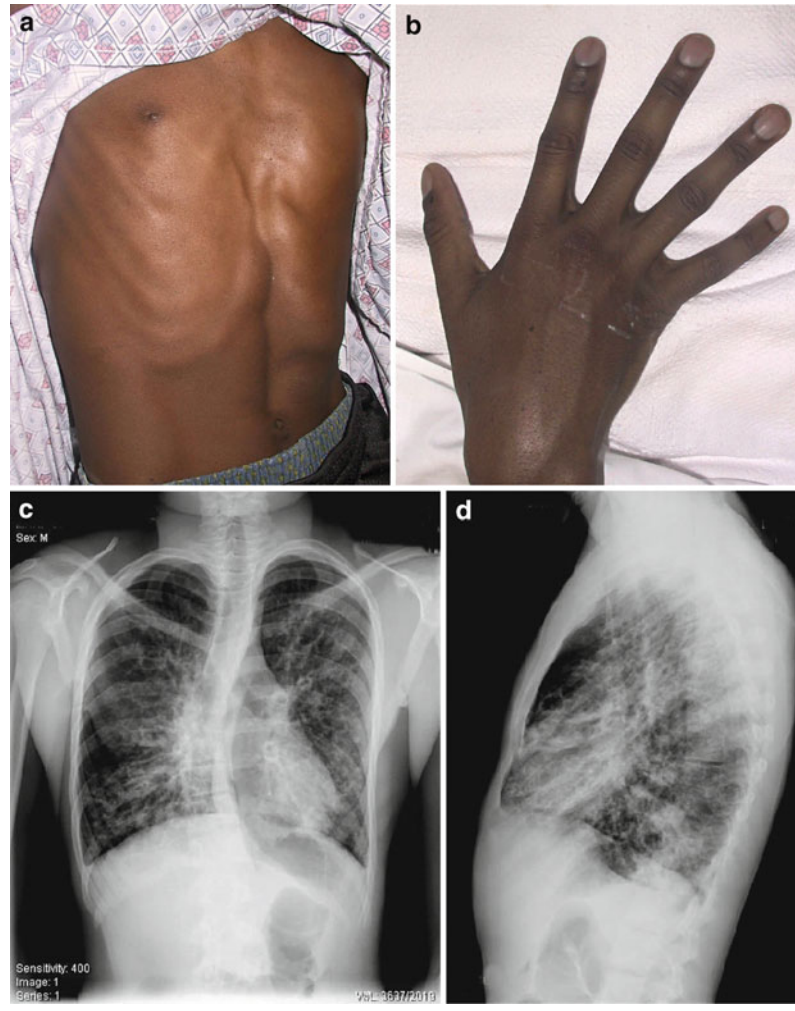

Fig. 2 (**a-d**) A 16-year-old boy with cystic fibrosis showing an emaciated chest (**a**), club fingers (**b**), and a honeycomb-like chest with air trapping illustrated by chest radiographs (**c**, **d**)

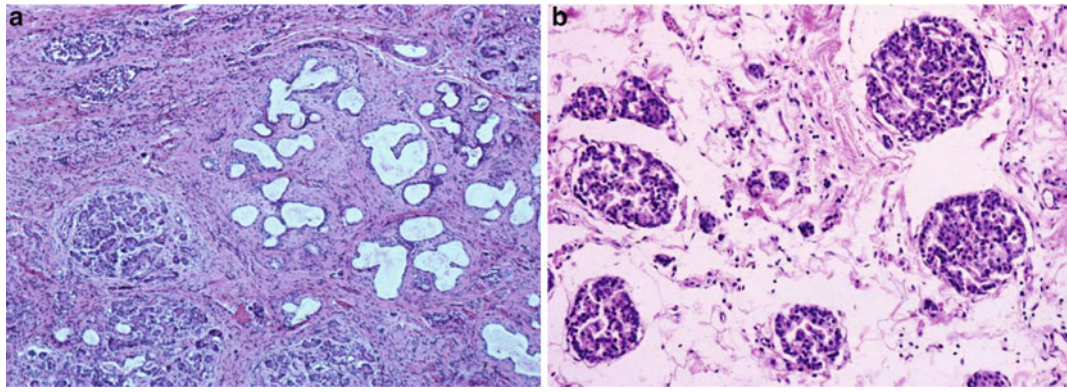

Fig. 3 (**a**, **b**) Photomicrograph of the pancreas of a 16-year-old male who died of bronchiectasis and bronchopneumonia. In the left photomicrograph (**a**), the exocrine glands (acini) are mostly absent. Irregularly dilated exocrine ductules are lined by flattened atrophic epithelium. Many unaffected islets of Langerhans are present at left lower corner. In the right photomicrograph with higher magnification (**b**) there are many islets of Langerhans but normal exocrine glands and ductules are absent

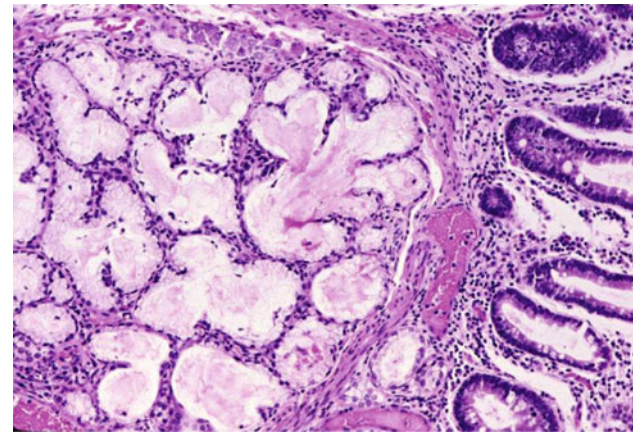

Fig. 4 Photomicrograph of the duodenum of the same patient. The Brunner's glands in the submucosa are distended by inspissated secretion. Three mucosal crypts are also slightly dilated

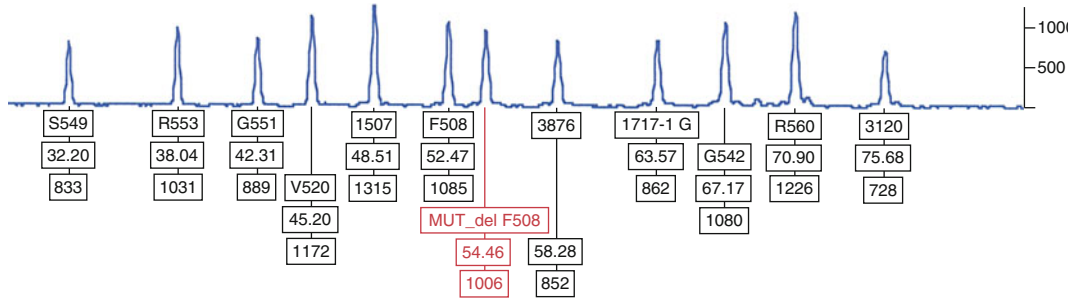

Fig. 5 Fragment size separation of CFTR mutations using capillary gel electrophoresis (ABI 310 genetic analyzer, Applied Biosystems). A mutation in ΔF508 is noted in *red*

Dandy–Walker Malformation

Contents

In 1954, Benda (Benda 1954) introduced the term Dandy–Walker syndrome to indicate the association of (1) ventriculomegaly of variable degree, (2) a large cisterna magna, and (3) a defect in the cerebellar vermis through which the cyst communicates with the fourth ventricle. Currently, the following findings are included in the Dandy–Walker syndrome or malformation: (4) cystic dilatation of the fourth ventricle, (5) dysgenesis of the cerebellar vermis, and (6) a high position of the tentorium. The Dandy–Walker malformation has a prevalence of about 1 in 30,000 live births and is found in 4–12% of infantile hydrocephalus.

Genetics/Basic Defects

1. Heterogeneous etiology (Murray et al. 1985)
    1. Isolated
    2. A part of a Mendelian disorder
    3. A part of a chromosome disorder (Nyberg et al. 1991; Liao et al. 2012)
        1. Trisomy 18
        2. Triploidy (69,XXX)
        3. Trisomy 13
        4. Trisomy 21
        5. Trisomy 9
        6. Turner syndrome
        7. Duplication 3q
        8. Deletion 3q25.1–25.33
        9. Deletion 13q
        10. Duplication 1q
        11. Duplication 1q
    4. Chromosome abnormalities and genetic loci associated with DWM in humans and animal models (Correa et al. 2011)
        1. Deletion of 3p2 (*ZIC1*, *ZIC4*)
        2. Deletion or duplication of 6p25.3 (*FOXC1*)
        3. Tetrasomy 9p
        4. Deletion of 13q
        5. Deletion of 2q36.1 (*PAX3*)
        6. Deletion and duplication of 7p21.3 (*NDUFA4*, *PHF14*) (Liao et al. 2012)
    5. Potential high incidence of subtelomeric anomalies in isolated DWM, especially 6p deletion (Guibaud et al. 2012)
    6. Environmental factors
2. Uncertain significance of the Dandy–Walker variant and mega-cisterna magna

Clinical Features

1. Maternal polyhydramnios/oligohydramnios
2. Fetal anomalies

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_64

1. Echogenic bowel
2. Effusions/hydrops
3. Single umbilical artery
4. Growth restriction
5. Abundant nuchal folds
6. Cystic hygroma

3. Dandy–Walker complex (Harwood-Nash and Fitz 1976): a triad of malformation
   1. Cystic dilatation of the fourth ventricle
   2. Complete or partial agenesis of the cerebellar vermis
   3. An enlarged posterior fossa with displacement of the tentorium and torcular and lateral sinus
4. Dandy–Walker variant (Harwood-Nash and Fitz 1976): cerebellar dysgenesis without enlargement of the posterior fossa and with variable hypoplasia of the cerebellar vermis
5. Associated intracranial anomalies (70% of cases) (Incesu 2015)
   1. An enlarged posterior fossa
   2. Ventriculomegaly
   3. Atresia of the foramina of Magendie and Luschka
   4. Midline anomalies
      1. Agenesis of the corpus callosum (17%) (Sawaya and McLaurin 1981)
      2. Holoprosencephaly
      3. Occipital meningocele and encephalocele
   5. Porencephalic cyst
   6. Migrational disorder
   7. Gyral abnormalities
   8. Microcephaly
6. Non-CNS-associated malformations
   1. Facial clefting
   2. Cardiovascular defects
   3. Diaphragmatic hernia
   4. Omphalocele
   5. Polycystic kidneys
   6. Spinal defects
   7. Limb defects
      1. Polydactyly
      2. Syndactyly
7. Common presenting signs and symptoms
   1. Macrocrania
   2. Bulging fontanel
   3. Upward gaze palsy
   4. Hypertelorism
   5. Strabismus
   6. Hypotonia
   7. Headache and vomiting
   8. Seizures
   9. Hemiparesis
   10. Facial palsy
   11. Palpebral ptosis
   12. Pyramidal signs
   13. Cerebellar dysfunction
   14. Motor dysfunction
   15. Mental retardation: subnormal intelligence reported in 40–70% of cases
8. Incidental asymptomatic Dandy–Walker syndrome (DWS) (Jha et al. 2012)
   1. Presentation at extremes of age signifies that slow degenerative changes in communicating channels between fourth ventricular cyst and surrounding basal cisterns may cause asymptomatic DWS to manifest.
   2. Cases having good communication between these structures can remain asymptomatic throughout their life.
9. Concurrent psychosis and Dandy–Walker complex of all four subtypes: might help further illuminate the role that the cerebellum plays in the etiology of schizophrenia or bipolar disorder (Gan et al. 2012)
10. Prognosis
    1. Grim but not uniformly fatal
    2. Prognosis and intellectual outcome: mostly depend on the presence of associated malformations, the degree of vermian malformation, and the adequate control of hydrocephalus (Spennato et al. 2011)
    3. Worst prognosis when there are associated anomalies and chromosome abnormalities (Kölble et al. 2000)
    4. Better chance of normal outcome for isolated Dandy–Walker variant (Maria et al. 1987)
    5. Dandy–Walker malformation (DWM) with an isolated and partially agenetic vermis (Klein et al. 2003): compatible with a normal life

6. DWM with a severely abnormally lobulated vermis and associated brain malformation (Klein et al. 2003): always accompanied by mental retardation

11. Classification of posterior fossa malformations (Shekdar 2011)
    1. Large posterior fossa
        1. Classic Dandy–Walker malformation
        2. Blake's pouch cyst (an inferior protrusion of the fourth ventricle, which results from a finger-like expansion of the posterior membranous area)
        3. Mega-cisterna magna
        4. Posterior fossa arachnoid cyst
    2. Normal or small posterior fossa
        1. Dandy–Walker variant
        2. Joubert syndrome (an autosomal-recessive syndrome characterized by hyperapneic/apneic spells, hypotonia, ataxia, abnormal ocular movements, and psychomotor delay; found in association with posterior fossa abnormality characterized by vermian hypoplasia and abnormal ponto-mesencephalic junction, which results in the classic "molar tooth" sign on imaging) (please see the chapter on "▶ Joubert Syndrome")
        3. Tecto-cerebellar dysgraphia
        4. Rhombencephalosynapsis
        5. Neocerebellar hypoplasias
        6. Cerebellar atrophy

Diagnostic Investigations

1. Sonography (Estroff et al. 1992; Ecker et al. 2000)
    1. Sonographic diagnosis of classic Dandy–Walker malformation: straightforward from mid-gestation
    2. Detection of Dandy–Walker malformation as early as 11 weeks using vaginal sonography (Achiron and Achiron 1991)
    3. In the transcerebellar view
        1. An enlarged cisterna magna connected to the area of the fourth ventricle through a defect in the cerebellar vermis
        2. Presence of borderline-to-overt ventriculomegaly
        3. Frequent association of other neural and extra-neural malformation
2. CT and MRI of the brain
    1. Large median posterior fossa cyst widely communicating with the fourth ventricle
    2. Cystic enlargement of the fourth ventricle
    3. Cerebellar vermis dysgenesis
    4. An upwardly displaced tentorium
    5. Hydrocephalus
    6. Atresia of the foramina of Magendie and Luschka
    7. Frequently associated CNS anomalies
        1. Agenesis of corpus callosum
        2. Occipital encephalocele
        3. Porencephalic cyst
        4. Holoprosencephaly
        5. Others
3. PET/CT appearance of Dandy–Walker syndrome: an ametabolic large cyst in the posterior fossa and hypoplasia of cerebellar vermis (Infante et al. 2016)
4. For prenatal purpose, subtelomeric analysis associated with investigation of *ZIC1–ZIC4* gene deletion in patients with normal karyotype was proposed, because of a potential high incidence of subtelomeric anomalies, especially 6p deletion, in apparently isolated DWM (Guibaud et al. 2012)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: a low recurrence risk in the order of 1–5% unless the Dandy–Walker malformation is a part of a Mendelian disorder or associated with chromosome anomaly.
    2. Patient's offspring: not surviving to reproductive age because of severe neurologic deficits associated with major malformations.
2. Prenatal diagnosis
    1. Ultrasonography for detecting unique previously described CNS malformations

2. First-trimester sonographic findings associated with a Dandy–Walker malformation and inferior vermian hypoplasia: evaluation of the fourth ventricle–cisterna magna complex by measuring the intracranial translucency or brain stem-to-occipital bone diameter may identify some cases with structural malformations (Bornstein et al. 2013)
3. MRI of the fetal DWM (Bernardo et al. 2015)
    1. Dorsal rotation of the vermis with enlarged fourth ventricle
    2. Widening of the tegmento-vermian angle
    3. Flat fastigium
    4. The "tail" sign: dysmorphic appearance of the posterior lobe of the vermis, which presents a thick and elongated nodulus with the appearance of a "tail"
4. Prenatal amniocentesis for fetal karyotyping
5. Array-based comparative genomic hybridization: three fetuses with a de novo adjacent microdeletion/duplication region mapping to chromosome 7p21.3 and suggesting that the critical region associated with DWM may be limited to the 7p21.3 region (Liao et al. 2012)

3. Management (Alexiou et al. 2010)
    1. Ventriculoperitoneal shunt
    2. Cyst-peritoneal shunt: avoids the risk of an entrapped fourth ventricle and is presently the best surgical procedure (Hirsch et al. 1984)
    3. Ventriculocystoperitoneal shunt (Kumar et al. 2001)
    4. Posterior fossa craniectomy with cyst fenestration (Almeida et al. 1990)

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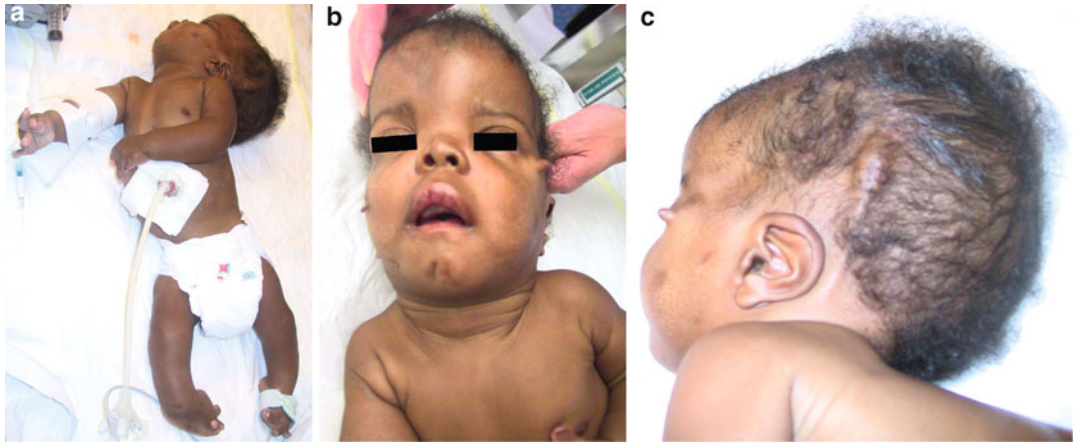

Fig. 1 (**a**–**c**) Eight-month-old patient with Dandy–Walker malformation associated with multiple congenital anomalies including facial dysmorphism, skin tags (pseudotails) on the cheek, and limb anomalies

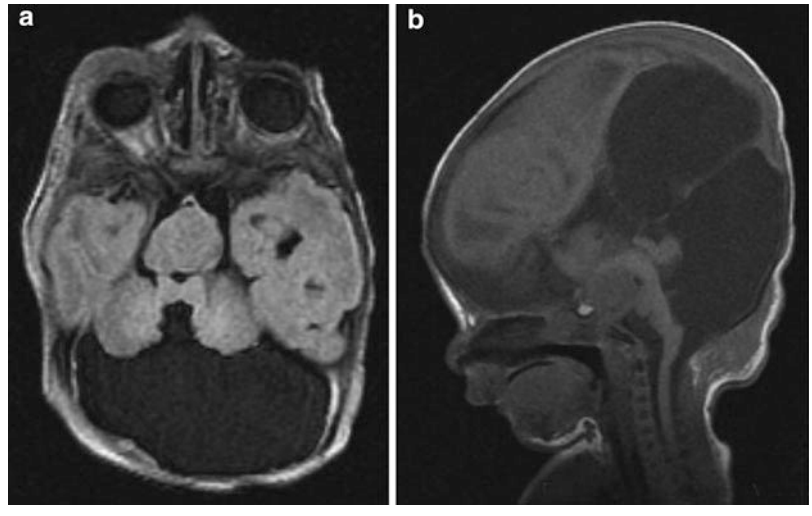

Fig. 2 (**a**, **b**) MRI of the brain of the patient in Fig. 1 shows Dandy–Walker malformation with a large posterior fossa cyst which communicates with dilated fourth ventricle. In addition, this patient also has agenesis of corpus callosum, hydrocephalus, and vermis dysgenesis

De Lange Syndrome

Contents

In 1933, Cornelia de Lange reported two nonfamilial infant girls with severe mental retardation and multiple abnormalities of the skull, face, and extremities (De Lange 1933). Earlier in 1916, Brachmann had described a child with similar features (Brachmann 1916). The syndrome is also called Brachmann-de Lange syndrome or Cornelia de Lange syndrome. The prevalence is estimated to be 1 in 10,000 births (Opitz 1985).

Synonyms and Related Disorders

Brachmann-de Lange syndrome; NIPBL-related Cornelia de Lange syndrome; SMC1A-related Cornelia de Lange syndrome; Typus degenerativus amstelodamensis

Genetics/Basic Defects

1. A heterogeneous clinical entity.
    1. Sporadic in vast majority of cases (99%) (Russell et al. 2001; Tekin et al. 2015)
    2. Striking concordance in MZ twins
    3. Rare familial occurrences (Beratis et al. 1971)
        1. Autosomal dominant inheritance
        2. Autosomal recessive inheritance: unlikely
2. Inconsistent chromosome abnormalities occasionally associated with de Lange phenotype (Kousseff et al. 1994). In addition, the following significant cytogenetic findings were reported:
    1. Deletions of chromosome 5p13 where Cornelia de Lange syndrome gene (*NIPBL*) has been reported in two cases (Taylor and Josifek 1981; Hulinsky et al. 2005).
    2. An increased rate of precocious sister chromatic separation has been reported in affected individuals (Kaur et al. 2005).
3. Combined mutations in *NIPBL*, *SMC1A*, and *SMC3*: identified in nearly 60% of patients with a confident clinical diagnosis of de Lange syndrome (Dorsett and Krantz

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2009; Boyle et al. 2014). Mutations in five genes (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, and *HDAC8*), all regulators or structural components of cohesin, have been identified (Mannini et al. 2013).

1. *Nipped-B-like* (*NIPBL*) gene on chromosome 5p13 (Krantz et al. 2004)
    1. At least 50% of cases are caused by loss-of-function mutations of *NIPBL* gene.
    2. Required for binding of the cohesion complex that mediates sister chromatid cohesion to chromosome (Dorsett 2007).
2. *SMC1A* gene
    1. X-linked (on Xp11.22).
    2. Encodes the SMC1 subunit of mitotic cohesion.
    3. Missense or small in-frame deletion was noted in approximately 5% of individuals with clinical diagnosis of de Lange syndrome.
3. *SMC3* gene
    1. On chromosome 10q25.
    2. Mutation is heteroallelic with a wild-type allele.
4. *HDAC8* gene (on Xq13.1)
5. *RAD21* gene (on 8q24.11)

4. De Lange syndrome, thus, considered to be a cohesinopathy, along with Roberts syndrome/SC phocomelia (Tekin 2015)
5. Genotype-phenotype correlations
    1. More severe *NIPBL* mutations (such as deletions or truncations) usually cause more severe clinical manifestations than missense mutations.
    2. Missense mutations in *NIPBL* are associated with mild phenotypic features.
    3. Mutations in SMC1A and SMC3 are associated with a milder phenotype with absence of limb defects and other structural anomalies.
    4. In the mildest forms, affected individuals generally have mild to moderate mental retardation and, at least at a young age, typical facial characteristics.

Clinical Features

1. Marked clinical variability (Pashayan 1969; Greenberg and Robinson 1989; Van Allen et al. 1993; Opitz 1994; Chrzanowska 2014)
2. General history
    1. Prenatal and/or postnatal growth deficiency
    2. Prematurity
    3. Diminished sucking and swallowing ability
    4. Low-pitched cry (74%) in the newborn period and in the early infancy but may disappear in the late infancy
    5. Global developmental delay
    6. Initial hypertonicity
    7. Recurrent respiratory tract infections
    8. Gastroesophageal reflux
    9. Failure to thrive
3. Growth
    1. Prenatal onset growth retardation (Jackson et al. 1993)
    2. Short stature
4. Skin
    1. Hypertrichosis (hirsutism) (78%): often with hairy whorls over the shoulders, lower back, and extremities
    2. Cutis marmorata (60%)
    3. Periorbital "cyanosis"
5. Characteristic craniofacial appearance (Boyle et al. 2014)
    1. Microcephaly (98%)
    2. Brachycephaly
    3. Hairy (low hairline) forehead
    4. Masklike (grim, devoid of expression) facies
    5. Hypertelorism
    6. Antimongoloid slant of palpebral fissures
    7. Synophrys (prominent bushy, confluent eyebrows joining at the nose) (99%)
    8. Long and curly eyelashes (99%)
    9. Depressed nasal bridge (83%)
    10. Small nose
    11. Anteverted nares (88%)
    12. Micrognathia (84%)
    13. Long bulging, prominent philtrum (94%)
    14. Thin upper lip (94%)
    15. Central depression below the lower lip

16. Down-turned corners of the mouth (94%)
17. Late eruption of teeth
18. Widely spaced teeth (86%)
19. High-arched palate (86%)
20. Low set, malformed, and hairy ears (70%)
21. Low posterior hairline (92%)
22. Short neck (66%)

6. Eye abnormalities (57%)
    1. Strabismus
    2. Nystagmus (37%)
    3. Myopia (60%)
    4. Ptosis (45%)
    5. Microcornea
    6. Astigmatism
    7. Optic atrophy
    8. Coloboma of the optic nerve
    9. Eccentric pupils
    10. Microphthalmia
    11. Blue sclerae
7. Limb abnormalities
    1. Upper extremities
        1. Micromelia (shortened limbs) (93%)
        2. Ectrodactyly/oligodactyly/phocomelia (27%)
        3. Clinodactyly of the fifth fingers (74%)
        4. Small hands
        5. Proximally placed thumbs
        6. Camptodactyly
        7. Webbings of fingers
        8. Brachydactyly
        9. Flexion contractures of the elbows common (64%)
        10. Restriction of supination and pronation
        11. Subluxation or dislocation of the radial head
    2. Lower extremities
        1. Small feet
        2. Cutaneous syndactyly of the second and third toes (86%)
        3. Tight Achilles tendon (equinus deformity)
        4. Pes planus
        5. Valgus heel
        6. Flexion contractures of the knees
8. CNS anomalies
    1. Variable mental retardation to near-normal intellect
    2. Seizures (23%)
    3. Abnormal speech development (Goodban 1993)
    4. Hearing deficits (60–100%)
    5. Hypoplasia of the vermis
    6. Hypertonia/hypotonia
9. Behavior disorder (Berney et al. 1999)
    1. Sleep disturbance (55%)
    2. Aggression (49%)
    3. Self-destructive tendencies (44%)
    4. Hyperactivity (40%)
    5. Low-pitched growling sound rather than cry
    6. Infrequent facial expressions of emotion
    7. Severe language delay
    8. Autistic-like behavior
    9. Repetitive stereotypic movement
    10. Eliciting pleasurable responses by vestibular stimulation or vigorous movement
10. Other anomalies
    1. Small hypoplastic nipples (55%)
    2. Small hypoplastic umbilicus (53%)
    3. Cardiovascular anomalies (15–20%)
        1. Ventricular septal defect
        2. Atrial septal defect
        3. Patent ductus arteriosus
        4. Aortic valve anomaly
        5. Hypoplasia of the aorta
        6. Persistent left superior vena cava
        7. Pulmonary stenosis
        8. Endocardial cushion defect
        9. Tetralogy of Fallot
    4. Gastrointestinal anomalies
        1. Inguinal hernia
        2. Hiatus hernia
        3. Congenital diaphragmatic hernia
        4. Gut duplication
        5. Malrotation of colon
        6. Pyloric stenosis
    5. Genitourinary anomalies
        1. Hypoplastic, dysplastic, or cystic kidneys
        2. Hypoplastic external genitalia, cryptorchidism or hypospadias in males
        3. Small labia majora, bicornuate or septate uterus in females

6. Otolaryngological presentations (Hamilton et al. 2014)
   1. Stridor/noisy breathing
   2. Laryngomalacia
7. Abnormal dermatoglyphics
   1. Transverse palmar creases (51%)
   2. Increased atd angle
   3. Hypoplastic finger ridge patterns

Diagnostic Investigations

1. Radiography (Braddock et al. 1993)
   1. Skull
      1. Microcephaly: frequent
      2. Brachycephaly: frequent
      3. Trigonocephaly with orbital hypotelorism
      4. Parietal foramina
      5. Micrognathia
      6. High-arched palate
      7. Cleft palate
   2. Spine
      1. Kyphoscoliosis
      2. Platyspondyly
      3. Scheuermann disease
      4. Spina bifida
      5. Square vertebrae
      6. Coxa valga
   3. Chest
      1. Aspiration pneumonia: frequent
      2. Thin ribs
      3. Short clavicles
      4. Short hypoplastic sternum with reduced number of ossification centers
      5. Abnormal sternal angle
      6. Cervical ribs
      7. Hypoplasia of the first rib
      8. Chronic pneumonia
      9. Bronchiolitis
   4. Congenital heart diseases
   5. Gastrointestinal tract
      1. Swallowing dysfunction: frequent
      2. Bowel rotation anomalies with bands: frequent
      3. Hiatal hernia
      4. Hypertrophic pyloric stenosis
      5. Duodenal stenosis
      6. Colon duplication
      7. Inguinal hernia
      8. Umbilical hernia
   6. Genitourinary tract
      1. Incomplete rotation of the kidneys
      2. Renal duplication
      3. Polycystic kidneys
      4. Chronic pyelonephritis
      5. Abnormal renal function with poor visualization on excretory urography
      6. Vesicoureteral reflux
      7. Divided uterine canal with septate vagina
   7. Limbs
      1. Micromelia: frequent
      2. Short humerus and/or forearm bones: frequent
      3. Elongated humeral neck (similar to femoral neck): frequent
      4. Subluxation or dislocation of malformed radius (Joubin et al. 1982) and/or ulna at elbow with fixation in flexion
      5. Absent or hypoplastic ulna: frequent
      6. Retarded bone maturation with abnormal sequence of appearance of ossification centers: frequent
      7. Absent carpals, metacarpals, and fingers (ectrodactyly/oligodactyly): frequent
      8. Short, broad metacarpals, particularly one and five: frequent
      9. Hypoplastic phalanges particularly middle fifth (curved) and middle second fingers: frequent
      10. Cutaneous syndactyly of second and third toes or other toes and fingers: frequent
      11. Cutis valgus
      12. Absent or hypoplastic radius
      13. Lunate and triquetral fusion
      14. Aplastic or hypoplastic ulnar styloid
      15. Double distal phalanges of thumbs and/or great toes
      16. Congenital dislocated hips
      17. Aseptic necrosis of femoral head
      18. Broad ischial bones
      19. Large obturator foramina

20. Short broad femoral necks
21. Absent tibia with deformed fibula
22. Fusion of phalanges of the fifth toe
23. Rocker-bottom foot
24. Metatarsus adductus
25. Planovalgus foot
26. Talipes equinovarus
27. Shortening of the femur and/or leg bones
28. Wide gap between first and second toes
29. Osteoporosis

2. Endocrinologic studies in patients with severe growth retardation
3. Echocardiography for evaluation of congenital heart defects
4. Abdominal ultrasonography for GU anomalies
5. EEG for seizures
6. Neuroimaging (Whitehead et al. 2015)
   1. Skull base dysplasia with coronal clival cleft
   2. Cerebral and brainstem volume loss
   3. Gyral simplification
   4. Membranous labyrinth dysplasia
   5. Anterior segment and optic pathway hypoplasia
   6. Basilar artery fenestration
   7. Absent massa intermedia
   8. Spinal anomalies
7. High-resolution chromosome analysis for associated chromosome anomaly
8. Mutation scanning and sequence analysis (Deardorff et al. 2011)
   1. Mutation scanning of *NIPBL* gene detected mutations in approximately 50% of 179 individuals from three studies (Borck et al. 2004; Gillis et al. 2004; Tonkin et al. 2004).
      1. Frameshift mutations
      2. Nonsense mutations
      3. Splice-site mutation
      4. Missense mutations
   2. Study by Musio et al. (2006).
      1. A *NIPBL* mutation was identified in 44% (24/54) of probands.
      2. A *SMC1A* mutation was detected in 4% (2/54) of probands.
9. Combination of massively multiplex PCR technology and next-generation sequencing was used to screen the coding sequences of the five known causative Cornelia de Lange syndrome genes in 163 individuals with Cornelia de Lange syndrome and Cornelia de Lange syndrome-like phenotypes (Ansari et al. 2014).
   1. As expected, intragenic mutations in *NIPBL* were, by far, the most common identifiable cause.
   2. 3/46 *NIPBL*, 1/5 *SMC1A*, and 1/5 *SMC3* mutations were found to be mosaic.

Genetic Counseling

1. Recurrence risk (Deardorff et al. 2011)
   1. Patient's sib
      1. Autosomal dominant inheritance
         1. An empiric risk of about 1–4%.
         2. Possibility of recurrence in siblings exists since gonadal mosaicism cases have been demonstrated (Niu et al. 2006).
      2. X-linked recessive inheritance
         1. The risk to sibs depends on the carrier status of the mother.
         2. If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
         3. If the disease-causing mutation cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.
   2. Patient's offspring
      1. Autosomal dominant inheritance.
         1. A 50% risk.
         2. While most familial recurrences are the result of germline mosaicism in a phenotypically normal parent, rare cases of

a mildly affected individual having affected children have been reported.
2. X-linked recessive inheritance: Males with X-linked de Lange syndrome will pass the disease-causing mutation to all of their daughters and none of their sons.

2. Prenatal diagnosis
   1. Ultrasonography (2-D and 3-D) (Ackerman and Gilbert-Barnes 1997; Sepulveda et al. 2009; Ghazle et al. 2011; Clark et al. 2012).
      1. Intrauterine growth retardation
      2. Characteristic facies
         1. Long eyelashes (Spaggiari et al. 2013)
         2. A small bulging nose
         3. Hypoplastic nasal bone
         4. A depressed nasal bridge
         5. Anteverted nostrils
         6. A long philtrum
         7. A protruding and overhanging upper lip
         8. Micrognathia
      3. Limb defects
         1. Micromelia
         2. Monodactyly
         3. Ulnar agenesis
      4. Diaphragmatic hernia (Marino et al. 2002)
   2. Molecular genetic diagnosis: Prenatal diagnosis is possible by demonstrating *NIPBL* mutation by DNA analysis of fetal cells obtained from amniocentesis or CVS or products of conception (Dempsey et al. 2014).
3. Management
   1. Adequate caloric intake
   2. Treat gastroesophageal reflux with thickened feeds in an upright position and pharmacotherapy
   3. Fitting of hearing aids and early consistent training for hearing-impaired children
   4. Early intervention and special education programs for psychomotor delay
   5. Behavioral modification
   6. Correction of refractory errors with glasses
   7. Anticonvulsants for seizures
   8. Surgical repairs
      1. Fundoplication and gastrostomy feedings necessary in patients with severe esophagitis and progressive failure to thrive despite conservative intervention
      2. Diaphragmatic hernia
      3. Cardiac defect
      4. Severe skeletal deformities
      5. Renal malformations
      6. Ptosis obstructing the visual axis
      7. Orchiopexy

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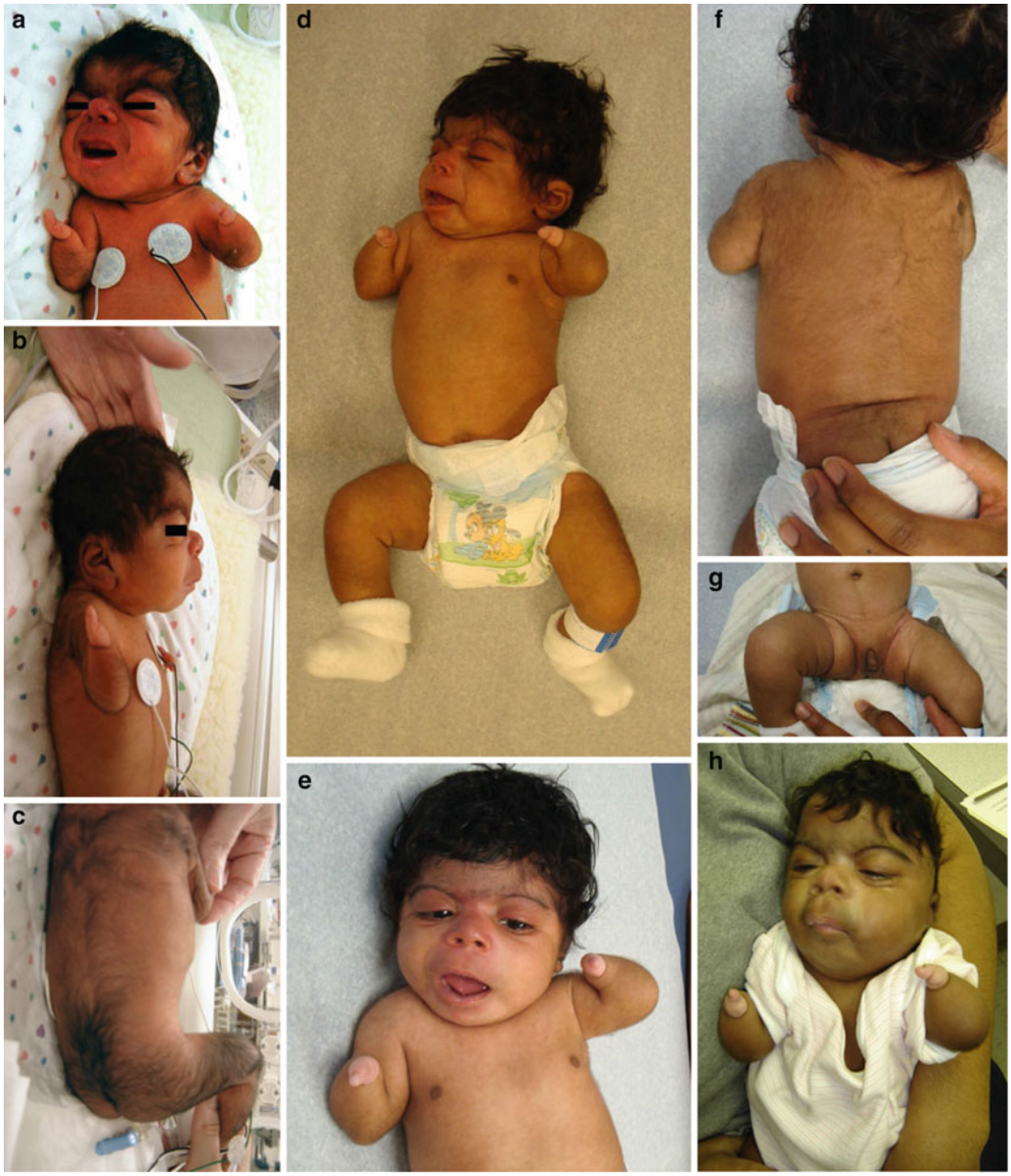

Fig. 1 (**a**–**h**) Three neonates with de Lange syndrome showing characteristic facies, oligodactyly, hirsutism, and ambiguous genitalia in one

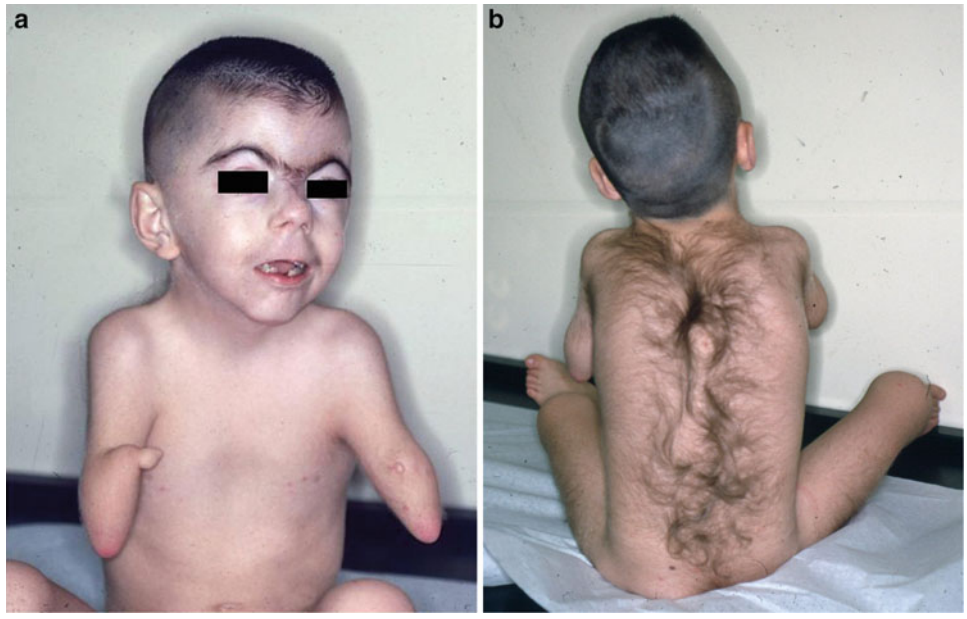

Fig. 2 (**a**, **b**) Another neonate with de Lange syndrome showing similar phenotype (characteristic facies, oligodactyly, and severe hirsutism)

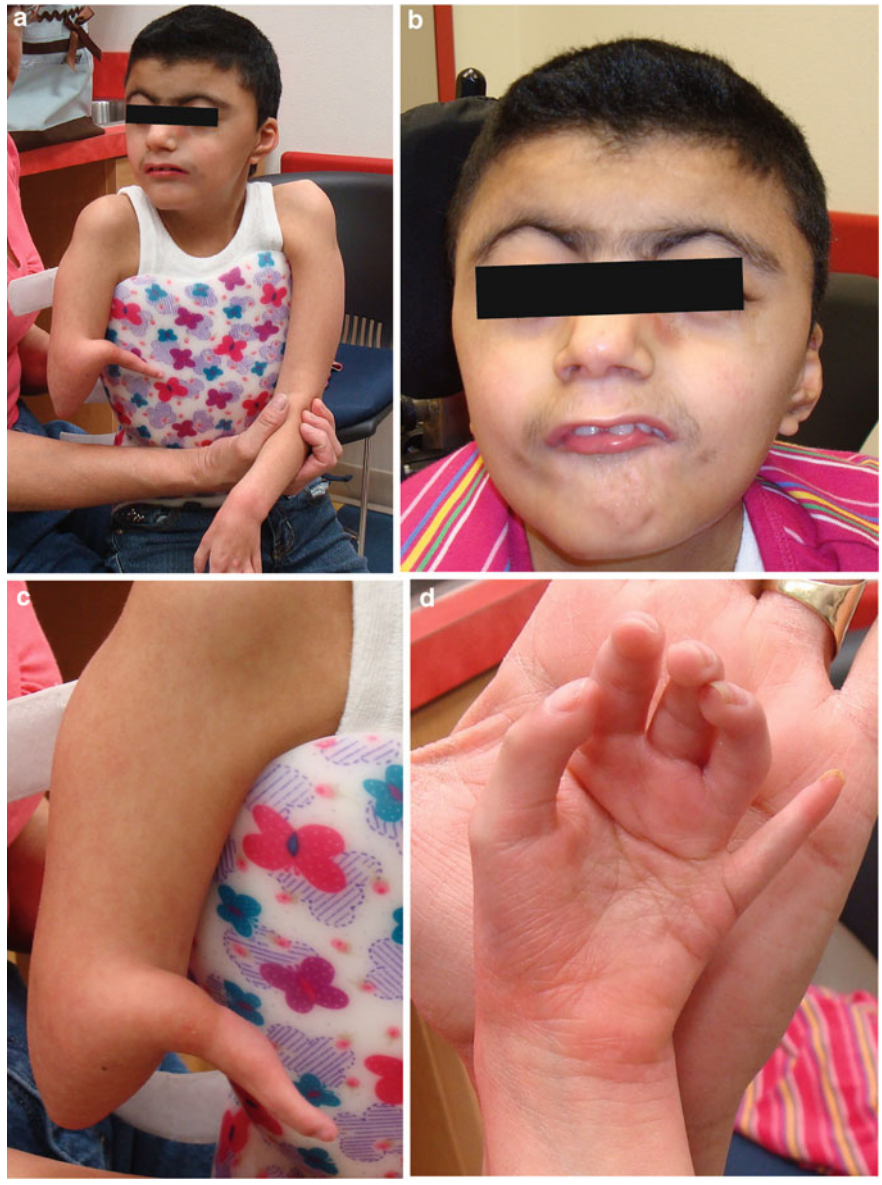

Fig. 3 (**a**–**d**) A 12-year-old boy with de Lange syndrome showing characteristic facies and reduction malformation with ectrodactyly/oligodactyly of the right arm and partial syndactyly of second to third fingers with transverse palmar crease of the left hand

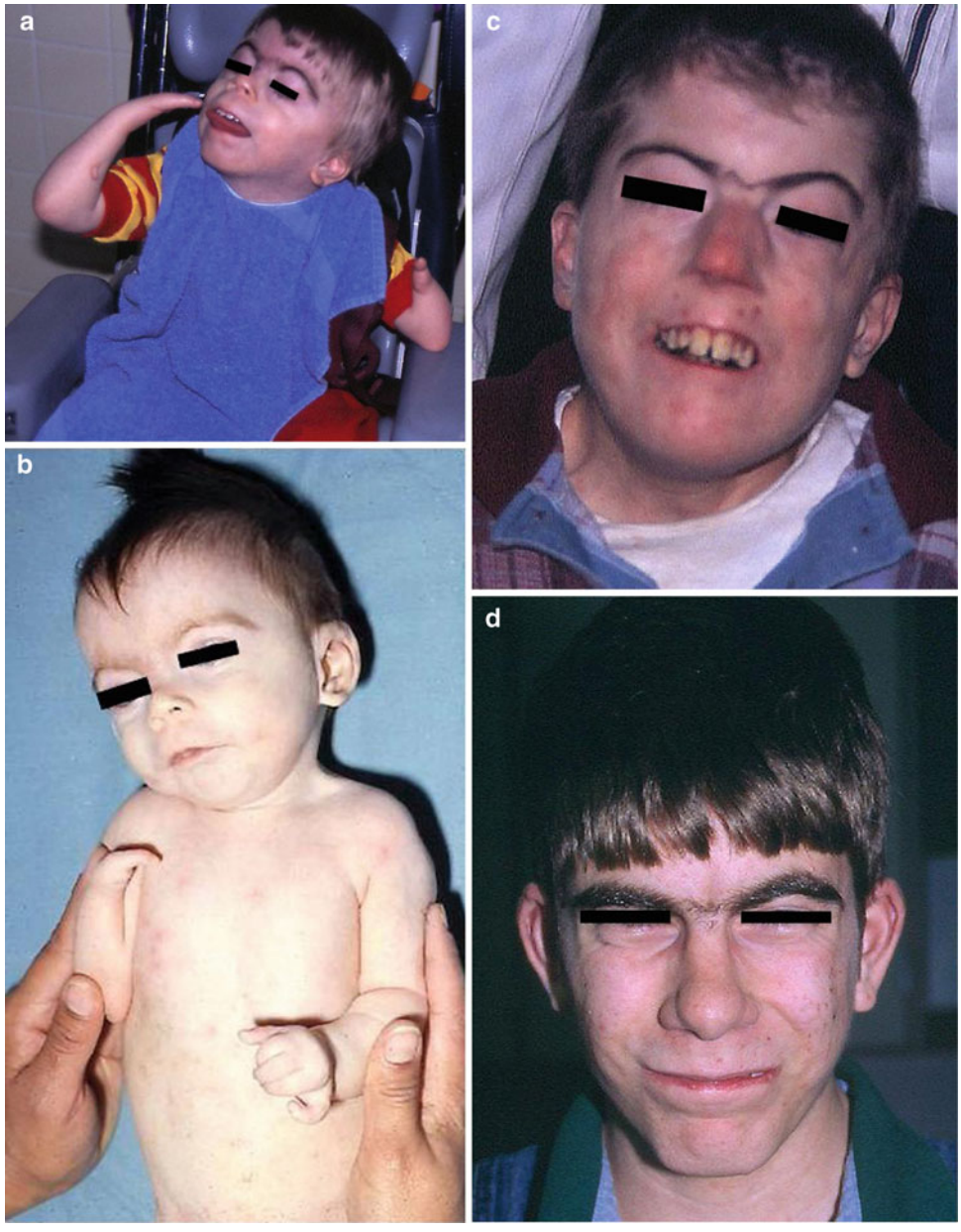

Fig. 4 (**a**–**d**) Four patients with classic de Lange syndrome of different ages showing typical facial appearance (synophrys, coarse eyebrows, long curly eyelashes, depressed nasal bridge with anteverted nares, long thin upper lip, down-turned angles of the mouth, and widely spaced teeth) and ectrodactyly/oligodactyly in the first two cases

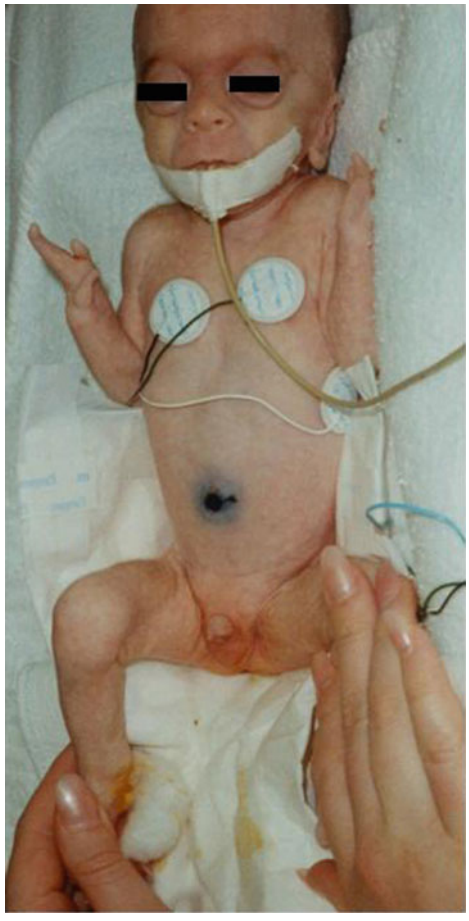

Fig. 5 A 46, XX male with de Lange phenotype

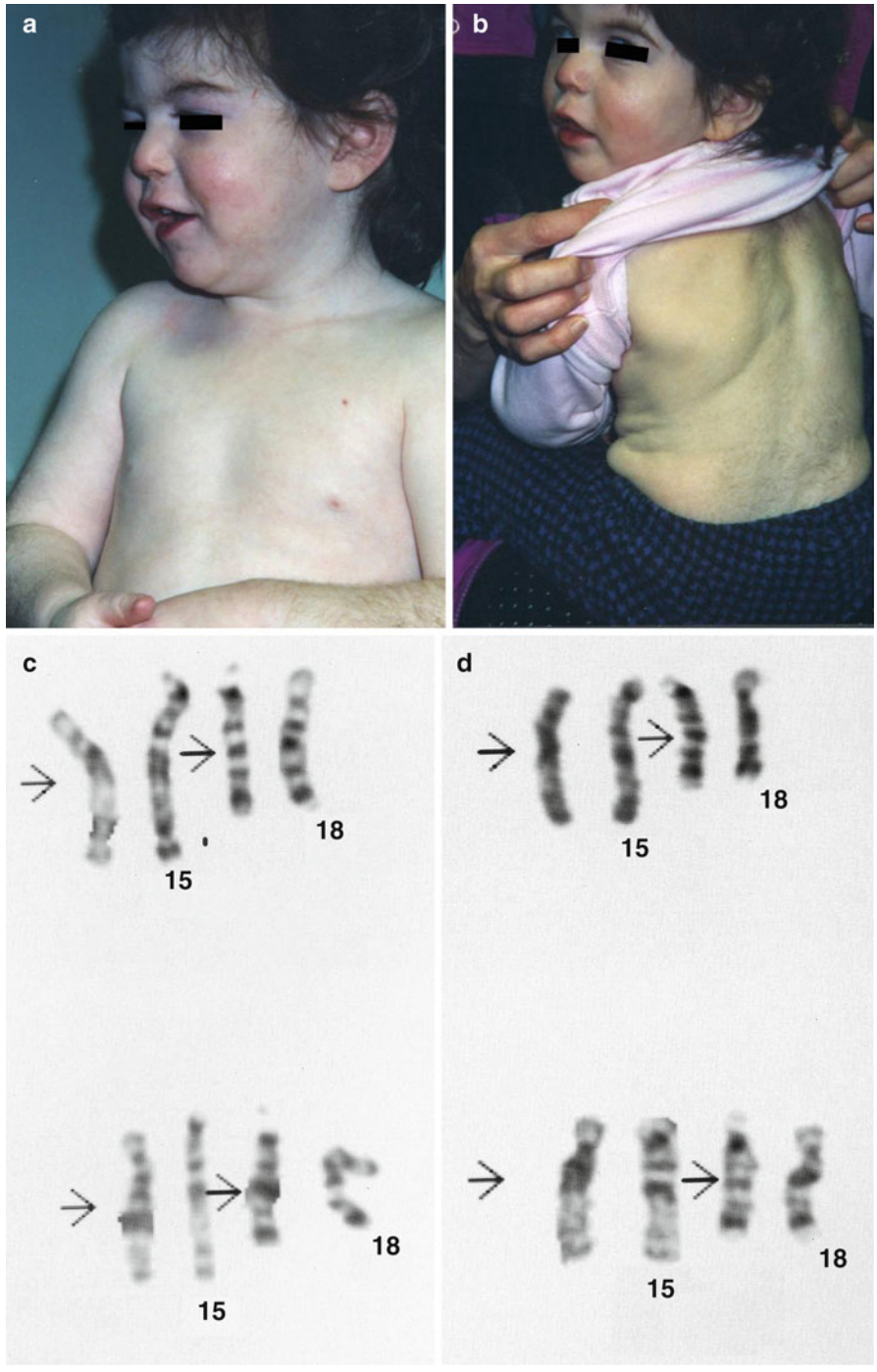

Fig. 6 (**a**–**d**) A child with t(15q;18q) showing de Lange phenotype

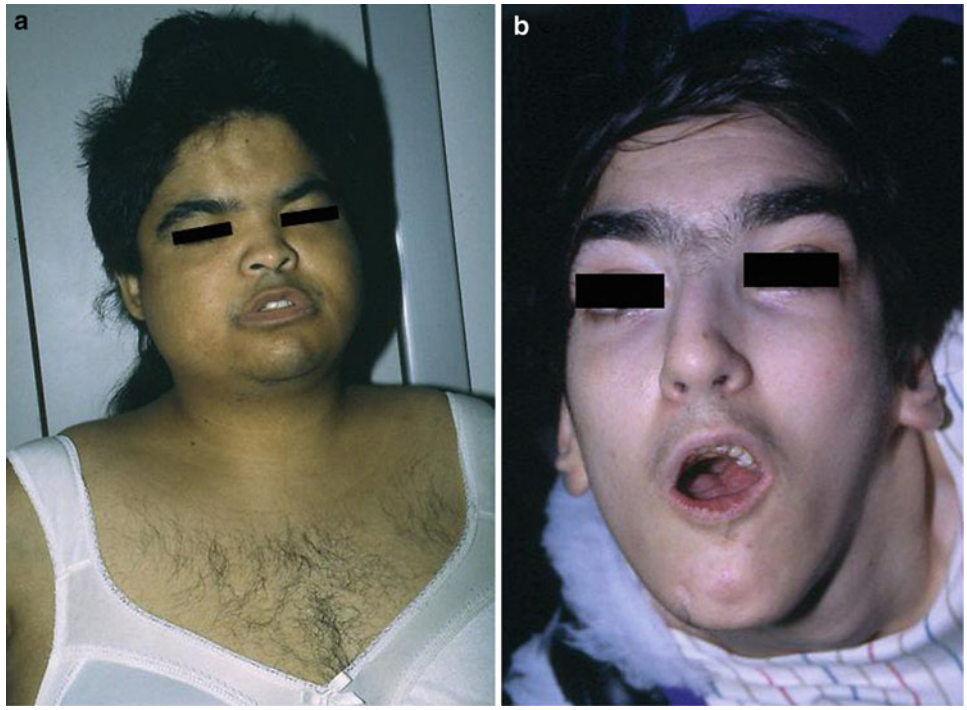

Fig. 7 (**a**, **b**) Two adults with de Lange syndrome showing hirsutism and mental retardation

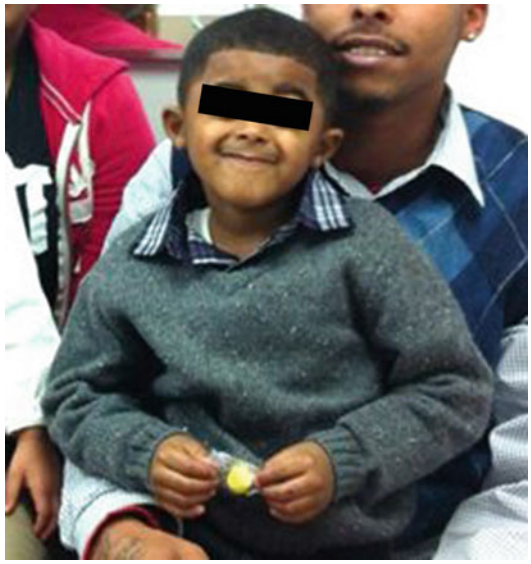

Fig. 8 This 3-year-old boy had a history of failure to thrive, gastroesophageal reflux, hiatal hernia, short stature, bilateral hydroceles, recurrent otitis media, ptosis of the left eye, strabismus, blocked tear ducts, cryptorchidism, and seizures. On examination, he has typical facies of de Lange syndrome. DNA sequence analysis of the *SMC1A* gene in this patient demonstrated a base pair change, c.1877G>A, which results in an arginine to histidine change at amino acid position 626, p.Arg626His. This is a nonconservative amino acid change that affects an evolutionarily conserved amino acid residue in a known functional domain of the SMC1A protein. While this particular sequence change does not appear to have been previously described in other patients with Cornelia de Lange syndrome, it is similar to other pathogenic sequence changes described in the *SMC1A* gene and occurs in the same area of the gene where other missense sequence changes have been described. This sequence change is the likely cause of this patient's disease phenotype (Courtesy of Dr. Susonne Ursin)

Del(18p) Syndrome

Contents

De Grouchy in 1963 (De Grouchy et al. 1963) reported the syndrome, the first example of a partial monosomy compatible with life. The incidence is approximately 1 in 50,000 live-born infants (Turleau 2008).

Synonyms and Related Disorders

18p- syndrome; Monosomy 18p syndrome

Genetics/Basic Defects

1. Monosomy 18p syndrome (Turleau 2008)
   1. Refers to a chromosomal disorder, resulting from the deletion of all or part of the short arm of chromosome 18
   2. One of the most frequent autosomal terminal deletion syndromes
2. Types of 18p deletion
   1. Monosomies of the entire short arm as well as partial monosomies 18p have been reported (Schaub et al. 2002).
   2. De novo deletions in most cases (about two-thirds).
   3. Consequences of an unbalanced whole arm translocation: usually occurring between the long arm of an acrocentric chromosome and the long arm of the chromosome 18 and resulting in a karyotype with 45 chromosomes (Wang et al. 1997).
   4. Consequences of malsegregation of a balanced parental translocation with a variable breakpoint on 18p and are accompanied by a partial trisomy for another chromosome.
   5. Cryptic subtelomeric deletions or translocations: evidenced using subtelomeric screening (Horsley et al. 1998; Babovic-Vuksanovic et al. 2004).
   6. Mosaicism or association with another aneuploidy.
   7. Ring 18 chromosome (Stankiewicz et al. 2001) or after recombination in a pericentric inversion leading to a 18p monosomy associated with a 18q trisomy (Leonard et al. 2000).
   8. Familial transmission of 18p- from one of the parents to the child reported in at least eight cases, all of them maternally inherited (Uchida et al. 1965; Velagaleti et al. 1996;

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_66

Tonk and Krishna 1997; Rigola et al. 2001; Tsukahara et al. 2001; Maranda et al. 2006; Portnoi et al. 2007; Misceo et al. 2009).
    1. 18p- may be in a homogeneous or a mosaic state in the parent.
    2. Intrafamilial clinical variability.
3. The most distal segment of 18p contains the critical region of HPE4 (Overhauser et al. 1995).
    1. Mutations in the *TGIF* gene located on 18p11.3 have been shown to cause holoprosencephaly (Gripp et al. 2000).
    2. Hemizygosity of HPE4 does not automatically confer the phenotype of HPE, since only 10–15 % of patients have features consistent with HPE, confirming that multiple genetic and environmental factors intervene in HPE spectrum phenotypes.

Clinical Features

1. Marked phenotype variability (Sebold et al. 2015)
    1. Neonatal complications
        1. The most common findings (jaundice, respiratory difficulties, and feeding problems)
        2. Additional findings (meconium staining, bradycardia, tachypnea, hypoglycemia, urosepsis, nuchal cord, and abdominal swelling of unknown etiology)
    2. Cardiac abnormalities: tetralogy of Fallot, VSD, ASD, pulmonary stenosis, mild aortic valve abnormality, trivial tricuspid regurgitation, and patent foramen ovale
    3. Neurologic abnormalities: seizures, hypotonia, and MRI abnormalities
    4. Orthopedic abnormalities: kyphoscoliosis, pectus excavatum, congenital hip dysplasia, sacral dysgenesis, elbow valgus deformity, genu recurvatum/valgus, pes planus/vagus, and toe syndactyly
    5. Gastrointestinal abnormalities: chronic constipation, hernias (hiatal, inguinal, umbilical), diastasis recti, and a proximally placed anus
    6. Genitourinary abnormalities: cryptorchidism and hydrocele
    7. Hearing loss: chronic otitis media
    8. Ophthalmologic abnormalities: strabismus, ptosis, refractive errors, astigmatism, myopia, hyperopia, congenital cataracts, nystagmus, iris coloboma, optic nerve hypoplasia, and transient cortical blindness
    9. Endocrinology: pituitary abnormalities (growth hormone deficiency, anterior pituitary hormone deficiency, ovary agenesis, Graves' disease, multinodular goiter, and precocious puberty)
    10. Dysmorphology: epicanthal folds, upslanting or downslanting palpebral fissures, a wide depressed nasal bridge, and a small nose
    11. Growth parameters: short stature and small head circumference
    12. Autoimmune disorders: Graves' disease, psoriasis, lupus, and immunodeficiency (IgA, IgG, IgM)
2. Very frequent clinical features (Turleau 2008)
    1. Mental retardation with variable severity
    2. Speech delay
    3. Short stature
    4. Hypotonia
3. Frequent clinical features
    1. Variable features of the holoprosencephaly (HPE) spectrum
    2. Ptosis
    3. Flat nasal bridge
    4. Wide mouth with short upper lip
    5. Small mandible
    6. Excessive caries
    7. Large, protruding ears
    8. Short, webbed neck
    9. Broad trunk
    10. Pectus excavatum
    11. Kyphoscoliosis
4. Rare clinical features
    1. Behavioral disorders
    2. Autoimmune diseases
    3. Alopecia
    4. Dystonia
5. Genotype-phenotype correlation: a correlation between the extent of the deleted region and the mental development (Wester et al. 2006)

Diagnostic Investigations

1. Cytogenetic analysis including subtelomeric FISH
    1. Patient: to detect absence of all or part of the short arm of one chromosome 18
    2. Parent: to determine if either parent is a balanced translocation carrier or has the unbalanced 18p deletion
2. MRI of the brain (Sebold et al. 2015)
    1. Normal
    2. Delayed myelination
    3. Septo-optic dysplasia
    4. Lobar holoprosencephaly
    5. Ventriculomegaly
    6. White matter abnormalities
    7. A CSF cystic area in the occipital horn as well as a "large pituitary"
    8. Areas of increased signal
3. Molecular analysis (Sebold et al. 2015)
    1. Array-based comparative genomic hybridization (CGH)
    2. Parental origin of the abnormal chromosome: using PCR-based polymorphic microsatellites

Genetic Counseling

1. Recurrence risk (Turleau 2008)
    1. Patient's sib
        1. A de novo case
            1. Not significantly increased above that of the general population.
            2. Caution: cryptic mosaicism may be present in one of the parents.
        2. Presence of a structural rearrangement in one of the parents (most frequently balanced translocation, followed by pericentric inversion)
            1. Recurrence risk depends on the type of rearrangement, in which chromosomes are involved, and on the size of the rearranged segments.
            2. A high recurrence risk of either a monosomy or a trisomy for 18p for some rearrangement.
        3. One of the parents with a 18p deletion.
            1. A 50 % risk if the parent has non-mosaic 18p deletion
            2. Lower than 50 % risk if the parent has mosaic 18p deletion
    2. Patient's offspring
        1. A 50 % risk if the patient has non-mosaic 18p deletion
        2. Lower than 50 % risk if the patient has mosaic 18p deletion
2. Prenatal diagnosis
    1. Cytogenetic analysis including FISH: can detect deletion 18p when a parent is heterozygous for a balanced rearrangement involving 18p or carrier of a 18p deletion, following detection of a holoprosencephaly-type defect at sonography, or after the birth of a first affected child
    2. Deletion 18p is rarely observed in first-trimester abortions suggesting that this imbalance is not selected against
3. Management
    1. No specific treatment available
    2. Early rehabilitative and education interventions, mainly speech therapy
    3. Physical therapy for hypotonia

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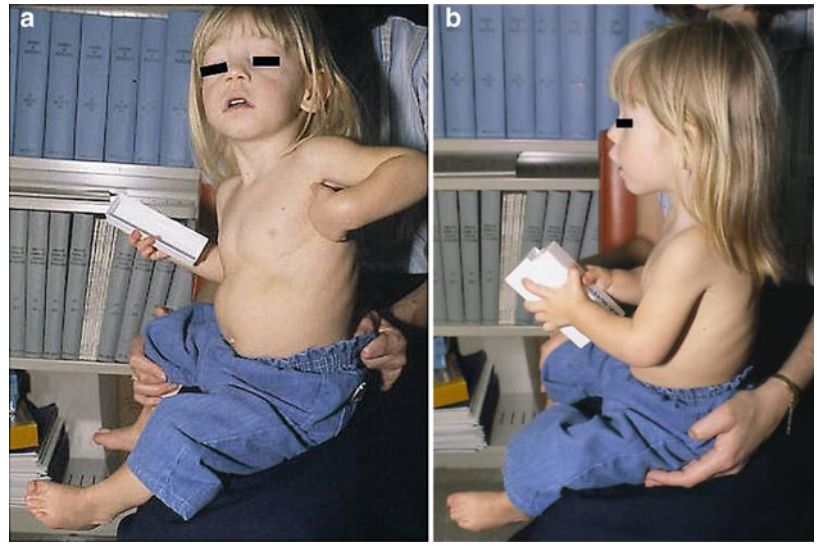

Fig. 1 (**a**, **b**) Girl with monosomy 8p syndrome showing flat nasal bridge and ptosis with history of developmental delay

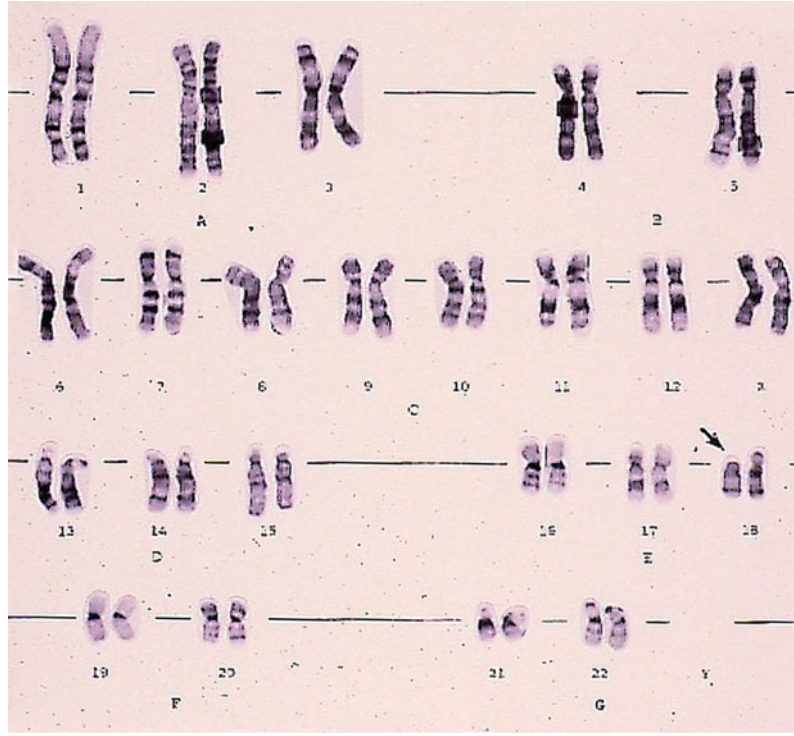

Fig. 2 Karyotype of the previous patient is illustrated here

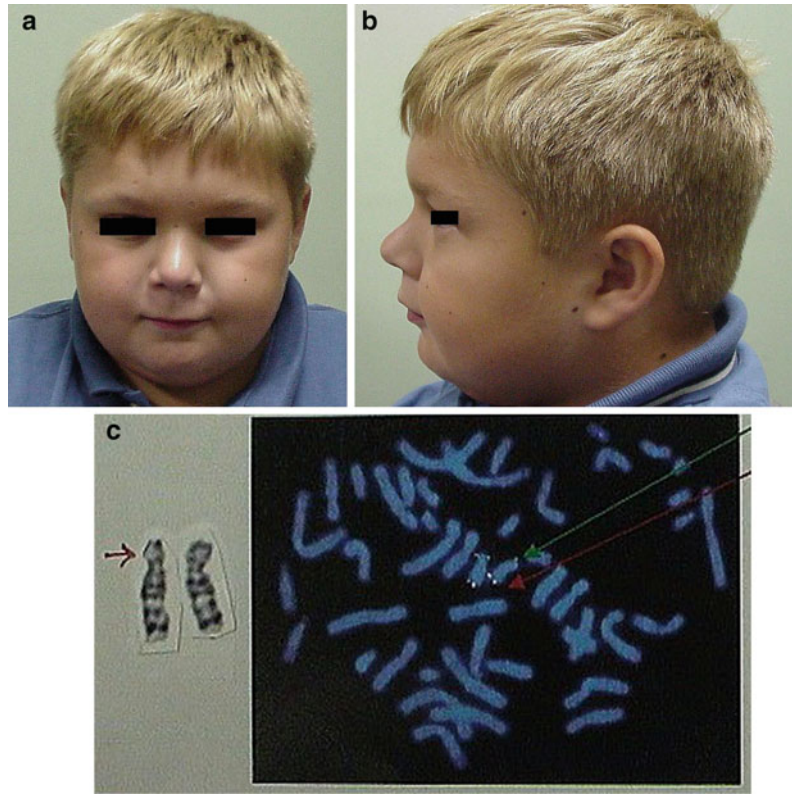

Fig. 3 (**a**–**c**) Eleven-year-old boy (**a**, **b**) with del(18p). He has a short stature, mild mental retardation, IgA deficiency, a round face, tricuspid/mitral regurgitation, glandular hypospadias, and small hands and feet. A partial karyotype with FISH is illustrated here (**c**)

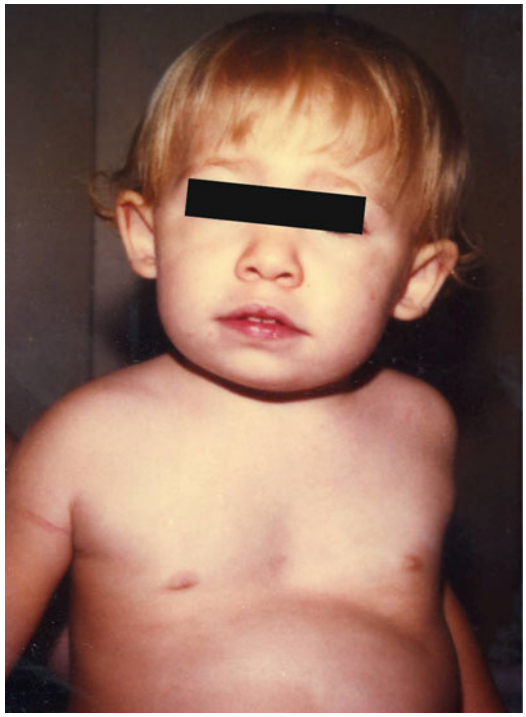

Fig. 4 Young girl with monosomy 18p syndrome [Del (18p)-Del(18)(qter-p111)]. In addition to developmental and speech delay, the patient has a round face, short upper lip, broad philtrum, everted lower lip, and protruding ears

Del(22q11.2) Syndrome

Contents

The 22q11.2 deletion syndrome is one of the most common multiple anomaly syndrome and the most common microdeletion syndrome. It is the most common syndrome associated with palatal clefts and congenital velopharyngeal dysfunction (Kirschner 2005) and the second most common cause of developmental delay accounting for about 2.4% of affected individuals. The occurrence is approximately 1 in 4,000 live births (Botto et al. 2003; Óskarsdóttir et al. 2005).

Synonyms and Related Disorders

22q11.2 Microdeletion Syndrome; CATCH-22 syndrome; Cayler cardiofacial syndrome associated with del(22q11.2); Congenital thymic hypoplasia associated with hypocalcemia; DiGeorge syndrome; Takao syndrome; Velocardiofacial syndrome (Shprintzen syndrome)

Historic overviews of the syndromes associated with 22q11.2 deletion (Driscoll 1994; Cuneo 2001; Emanuel et al. 2001; McDermid and Morrow 2002):

1. Congenital thymic hypoplasia associated with hypocalcemia
2. DiGeorge syndrome (DGS) (De la Chapelle et al. 1981)
    1. Congenital thymic hypoplasia
    2. Hypocalcemia
    3. T-cell dysfunction
    4. Typical facial anomalies
    5. Typical cardiac anomalies
3. Takao syndrome (conotruncal anomaly face syndrome) (Burn et al. 1993; Matsuoka et al. 1998)
    1. Conotruncal cardiac anomalies (Momma et al. 1996)
    2. Typical facial appearance
    3. Velopharyngeal insufficiency
    4. Learning disability
4. Velocardiofacial syndrome (VCFS) (Shprintzen syndrome) (Driscoll et al 1992; Goldberg et al. 1993; Motzkin et al. 1993; Carlson et al. 1997; Shprintzen 2000; Horenstein et al. 2014)
    1. Velopharyngeal abnormalities
    2. Cardiac abnormalities
    3. Facial abnormalities
    4. The birth incidence of 1/1,800–1/4,000, making VCFS the second most common cause of congenital heart disease after Down syndrome
5. DiGeorge syndrome speculatively linked to chromosome 22

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6. Partial monosomy of chromosome 22
7. "CATCH-22 syndrome" (Hall 1993): not a preferred term (Burn 1999)
    1. *C*ardiac disease
    2. *A*bnormal facies
    3. *T*hymic hypoplasia
    4. *C*left palate
    5. *H*ypocalcemia
    6. Associated with a deletion in chromosome-*22*
8. Cayler cardiofacial syndrome associated with del(22q11.2) (Giannotti et al. 1994)
    1. Asymmetric crying facies
    2. Phenotypic spectrum expanded to include extracardiac anomalies
    3. Associated with del(22q11.2)
9. Some cases of autosomal dominant Opitz G/BBB syndrome (McDonald-McGinn et al. 1995)
    1. Hypertelorism
    2. Laryngotracheoesophageal cleft
    3. Cleft palate
    4. Swallowing difficulty
    5. Genitourinary defects
    6. Mental retardation
    7. Congenital heart defects

Genetics/Basic Defects

1. Inheritance (Thomas and Graham 1997)
    1. De novo deletions in the majority of cases (80–90%) (Yamagishi and Srivastava 2003)
    2. The deletion can be transmitted as an autosomal dominant trait
    3. Familial deletions identified in 7% of probands
    4. Deletions within chromosome 22q11: an important cause of familial heart defects (Wilson et al. 1992)
2. Cause: hemizygous deletion of 22q11.2
    1. Deletions inherited from an affected parent (<14%)
    2. Up to 89% of patients show a typical phenotype of DiGeorge syndrome.
    3. Occupy roughly 15% of the patients with congenital heart disease
    4. Microdeletions detected by fluorescence in situ hybridization (FISH) probes
3. Molecular/cytogenetic basis (Amati et al. 1999)
    1. DiGeorge critical region (300–600 kbp containing approximately 25–30 candidate genes) mapped to 22q11.2
    2. Candidate genes (Yamagishi 2002)
        1. Ubiquitin-fusion-degradation-1-like (*UFD1L*) gene located in the DiGeorge critical region, which is most consistently deleted in patients with DGS (88%) or VCFS (76%). A significant percentage of cardiac patients with conotruncal cardiac malformations have a 22q11.2 deletion.
        2. Mutation in *TBX1* gene (belongs to the T-box family of transcription factors) located in 22q11.2 region has been suggested as a rare cause of the syndrome (Yagi et al. 2003; Gao et al. 2013). *TBX1* haploinsufficiency is likely the major determinant of aortic arch defects in patients with 22q11.2 deletion syndrome.
4. Cardiac embryogenesis and branchial arch abnormalities
    1. Cardiac structures (derived from the cardiogenic cord in the embryonic mesoderm during very early embryogenesis)
    2. Conotruncus (outflow structures of the heart, derived from branchial arches IV and VI, which differentiate into aorta and pulmonary artery respectively). Malalignment of these structures and incomplete septation give rise to the following diverse congenital heart disease associated with DiGeorge syndrome (Wilson et al. 1991):
        1. Arch abnormalities (interrupted aortic arch, aortic coarctation) (Goldmuntz et al. 1993)
        2. Conotruncal abnormalities (truncus arteriosus, pulmonary artery atresia) (Johnson et al. 1995)
        3. Malalignment of the interventricular septum with the conotruncus (VSD, ASD, Tetralogy of Fallot, DORV)
        4. Valvular or myocardium abnormalities (unusual)

3. Branchial arches are also the embryological origin of the anterior facial structures, thyroid, thymus, and parathyroids. Their abnormalities are the phenotypic hallmark of the DiGeorge syndrome groups.

5. Heterogeneous etiology of congenital heart defects
    1. Deletion 22q11.2 (the second most common chromosomal cause of significant congenital heart disease)
    2. Aneuploidy (trisomy 21 remains the most common chromosomal cause of significant congenital heart disease) (Goodship et al. 1998)
    3. Single gene disorder (De Decker and Lawrenson 2001)
    4. Multifactorial trait
    5. Maternal disease such as diabetes mellitus
    6. Teratogen exposure

Clinical Features

1. Marked variability of phenotype (Ryan et al. 1997; Di Rocco et al. 1998; Akiba et al. 2000; McDonald-McGinn et al. 2001)
2. Intrafamilial phenotypic variability (Vergaelen et al. 2015)
3. Endocrine abnormalities: common in patients with a 22q11.2 deletion (Weinzimer 2001)
    1. Hypocalcemia (30%)
        1. Invariably due to hypoparathyroidism, documented by aplasia or hypoplasia of the parathyroid glands at surgery or autopsy.
        2. Symptoms of hypocalcemia most likely manifest in the neonatal period, because maternal calcium supply by fetal circulation is abruptly interrupted at birth and the calcium intake within the first few days of life is usually insufficient.
            1. Seizures
            2. Tremors
            3. Tetany
        3. Other signs of hypocalcemia.
            1. Paresthesias
            2. Muscle cramps
            3. Rigidity
    4. Prevalence of hypocalcemia by phenotypic characteristics.
        1. DiGeorge syndrome (69–72%)
        2. Velocardiofacial syndrome (13–22%)
        3. Conotruncal anomaly face syndrome (10%)
        4. 22q11.2 deletion (49–60%)
    5. Autoimmune enteropathies
    2. Growth disorders
        1. Growth hormone deficiency
        2. Short stature
    3. Thyroid disorders
        1. Congenital hypothyroidism
            1. Noted in 7% of patients with VCFS
            2. Noted in 5% of patients with DGS
        2. Hyperthyroidism due to Graves disease
4. Immunodeficiency (highly variable) (77%) (Sullivan et al. 1998)
    1. Primary T-cell dysfunction (decreased production of T cells caused by impaired formation of thymic tissue) (67%)
    2. Secondary T-cell functional defects (19%)
    3. Humoral immune deficits (23%)
    4. IgA deficiency (13%) (Smith et al. 1998)
    5. Associated autoimmune disease
        1. Polyarticular juvenile rheumatoid arthritis, a frequency 150 times that of the general population rate
        2. Autoimmune hemolytic anemia
        3. Idiopathic thrombocytopenic purpura
        4. Autoimmune enteropathies (celiac disease)
        5. Vitiligo
5. Cardiovascular malformations (75%, the most common structural anomaly)
    1. Conotruncal heart defects (Marino et al. 2001)
        1. Tetralogy of Fallot (the most common heart anomaly)
        2. Pulmonary atresia with ventricular septal defect
        3. Truncus arteriosus (25%)
        4. Interrupted aortic arch type B (30%)
        5. Atrial septal defect
    2. Right-sided, cervical, or double aortic arch/aberrant subclavian artery
    3. Pulmonary artery abnormalities
        1. Discontinuity of the pulmonary arteries
        2. Diffuse hypoplasia

3. Discrete stenosis
4. Defect of arborization
5. Major aortopulmonary collateral arteries

4. Infundibulum abnormalities
   1. Malaligned
   2. Hypoplastic
   3. Absent
5. Semilunar valve abnormalities
   1. Bicuspid
   2. Severely dysplastic
   3. Insufficient
   4. Stenotic

6. Craniofacial features
   1. Palate
      1. Velopharyngeal incompetence (27%)
      2. Submucous cleft palate (16%)
      3. Overt cleft palate (11%)
      4. Bifid uvula (5%)
      5. Cleft lip/palate (2%)
      6. Suspected velopharyngeal incompetence
      7. Normal
   2. Ears
      1. Low-set ears
      2. Over-folded helices
      3. Squared off helices
      4. Cupped, microtic, and protuberant ears
      5. Preauricular pits/tags
      6. Narrow canals
      7. Chronic otitis media
      8. Conductive hearing loss
   3. Nose
      1. Prominent nasal root
      2. Bulbous nasal tip
      3. Hypoplastic alae nasae
      4. Nasal dimple/bifid nasal tip
      5. Chronic sinusitis
   4. Throat
      1. Stridor caused by a vascular ring
      2. Laryngomalacia
      3. Laryngeal webs
   5. Eyes
      1. Tortuous retinal vessels (58%)
      2. Posterior embryotoxon (69%)
      3. Hooding of the upper and/or lower lid (47%)
      4. Ptosis (9%)
      5. Epicanthal folds (3%)
      6. Distichiasis (3%)
   7. Skeletal abnormalities
      1. Vertebral anomalies (19%)
         1. Coronal clefts
         2. Hemivertebrae
         3. Butterfly vertebrae
         4. Scoliosis
      2. Rib anomalies including supernumerary ribs (19%)
      3. Hypoplastic scapulae
      4. Upper limb anomalies including pre/postaxial polydactyly (6%)
      5. Lower limb anomalies (15%)
         1. Postaxial polydactyly
         2. Club foot
         3. Over-folded toes
         4. 2, 3 syndactyly
      6. Craniosynostosis
   8. Renal abnormalities (37%)
      1. Calculi
      2. Single kidney
      3. Small kidneys
      4. Echogenic kidney
      5. Horseshoe kidney
      6. Bladder wall thickening
      7. Multicystic dysplastic kidney
      8. Duplicated collecting system
      9. Renal tubular acidosis
   9. Neuromuscular development
      1. Developmental delays
      2. Hypotonia
      3. Feeding disorders
   10. CNS manifestations
      1. Mental retardation
      2. Seizures (with or without hypocalcemia)
      3. Asymmetric crying facies
      4. Ataxia
      5. Cerebellar hypoplasia
      6. Enlarged Sylvian fissures
      7. Pituitary abnormalities
      8. Polymicrogyria
      9. Mega cisterna magna
      10. Neural tube defects
   11. Neuropsychological manifestations (Woodin et al. 2001; Cancrini et al. 2014; Jonas et al. 2014)
      1. Attention deficit/hyperactivity disorder

2. Anxiety disorders (most commonly specific and social phobia)
3. Mood disorders
4. Autism spectrum disorders
5. Nonverbal learning disability
6. Speech and language deficits
7. Psychomotor developmental delay
8. Social/emotional concern
9. Psychiatric disorders

12. Adult phenotype (Cohen et al. 1999)
    1. Lower rates of congenital heart defects
    2. Higher rates of palate anomalies, learning disabilities/mental retardation, and psychiatric disorders
    3. B cell and immunoglobulin defects have been described and appear to be increased in the adult population (Derfalvi et al. 2016)

Diagnostic Investigations

1. Cytogenetic studies
    1. High-resolution chromosome analysis to detect del(22q11.2)
    2. Fluorescence in situ hybridization (FISH) for the chromosome region 22q11.2 to detect submicroscopic deletion (Kornfeld et al. 2000)
2. Parental cytogenetic studies are warranted in all families with an affected child in order to identify mildly affected parents, as well as to rule out low level mosaicism (McDonald-McGinn and Zackai 2008).
3. Genetic studies (Bawle 2015)
    1. Chromosome microarray analysis or array comparative genomic hybridization
    2. Fluorescent in situ hybridization
    3. Multiplex ligation-dependent probe amplification
    4. TBX1 gene studies (DiGeorge syndrome)
4. Echocardiography for cardiovascular anomalies
5. Chest X-ray
    1. Presence of a heart defect
    2. Absence of thymus shadow
6. Renal ultrasound examination at irregular intervals for the development of renal stones
7. MRI of the brain: detects high prevalence of brain abnormalities that are most likely neurodevelopmental and may partially explain the high prevalence of learning disability and psychiatric disorder (Van Amelsvoort et al. 2001)
    1. Cerebellar atrophy
    2. Agenesis of the corpus callosum
    3. White matter hyperintensities
    4. Cavum septum pellucidum
    5. Cerebral atrophy
    6. Widespread differences in white matter bilaterally
    7. Region-specific differences in gray matter in the left cerebellum, insula, and frontal and right temporal lobes
8. Blood calcium levels
9. Initial immunological investigations (Gennery 2012)
    1. Full blood count and differential leukocyte count
    2. Immunoglobulins (IgM, IgA, IgG,)
    3. Lymphocyte phenotyping (CD3, CD4, CD8, CD19, or CD20, CD16 or CD56)
    4. Lymphocyte proliferations to phytohemagglutinin if T lymphocyte counts low
    5. Postvaccination antibody responses to tetanus, and polysaccharide-protein conjugated *Haemophilus influenzae* type B capsular (Hib) and/or
    6. Pneumococcal antigens
    7. Beyond 2 years of age – assessment of polysaccharide antigen response
    8. Assessment of autoantibodies, if clinically indicated, including direct antiglobulin test and thyroid antibodies

Genetic Counseling

1. Recurrence risk (McDonald-McGinn et al. 2013)
    1. Patient's sib
        1. Low recurrence risk, provided parents are phenotypically normal and neither one is a carrier of del(22q11.2)
        2. A higher recurrence risk in case of a parent with germline mosaicism or

low-level somatic mosaicism for a microdeletion syndrome
3. A 50% recurrence risk if a parent is also found to have the 22q11.2 deletion syndrome
2. Patient's offspring: 50% affected

2. Prenatal diagnosis (Driscoll 2001)
1. Indications for prenatal testing for the 22q11.2 deletion
1. A previous child with a 22q11.2 deletion or DiGeorge/velocardiofacial syndrome
2. An affected parent with a 22q11.2 deletion
3. In utero detection of a fetus with a conotruncal cardiac defect (Boudjemline et al. 2002)
2. Prenatal ultrasonography and fetal echocardiography for a fetus at risk for the 22q11.2 deletion
1. Conotruncal cardiac defect with associated anomalies
2. Conotruncal cardiac defect without associated anomalies
3. Aplasia or hypoplasia of the fetal thymus in the presence of conotruncal cardiac anomalies: very specific for deletion 22q11.2 (Chaoui et al. 2002)
4. Cardiac lesions with the deletion
1. Interrupted aortic arch (50–80%)
2. Truncus arteriosus (35%)
3. Tetralogy of Fallot (15%)
4. Rare in double outlet right ventricle and transposition of the great vessels
5. Sensitivity of different sonographic features allowing discrimination of a subgroup likely to be associated with microdeletion 22q11.2
1. Nuchal translucency (12%) (Machlitt et al. 2002)
2. Polyhydramnios (20%)
3. IUGR (8%)
4. Extracardiac anomalies (36%)
3. Prenatal diagnosis of 22q11.2 deletion by amniocentesis or CVS
1. Fluorescence in situ hybridization (FISH) analysis with probes from the DiGeorge chromosomal region (DGCR)
2. Preimplantation genetic diagnosis by FISH reported in an at-risk mother with a 22q11.2 deletion
3. Occasional detection of an unbalanced translocation or an interstitial deletion of 22q11.2 by cytogenetic analysis
4. Molecular genetic analysis
1. Demonstrate failure to inherit a parental allele or hemizygosity in the deleted region
2. Restriction fragment length polymorphism (RFLP) analysis and quantitative hybridization
3. PCR assays using short tandem repeat polymorphisms (STRs) within the DGCR
4. Array comparative genomic hybridization characterization using uncultured amniocytes: has the advantage of detecting uncharacterized chromosomal deletions or genomic imbalance with haploinsufficiency of the genes responsible for conotruncal heart malformations and tetralogy of Fallot, as well as refining the 22q11.2 deletion breakpoints (Chen et al. 2013)
5. Limitations of prenatal testing for the 22q11.2 deletion
1. DGS/VCFS, a heterogeneous disorder in which 10–15% of patients do not have the deletion. Therefore, FISH analysis is of limited value in couples who have had a previously affected child without a deletion.
2. Atypical deletions of 22q11.2, unbalanced chromosomal translocations, deletions involving other chromosomes have not been detected by FISH using commercially available probes.
3. Consider other causes of congenital heart defects such as aneuploidy, single gene defects, maternal diseases such as diabetes, and exposure to teratogens.
4. Inability to predict accurately the phenotype prenatally.

4. Preimplantation genetic diagnosis: available for families in which the diagnosis of the 22q11.2 deletion syndrome has been established in an affected family member (Iwarsson et al. 1998)

3. Management (Sullivan 2008)
    1. Medical care
        1. Manage the feeding problems
            1. Modification of spoon placement when eating
            2. Treat gastroesophageal reflux with acid blockade, prokinetic agents, postural therapy, and medication to treat gastrointestinal dysmotility and to facilitate bowel evacuation
        2. Early intervention programs including speech therapy for developmental delay
        3. Management of psychiatric disorder
        4. Hypocalcemia
            1. Asymptomatic hypocalcemia: treat with oral calcium supplements
            2. Severe symptomatic hypocalcemia: treat with prompt administration of parenteral calcium
            3. Goal of treatment: maintain calcium in the low-normal range (8–9 mg/dL) to minimize hypercalcinuria
            4. Over supplementation of calcium leads to nephrocalcinosis
        5. Management of immunodeficiency
            1. Most patients have diminished T-cell numbers as a consequence of thymic hypoplasia.
            2. Most patients do not demonstrate a susceptibility to opportunistic infections.
            3. Risk of using live viral vaccines in infants seems to be low except for patients who have thymic aplasia and/or very low T-cell counts (McDonald-McGinn et al. 1999).
            4. Both the measles, mumps, rubella, and the varicella vaccine are found to be safe and efficacious in children who had the deletion and who had mild to moderate T-cell compromise (Junker and Driscoll 1995; Pierdominici et al. 2003).
            5. Management of thymic aplasia: A thymus transplant, fully matched peripheral blood transplant, or donor lymphocyte infusions are required.
        6. Thyroid hormone for hypothyroidism
        7. Growth hormone therapy in growth hormone–deficient children with a 22q11.2: associated with sustained improvements in height and growth velocity
        8. Guidelines focused on managing the neuropsychiatric, endocrine, cardiovascular, reproductive, psychosocial, genetic counseling, and other issues that are the focus of attention in adults with 22q11.2 deletion syndrome (practical strategies for the recognition, evaluation, surveillance, and management of the associated morbidities) (Fung et al. 2015)
    2. Surgical care
        1. Congenital heart diseases
            1. Palliative operation
            2. Corrective operation
        2. Velopharyngeal dysfunction
            1. Pharyngoplasty
            2. Plastic surgery of cleft lip/palate
        3. Surgery
            1. Gastrointestinal anomalies
            2. Renal anomalies
            3. Musculoskeletal anomalies

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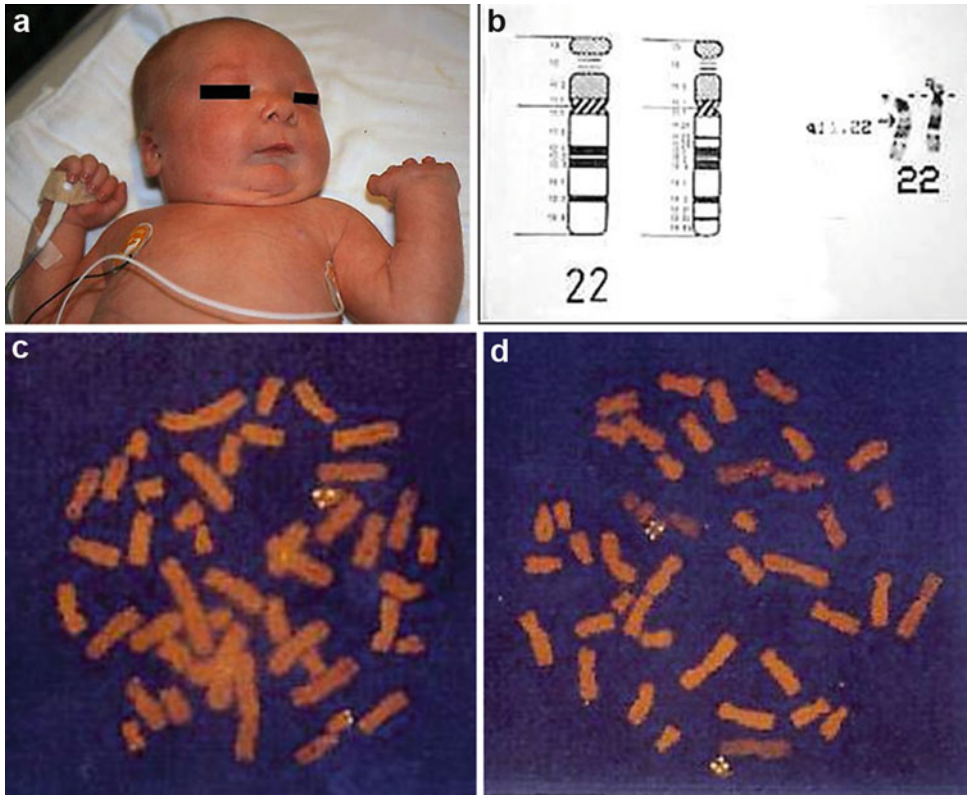

Fig. 1 An infant (**a**) with DiGeorge syndrome. The deletion of 22q11.2 was shown by partial karyotype with ideogram (**b**) and FISH with DiGeorge cosmid probe (**c**). The FISH in (**d**) is a control

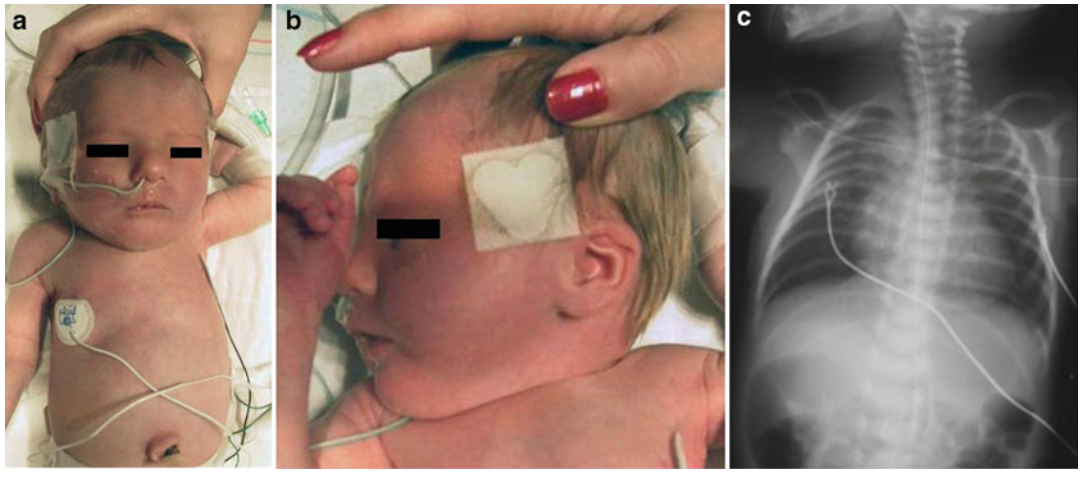

Fig. 2 (**a**–**c**) A newborn infant with conotruncal anomaly facies syndrome. The radiograph shows a conotruncal heart anomaly and absent thymus

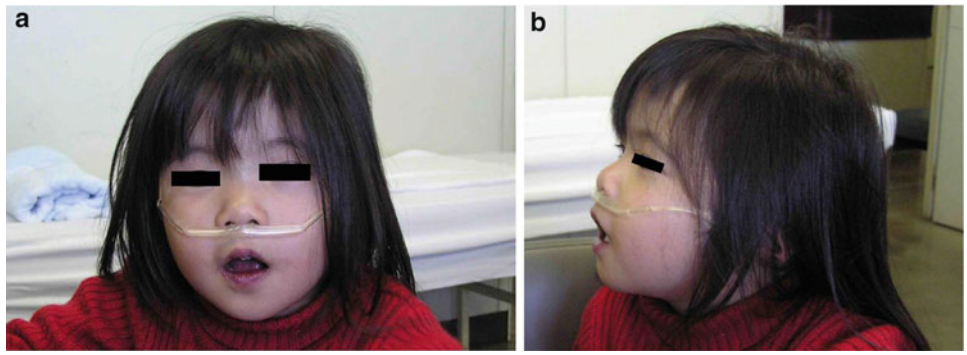

Fig. 3 (**a**, **b**) A girl 4 years and 6 months old with tetralogy of Fallot, growth retardation, developmental delay, and del (22q11.2)

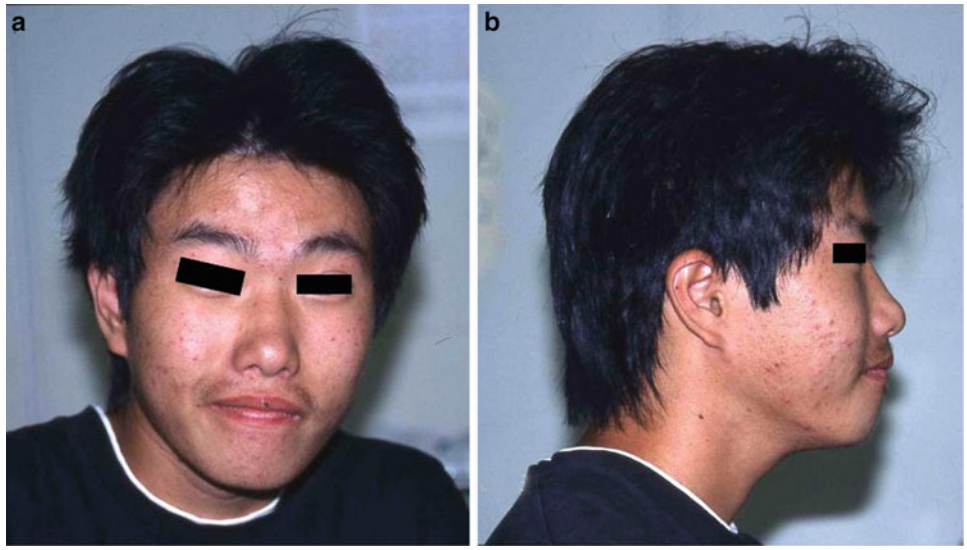

Fig. 4 (**a**, **b**) A 16-year-old boy with tetralogy of Fallot, inguinal hernia, developmental delay, bilateral conductive hearing loss (late onset at 15 years of age), and del(22q11.2) shown in the next figure

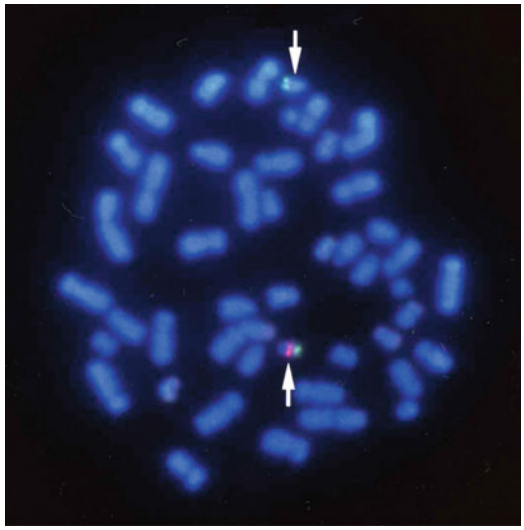

Fig. 5 FISH of the patient in the Fig. 1d. showing two green signals (a probe for 22q13; ARSA) and only one red signal (a probe for 22q11.2; TUPLE1) demonstrating del (22q11.2)

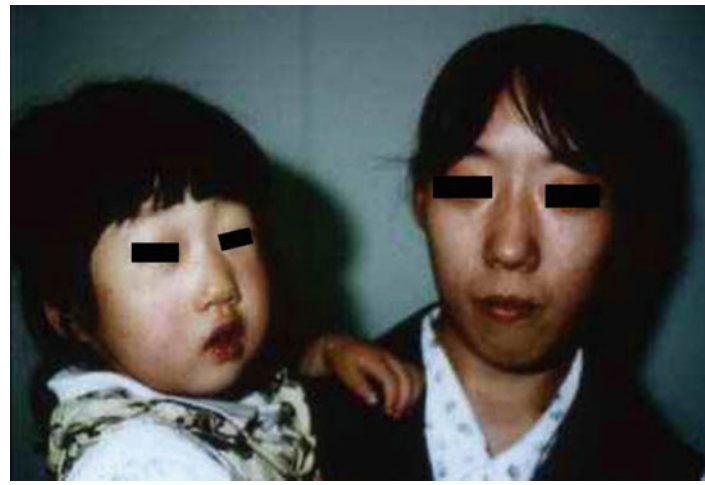

Fig. 6 A mother and daughter both have deletion 22q11.2

Del(Yq) Syndrome

Contents

In 1976, Tiepolo and Zuffardi (1976) first recognized the deletions of the long arm of the Y chromosome, large enough to be recognized by light microscopy, in six azoospermic men. Large structural rearrangements of the Y chromosome are known to be commonly associated with a 45, X/46,XY chromosomal mosaicism (Siffroi et al. 2000). Majority of Yq deletions are microdeletions and, therefore, require analysis by molecular means (Martin 2008).

Synonyms and Related Disorders

Chromosome Yq deletion syndrome

Genetics/Basic Defects

1. Role of Yq deletions in male infertility (Ma et al. 2000)
    1. Factors controlling human spermatogenesis: postulated to be located on the distal portion of the euchromatin segment of the long arm of the Y chromosome, Yq11 (Tiepolo and Zuffardi 1976).
    2. This spermatogenesis locus at Yq11.23, as demonstrated with high-resolution banding techniques, has since come to be known as the "azoospermia factor" or "AZF" (Bühler 1985).
    3. Further molecular investigations into genotype-phenotype correlation in azoospermic men led to the localization of the *AZF* locus to interval 6 of the Y chromosome (Vergnaud et al. 1986; Affara et al. 1986; Andersson et al. 1988).
    4. Microdeletions of the long arm of the Y chromosome.
        1. Represents the most frequent molecular genetic cause of severe male infertility (Ferlin et al. 2006; Krausz and Degl'Innocenti 2006)
        2. The first solid molecular evidence that failure of spermatogenesis may be caused by cytologically undetectable deletions on the Y chromosome: identification of two nonoverlapping microdeletions mapped to the distal region of intervals 5 and 6, carried by two azoospermic otherwise normal men (Ma et al. 1992)
        3. Further studies led to the proposal of the existence of three *AZF* subregions

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termed *AZFa* (formerly JOLAR region), *AZFb*, and *AZFc* (formerly KLARD region), respectively (Vogt et al. 1996).
   1. Deletion of AZFa: associated with lack of germ cells or Sertoli cell-only syndrome.
   2. Deletion of *AZFb*: associated with spermatogenesis arrest.
   3. *AZFc* gene products: involved in the maturation process of postmeiotic germ cells (Vogt et al. 1996).
   4. The above hypothesis remains controversial and it is generally accepted that the completion of spermatogenesis requires multiple genes not only on the Y chromosome but elsewhere as well.
4. Recent description of another *AZF* subregion further complicated the issue: *AZFd*: localized between *AZFb* and *AZFc* (Kent-First et al. 1999).
5. The discovery of the two separate microdeletions on the Yq in infertile men subsequently led to the identification of four candidate gene families for *AZF*:
   1. RNA-binding motif (*RBM*), previously named Y-linked RNA recognition motif (*YRRM*) (Ma et al. 1993)
   2. Deleted in azoospermia (*DAZ*) (Reijo et al. 1995)
   3. *Drosophila* fat facets related Y (*DFFRY*) (Brown et al. 1998)
   4. *C*hromodomain Y (*CDY*) (Lahn and Page 1999)
5. Male infertility: most likely result from deletions and/or mutations of one or more of the myriad of genes necessary for spermatogenesis (Krausz et al. 2003)

2. 45,X cell line associated with large cytogenetically visible Yq deletions (Hwa et al. 2004; Cui et al. 2007)
   1. Structural aberrations of the Y chromosome, such as large cytogenetically visible deletions of the long arm, ring Y, *iso*- or isodicentric short arm, are unstable and usually lost during mitosis, leading to mosaic 45,X (Hsu 1994; Kirsch et al. 2000; Siffroi et al. 2000; Bertini et al. 2005).
   2. In the presence of a 45,X cell line, a fetus has a risk of being a phenotypic female with Turner syndrome manifestations or to have ambiguous external genitalia, whether the other cell line is Yp, Yq, Yp plus Yq, or even a free Y chromosome (Hsu 1994).
   3. Patients with Turner syndrome with a Y-derived marker have milder phenotypic abnormalities than those with an X-derived marker. In general, patients with a Y-derived marker are not as short as, and have fewer somatic abnormalities than, patients with an X-derived marker chromosome (Schwartz et al. 1997).

Clinical Features

1. Deletion/microdeletion of the long arm of the Y chromosome
   1. Men with deletions, in general, are infertile and therefore deletions are not transmitted to sons unless in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are performed.
   2. Associated with severe oligozoospermia.
2. Phenotype-genotype correlative analyses (Cram et al. 2000)
   1. Identified four subregions within AZF, called AZFa, b, d, and c
   2. Most deletions observed in infertile men occur in the AZFc region (Totonchi et al. 2012; Elfateh et al. 2014): associated with severe oligospermia or azoospermia and occasionally oligozoospermia
   3. Men with more extensive deletions in the AZFb region that extend into the AZFa region: commonly exhibit histologic phenotypes such as germ cell arrest or Sertoli cell-only syndrome and as a result are usually azoospermic
   4. Men with deletions localized exclusively to AZFd: present with mild oligozoospermia or even normal sperm counts

associated with abnormal sperm morphology (Kent-First et al. 1999)

3. Phenotypes of 45,X/46,X,del(Y)(q11) (Werner et al. 1985; Hwa et al. 2004)
    1. Phenotypic males (34.2%): small testes, short stature, small penis, hypospadias, azoospermia, Turner syndrome, and gonadoblastoma (Hsu 1994).
    2. Intersex (47.4%).
    3. Phenotypic females (18.4%).
    4. Only a few cases of mos45,X/46,X,del(Y) reported with normal male external genitalia (Bühler 1980; Hoshi et al. 1998).
    5. The deletions of Y chromosomes are associated with abnormalities of the external genitalia, secondary sexual characteristics, and/or gonadal function.
    6. These phenotypic differences are related not only to the presence or absence of the *SRY* gene on Yp but also to the proportion of 45,X line in gonadal tissue.
        1. A sufficient SRY transcript level is necessary to trigger testes formation: once testes differentiate, male endocrine function is responsible for the rest of the events involving male phenotypic sexual differentiation.
        2. When the 45,X line is predominant in gonadal tissue, the phenotype of Turner syndrome would appear.
4. A case of Y chromosome with terminal deletion associated with nondisjunction, leading to mosaicism of three cell lines, has been reported (Cui et al. 2007): an azoospermic male with complete masculinization associated with karyotype 45,X/46,X,del(Y)/ 47,X,del(Y),del(Y)

Diagnostic Investigations

1. Diagnostic investigations of all infertile men (Bhasin 2007)
    1. Several semen analyses
        1. Sperm count
        2. Sperm motility
        3. Sperm morphology
    2. Hormone measurements (testosterone, LH, and FSH levels) to help determine:
        1. Low testosterone and low or inappropriately normal LH and FSH: gonadotropin deficiency: hypogonadotropic hypogonadism (Gnoth et al. 2005)
        2. Low testosterone, elevated LH, and FSH: obtain karyotype: primary testicular failure
        3. Normal testosterone and LH, elevated FSH: spermatogenic failure, test for Yq microdeletion
        4. High testosterone, elevated LH: androgen resistance
        5. Normal testosterone, normal LH, and FSH (Templeton 2000)
            1. Majority of infertile men: have normal testosterone, LH, and FSH levels
            2. Azoospermia: rule out obstruction by postejaculatory urine and seminal fructose and screen for Yq microdeletions
            3. Oligo/asthenozoospermia: exclude antisperm antibodies
2. Genetic testing of infertile couples and the offspring: important, especially in couples who are being considered for ICSI
    1. All infertile men with nonobstructive azoospermia, severe oligozoospermia, or very small testes should be offered a karyotype (Simpson and Lamb 2001; Allen et al. 2006).
    2. Screen infertile men with azoospermia or severe oligozoospermia for Yq microdeletions (Cram et al. 2006; Ferlin et al. 2007).
    3. Azoospermic men with at least one absent vas deferens or with evidence of normal spermatogenesis should be tested for CFTR mutations (Anguiano et al. 1992).
    4. Consider CREM mutations in men with postmeiotic maturation arrest (Blendy et al. 1996; Peri et al. 1998; Weinbauer et al. 1998).
    5. Genetic testing is indicated in men in whom personal or family history suggests disorders that have a genetic basis such as hemoglobinopathies and myotonic dystrophy (Takeda and Ueda 1977; Kletzky et al. 1979; Marchini et al. 2000); these patients also need genetic counseling.

3. Yq microdeletions are detected by PCR-based mapping of several conserved molecular markers or genes located within and outside the AZF region; these tests are available from commercial laboratories. With the availability of precise Y chromosome maps, more specific molecular markers have been developed, and guidelines for standardized testing of Yq microdeletions have been published by the European Molecular Genetics Network (Simoni et al. 2004). A novel universal multiplex PCR improves detection of AZFc Y-chromosome microdeletions (Zheng et al. 2014).
4. Array comparative genomic hybridization approach: a reliable high-resolution alternative to multiplex polymerase chain reaction for the discovery of pathogenic chromosome Y microdeletions in male infertility (Osborne 2007; Yuen et al. 2014).
5. GENOSEARCHTM AZF Deletion kit for the detection of a panel of AZF deletions using Luminex xMAP arrays: provides a routine tool for the diagnosis of AZF deletions in male infertility in Japan and also be useful for the detection of atypical microdeletions (Iijima et al. 2014).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Father without Yq deletion: since most Yq microdeletions occur de novo, the recurrence risk to the male sibling is not significantly increased.
        2. Father with Yq deletion: Father's Yq deletion will be transmitted to the male sibling.
    2. Patient's offspring
        1. The genetic defects responsible for infertility in the parent may be transmitted to the offspring through ICSI: Yq deletions will be transmitted to male offspring (Page et al. 1999; Cram et al. 2000; Simpson and Lamb 2001; Ferlin et al. 2007).
        2. Children born through ICSI have increased risk of sex chromosome aneuploidy (45,X and 47,XXY embryos) (Palermo et al. 1999; Ferlin et al. 2007).
        3. Children born through ICSI to infertile couples may have a higher risk of being infertile or subfertile (Cram et al. 2006): may need counseling upon reaching adulthood and surveillance of their reproductive function.
2. Prenatal diagnosis
    1. Prenatal testing, including chorionic villous sampling, may be appropriate in some couples undergoing ICSI.
    2. A fetus with a prenatally diagnosed mosaic 45,X/46,X,del (Y)(q11.2) karyotype from amniotic fluid, in which the deletion was defined by polymorphic microsatellite markers analysis and multiplex STS-PCR.
3. Management (Krausz and Degl'Innocenti 2006; Bhasin 2007)
    1. Gonadotropin therapy: highly effective in gonadotropin-deficient men
    2. Intracytoplasmic sperm injection (ICSI): emerges as the treatment of choice for idiopathic male factor infertility
        1. Expensive
        2. Associated with the following higher risks compared to naturally conceived pregnancies:
            1. Multiple gestation
            2. Low birth weight
            3. Preterm delivery
            4. Perinatal complications
            5. Chromosome aneuploidy
    3. Men with Yq microdeletions considering ICSI should be offered:
        1. Karyotyping
        2. Yq microdeletion testing
        3. Genetic counseling
            1. Obligatory transmission of Yq deletion to male offspring
            2. The phenotype of son: varies substantially and the extent of spermatogenic failure cannot be predicted entirely due to different genetic background and the presence or absence of

environmental factors with potential toxicity to reproductive function
3. A significant proportion of spermatozoa from men with Y microdeletion are nullisomic for sex chromosomes (Siffroi et al. 2000; Jaruzelska et al. 2001), indicating a potential risk for the offspring to develop 45, X Turner syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia.
4. Screening for Y chromosome microdeletions in patients bearing a mosaic 45,X/46,XY karyotype with sexual ambiguity and/or Turner stigmata has shown a relatively high incidence of AZFc deletions (33%) (Patsalis et al. 2002).
5. Yq microdeletions could be associated with an overall Y chromosomal instability leading to the formation of 45,X cell lines (Le Bourhis et al. 2000; Jaruzelska et al. 2001; Patsalis et al. 2005).
6. Despite this theoretical risk, the 36 babies (18 male and 18 female) born from fathers affected by Yq microdeletions are phenotypically normal (Krausz et al. 2003). This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortions of embryos bearing a 45,X karyotype.
7. In order to avoid the transfer of embryos with sex chromosome mosaicism, preimplantation diagnosis could be offered to the couple. This analysis, together with the abortion rate, would provide a more realistic estimation about the real risks of 45, X/46,XY mosaicism and Turner syndrome.

4. The screening for Yq deletions: of additional clinical utility in azoospermic men in which the type of deletion may have prognostic value for testicular sperm retrieval
5. Testicular sperm extraction (TESE): not recommended for complete AZFa or AZFb deletions since the probability of the presence of mature sperm is virtually zero
6. Advice cryoconservation of sperm as a preventive therapy since it is a noninvasive procedure.
7. The development of assisted reproductive techniques (intracytoplasmic sperm injection and testicular sperm extraction) helps to bypass the natural barriers of fertilization, but it increases the concern about the transmission of genetic defects such as Y chromosome microdeletions (Suganthi et al. 2014).

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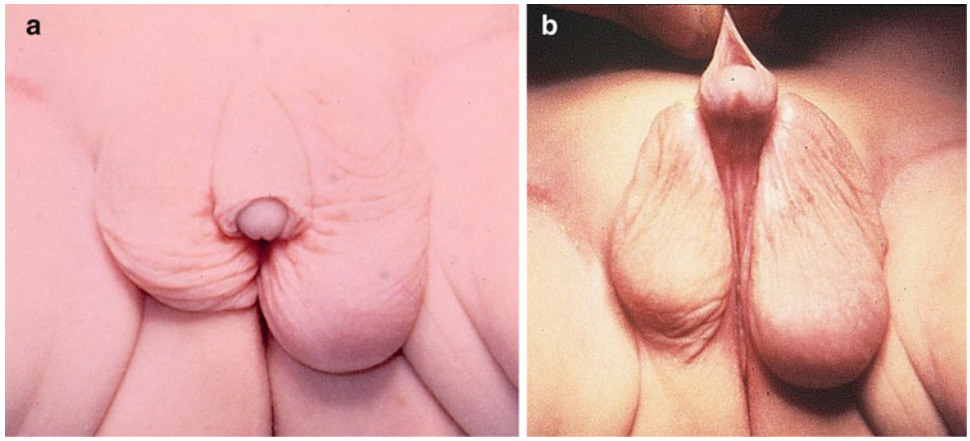

Fig. 1 (**a**, **b**) An infant with del(Yq) showing ambiguous genitalia with a palpable gonad in the left scrotal sac

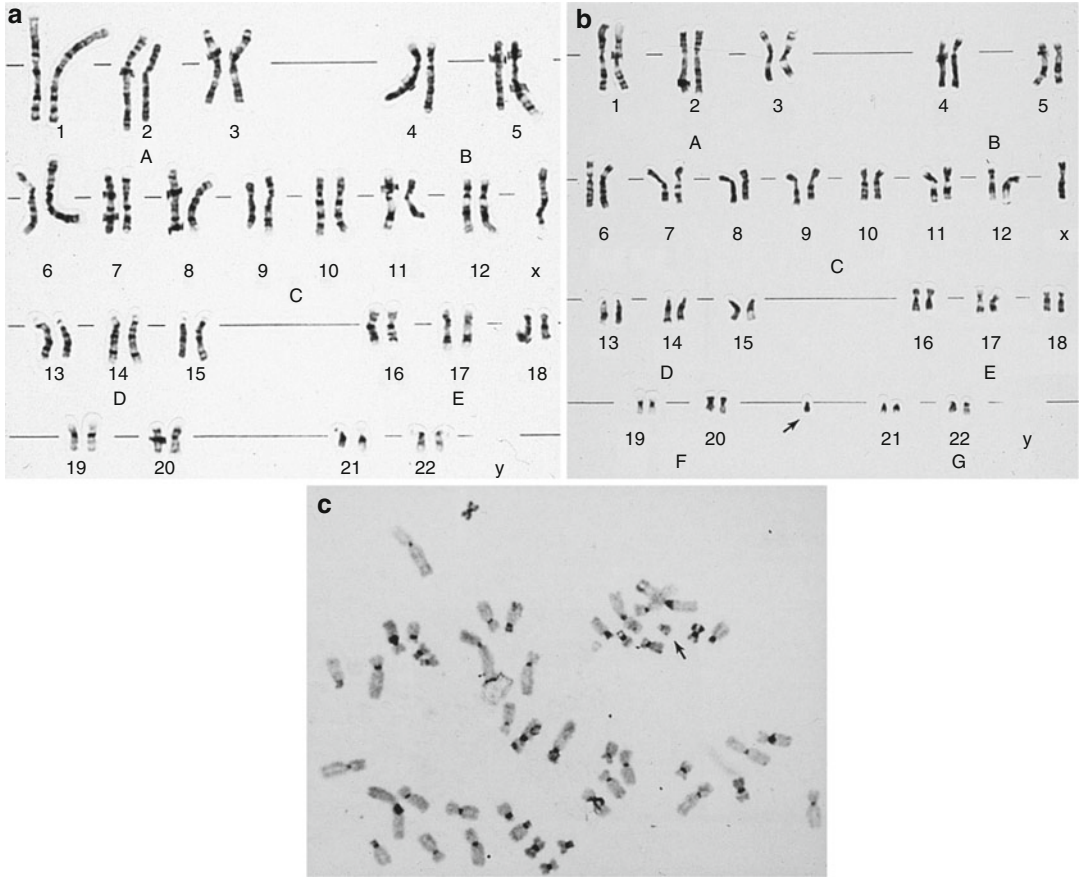

Fig. 2 (**a**–**c**) G-banding karyotypes showed mosaic 45,X/46,X,del(Yq). The del(Yq) (*arrow*) is shown in a C-banded metaphase

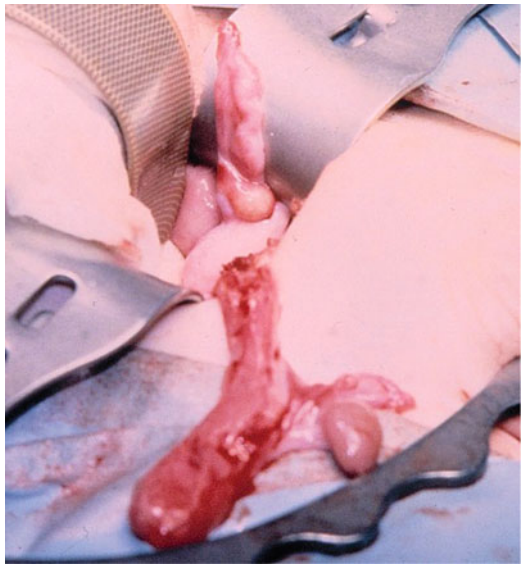

Fig. 3 A gonad is noted at the surgery

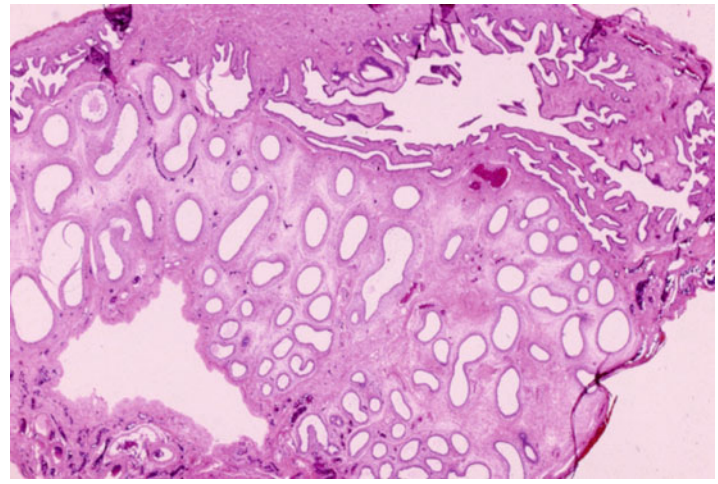

Fig. 4 Fallopian tube-epididymus is shown here on the histologic examination of the specimen

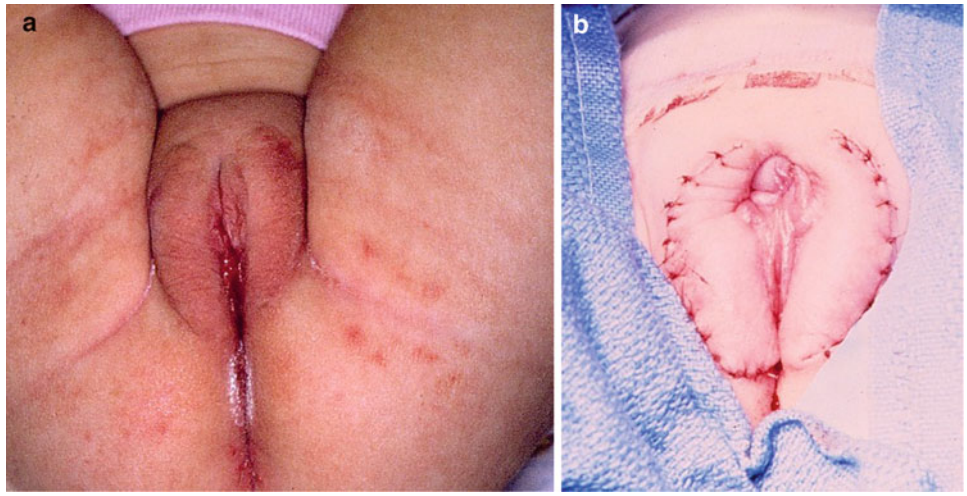

Fig. 5 (**a**, **b**) Successful vaginal reconstruction surgery

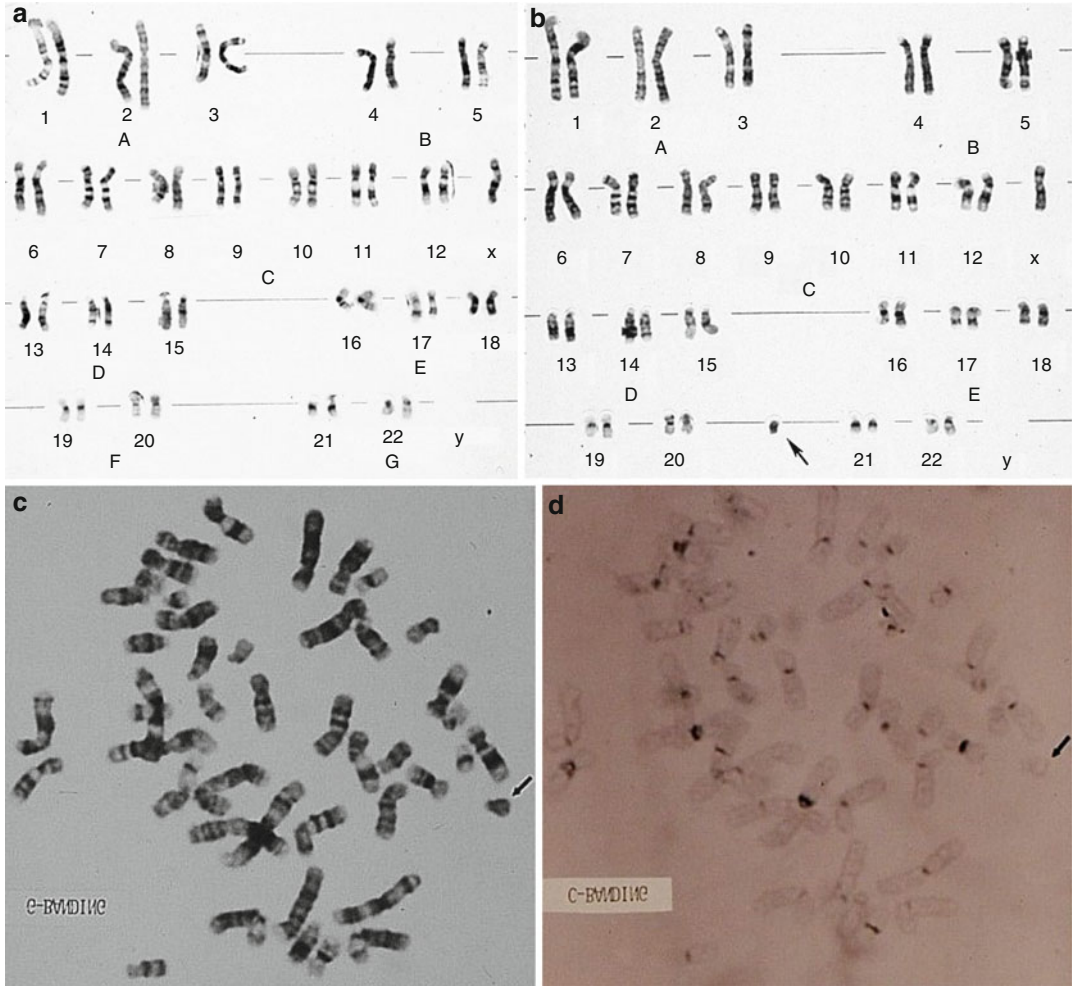

Fig. 6 (**a**–**d**) Another patient with del(Yq) with G- and C-bands showing 45,X/46,X,del(Yq)

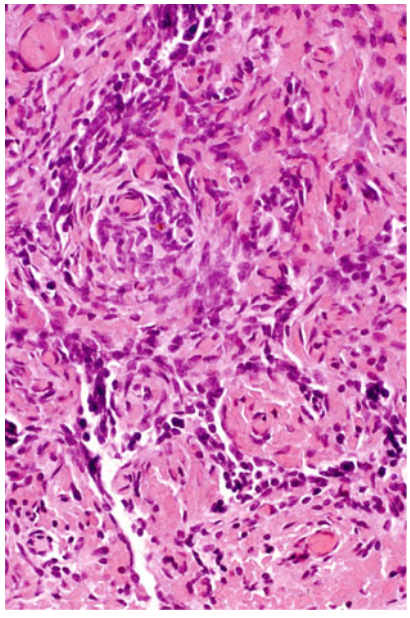

Fig. 7 Dysplastic ovary is shown here

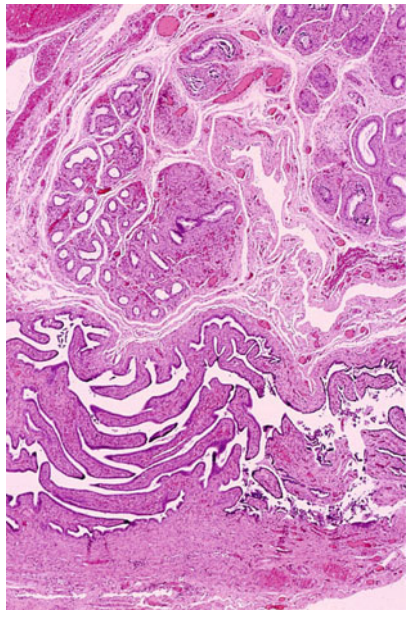

Fig. 8 Epididymus-fallopian tube is shown here

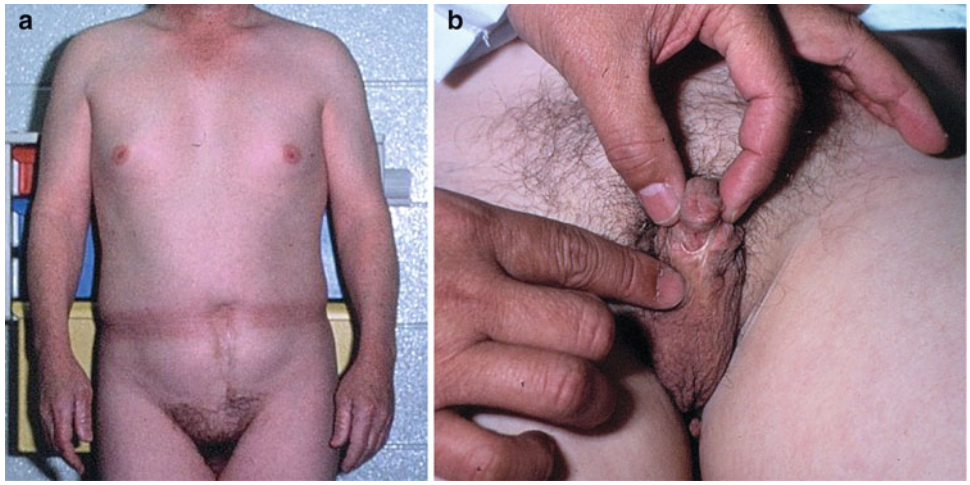

Fig. 9 (**a**, **b**) Another adult male patient with del(Yq) showing short stature, female distribution of the pubic hair, and ambiguous genitalia

Diabetic Embryopathy

Contents

Maternal diabetes adversely affects the fetus during pregnancy. The risk of developing congenital malformations has been well documented (Reece and Homko 2000; Correa et al. 2008). The frequency of congenital anomalies among insulin-dependent diabetic offspring is estimated at 3–6% of all infants at birth, representing a twofold to threefold increase, when compared with nondiabetics (Reece and Hobbins 1986).

Synonyms and Related Disorders

Infant of diabetic mother

Genetics/Basic Defects

1. Diabetes mellitus (Zhao and Reece 2013):
    1. Type 1 (insulin deficiency) or insulin-dependent diabetes: caused by autoimmune destruction of insulin-producing β cells in the pancreas
    2. Type 2 (insulin resistance) diabetes: caused by failure in insulin signaling to regulate cellular glucose uptake
    3. Pre-gestational diabetes: refers to diabetes mellitus, either type 1 or type 2, diagnosed in women before pregnancy
    4. Gestations diabetes: pregnant women with hyperglycemia detected after the onset of pregnancy, usually in the third trimester (24–28 weeks) (women who have a fasting plasma glucose $\geq$126 mg/dL and HbA_{1c} $\geq$ 6.5% are diagnosed as having gestational diabetes mellitus)
2. Gestations diabetes mellitus (GDM) (Gabbay-Benziv and Baschat 2015):
    1. Gestational diabetes can be regarded as one of the great obstetric syndromes where early placental development coupled with maternal predisposition initiates a chain of events that affects placental, maternal, and fetal development with lasting impacts on mother and child.
    2. The placentas of diabetic pregnancies are characterized by increased placental to fetal ratio and by histological findings such as villous fibrinoid necrosis, villous immaturity, chorangiosis, and ischemic changes.
    3. Placental changes depend on GDM onset at gestation. Structural placental changes are seen in early GDM while more functional changes are seen in late-onset GDM.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. GDM-associated fetal and neonatal adverse outcome may be associated with placental structural and functional changes.

3. Teratogenicity of maternal diabetes mellitus in human:
   1. Occurring during embryogenesis at the end of blastogenesis and organogenesis between the third and seventh weeks of gestation
   2. Leading to a spectrum of malformations known as diabetic embryopathy (Becerra et al. 1990)
4. Diabetic fetopathy:
   1. Occurs during fetal development (after the tenth week of gestation)
   2. Not associated with malformations
   3. Fetal hyperinsulinism: the cause of macrosomia and numerous other postnatal complications
5. Genotoxicity and diabetic embryopathy: impaired expression of developmental control genes as a cause of defective morphogenesis (Chang and Loeken 1999)
6. Potential pathogenetic mechanisms of diabetic embryopathy: most likely multifactorial (Reece et al. 1996b; Dhanasekaran et al. 1999; Chugh et al. 2003):
   1. Oxidant stress
   2. Perturbed biosynthesis of prostaglandins and DNA
   3. Altered expression of some of the morphogenetic regulatory molecules:
      1. Extracellular matrix (ECM) proteins
      2. Transcription factors
      3. Proto-oncogene

Clinical Features

1. General features of infants of diabetic mothers (Cowett and Schwartz 1982; Grix et al. 1982; Khoury et al. 1989; Kousseff 1999; Hay 2012; Moore 2014; Potter and Kicklighter 2016):
   1. Higher rate of congenital malformations
   2. Signs of diabetic fetopathy:
      1. Macrosomia (increase in adipose tissue and organomegaly) (Tyrala 1996):
         1. Classic appearance: a large, ruddy, puffy, fat, and often limp infant, with legs held in a flexed and abducted position
         2. The presence of prominent fat pads over the upper back and around the lower jaw to produce the image of a round cherubic face
         3. A predisposing factor for the occurrence of a variety of birth trauma-related injuries
      2. Birth trauma-related injuries due to difficult vaginal delivery secondary to shoulder dystocia:
         1. Cephalohematoma
         2. Subdural hemorrhage
         3. Clavicular fracture
         4. Cranial nerve palsies
         5. Brachial plexopathy (palsy)
      3. Hypoglycemia (hyperinsulinemia) (Agrawal et al. 2000)
      4. Polycythemia
      5. Hypomagnesemia
      6. Hyperbilirubinemias (jaundice)
      7. Hypocalcemia
      8. Cardiomyopathy (thickened interventricular septum)
      9. Renal vein thrombosis
   3. Other features:
      1. Large for gestational age
      2. Higher fetal death rate
      3. Fetal growth retardation in diabetic women with vasculopathy
      4. Higher risk of respiratory distress (hyaline membrane disease)
      5. Asphyxia
      6. Acidosis
      7. Apneic spells
      8. Sepsis
      9. Intracranial bleeding
      10. Neuromuscular excitability
      11. Single umbilical artery
      12. Small left colon syndrome
      13. Transient hematuria
      14. Abnormal vernix caseosa
      15. Hirsutism
2. Spectrum of diabetic embryopathy: Malformations vary in extent and severity:

1. CNS abnormalities (Reece and Hobbins 1986):
    1. Neural tube defects: a higher incidence of 19.5 per 1,000 in the diabetic gestation, compared with 1–2 per 1,000 in the general population
    2. Anencephaly:
        1. The most common anomaly affecting the CNS
        2. An incidence of 0.57% in the diabetic pregnancy, representing a threefold increase over the general population
    3. Holoprosencephaly
    4. Hydrocephalus
    5. Absent corpus callosum
    6. Arnold-Chiari anomaly
    7. Schizencephaly
    8. Microcephaly
    9. Macrocephaly
    10. Agenesis of olfactory tracts
    11. Intracranial lipoma
    12. Facial nerve palsy
    13. Calcified falx cerebri
    14. Bizarre undergrowth or overgrowth of the brain
    15. Postnatal developmental delay
2. Facial features (85%)
    1. Hemifacial microsomia (oculoauriculovertebral anomalies) (Ewart-Toland et al. 2000)
    2. Macrostomia/lateral facial cleft
    3. Cleft lip/palate
    4. Micrognathia
    5. Branchial cleft cyst (Johnson and Fineman 1982)
    6. Frontonasal dysplasia
    7. Choanal atresia
    8. Short nose
    9. Nasal milia
    10. Fat pad across nose
    11. Facial skin tags
3. Eye anomalies (48%):
    1. Lens opacity
    2. Cataracts
    3. Microophthalmia/optic nerve hypoplasia
    4. Colobomas of iris or chorioretina
    5. Anterior chamber dysgenesis
    6. Epibulbar dermoid/oculolipoma
    7. Laterally displaced inner canthi
    8. Tear duct obstruction
4. Ear anomalies (95%):
    1. Microtia
    2. Sensorineural/conductive hearing loss
    3. Preauricular tags
    4. Anotia
    5. Atretic ear canal
    6. Additional ear malformations
5. Cardiovascular anomalies:
    1. Complex transposition of the great vessels
    2. Single ventricle
    3. Hypoplastic left heart
    4. Tricuspid atresia
    5. Tetralogy of Fallot
    6. Ventricular septal defect
    7. Atrial septal defect
    8. Double outflow right ventricle
    9. Pulmonary atresia
    10. Coarctation of the aorta
    11. Subaortic stenosis
    12. Right aortic arch
    13. Tricuspid regurgitation
    14. Cleft mitral valve
    15. Symmetric hypertrophy of interventricular septum
    16. Hypertrophic cardiomyopathy
6. Gastrointestinal anomalies:
    1. Situs inversus
    2. Pyloric stenosis
    3. Duodenal atresia
    4. Small bowel atresias
    5. Small left colon (microcolon) syndrome
    6. Rectal atresia
    7. Anal atresia (imperforate anus)
    8. Meckel diverticulum
    9. Diaphragmatic hernia
    10. Omphalo-enteric cyst/fistula
7. Genitourinary anomalies (19%):
    1. Renal agenesis
    2. Cystic kidneys
    3. Ectopic kidney
    4. Hydronephrosis
    5. Ureteral duplication

6. Ureterocele
7. Ambiguous genitalia
8. Hypospadias
9. Micropenis
10. Cryptorchidism
11. Uterine agenesis
12. Hypoplastic vagina

8. Skeletal anomalies (52%):
    1. Hand anomalies (limb reduction defects):
        1. Radial clubbing
        2. Bifid thumbs
        3. Hypoplastic/absent thumb
        4. Radial hypoplasia
    2. Polysyndactyly.
    3. Contractures.
    4. Costovertebral anomalies:
        1. Fused cervical vertebrae
        2. Hemivertebrae
        3. Torticolis
        4. Bifid/fused ribs
    5. Hip dislocation.
    6. Femoral hypoplasia (Johnson et al. 1983).
    7. Caudal regression (sirenomelia) (Assemany et al. 1972): it is very rare, but it is one of the most unique and commonly associated lesion with maternal diabetes (occurring in 0.2–0.5% of infants of diabetic pregnancies, a 200-fold increase over the general population) (Reece and Hobbins 1986):
        1. Agenesis of sacrum and lumbar spine
        2. Hypoplasia of the lower extremities
        3. Phocomelia
    8. Craniosynostosis.
    9. Skin anomalies:
        1. Aplasia cutis
        2. Cutaneous vascular dysplasia
3. Maternal diabetes: an independent risk factor for major cardiovascular malformations with increased mortality of affected infants (Loffredo et al. 2001)
4. Exposure to hypoglycemia in utero may have long-term effects on offspring including neuropsychological defects (Ter Braak et al. 2002)

Diagnostic Investigations

1. Complete blood cell count to detect polycythemia
2. Serum or whole blood glucose concentration to detect neonatal hypoglycemia
3. Serum magnesium concentration (ionized or total levels) to detect hypomagnesemia
4. Serum calcium concentration to detect hypocalcemia
5. Serum bilirubin level (total and unconjugated) to detect hyperbilirubinemia
6. Arterial blood gas to assess oxygenation and ventilation with evidence of respiratory distress
7. Radiography for cardiopulmonary distress and skeletal and vertebral anomalies
8. Echocardiography for detecting cardiomyopathy and congenital heart defects
9. Renal ultrasonography for renal anomalies

Genetic Counseling

1. Risk of congenital malformation in infants of mothers with insulin-dependent diabetes (Hajianpour 1993):
    1. Relative risk (per 100 live births):
        1. Major malformations: 7.9
        2. Major CNS malformations: 15.5
        3. Cardiovascular malformations: 18.0
    2. Absolute risks (per 100 live births):
        1. Major malformations: 18.4
        2. Major CNS malformations: 5.3
        3. Major cardiovascular malformations: 8.5
2. Risk of congenital malformation in infants of mothers with gestational diabetes mellitus who required insulin during the third trimester of pregnancy (Hajianpour 1993):
    1. Relative risk: 20.6 times more likely to have major cardiovascular system defects than infants of nondiabetic mothers
    2. Absolute risk: 9.7%
3. Prenatal diagnosis:
    1. Determination of glycosylated hemoglobin (HbA_{1c}) of the diabetic mother during the first trimester (Miller et al. 1981). There is a

significantly higher incidence of major congenital anomalies in the offspring of diabetic women with elevated first trimester HbA_{1c} values (>8%) (Reece and Hobbins 1986).
2. Maternal serum alpha-fetoprotein determination for the presence of associated neural tube defect.
3. Prenatal ultrasonography (Diabetic forum) (Reece et al. 1996a):
    1. Estimation of gestational age
    2. Evaluation of congenital malformations:
        1. Cardiac anomalies
        2. Skeletal anomalies
        3. CNS anomalies
        4. Renal anomalies
        5. Other anomalies
    3. Evaluation of fetal growth:
        1. Macrosomia
        2. Intrauterine growth retardation
    4. Assessment of fetal status
    5. Maternal hydramnios
4. Fetal echocardiography for congenital heart defects

4. Management (Fischer 1961):
    1. Pre-pregnancy and antenatal care in women with preexisting diabetes (Visser and de Valk 2015):
        1. Pre-pregnancy:
            1. Folic acid, 3–5 mg per day
            2. Optimization of glucose control
            3. Retinal examination
            4. Examination of urine for (micro) albuminuria
            5. Blood pressure control and medication in case of hypertension
            6. Counseling regarding increased incidence of fetal morphological malformations and regarding increased risk of (severe) hypoglycemic events during the first trimester
        2. Pregnancy:
            1. Adequate glucose control throughout pregnancy
            2. Counseling as to optimal weight gain during pregnancy, based on the maternal body mass index (BMI)
            3. Ultrasound examination for fetal malformations at 12–14 weeks and around 20 weeks of gestation
            4. Fetal growth assessment (abdominal and head circumference) every 4 weeks from 20 weeks onward and every 2 weeks after 28 weeks. Assessment of the amount of amniotic fluid volume
            5. Assessment of the incidence of fetal movements (as observed by the mother)
            6. Determining the timing and mode of delivery based on gestational age, glucose control, and estimated fetal weight
    2. To reduce the rate of congenital malformations in offspring of mothers with diabetes mellitus (Reece and Hobbins 1986):
        1. Preconceptional care and counseling
        2. Pregnant glycemic control to provide endocrine milieu necessary for normal embryogenesis
    3. Plan of delivery:
        1. Deliver newborn infant of the diabetic mother between 35th and 37th weeks of gestation
        2. Anticipate Cesarean section with identification of the macrosomic fetus
    4. Management of respiratory distress
    5. Management of hypoglycemia, hypocalcemia, and hypomagnesemia
    6. Management of cardiomyopathy and heart failure
    7. Management of congenital anomalies

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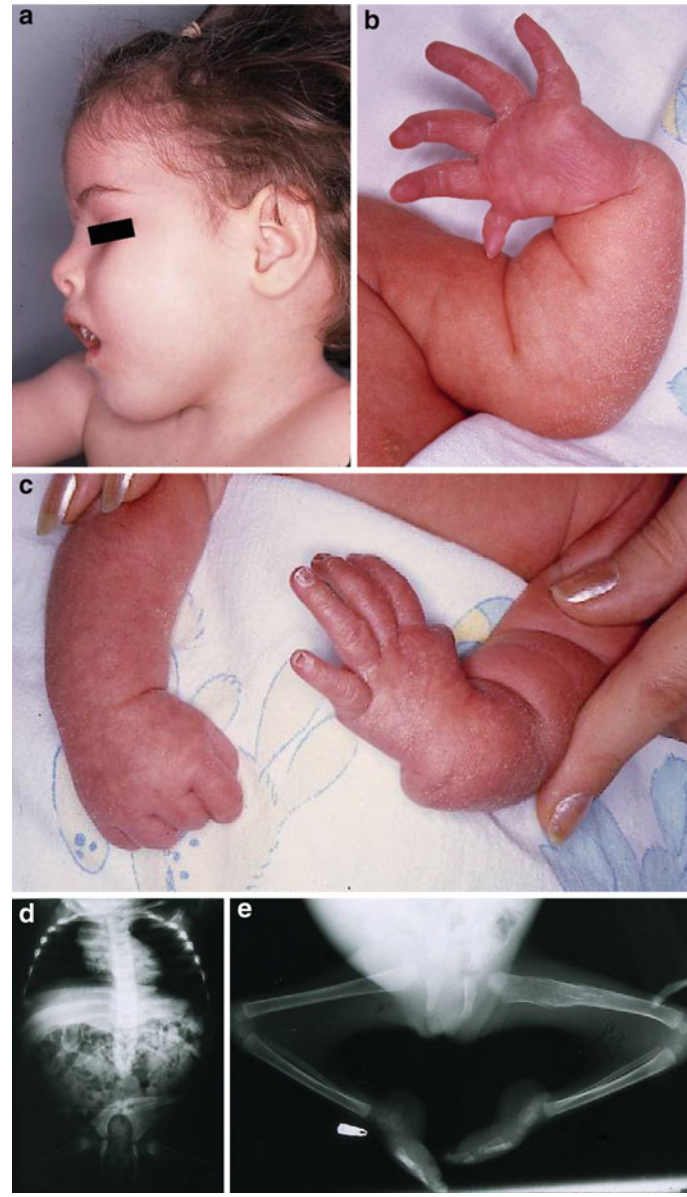

Fig. 1 (**a**–**e**) A girl, 2 years and 9 months old, with diabetic embryopathy showing left club hand with hypoplastic thumb and sacral agenesis with contractures of knees illustrated by radiographs

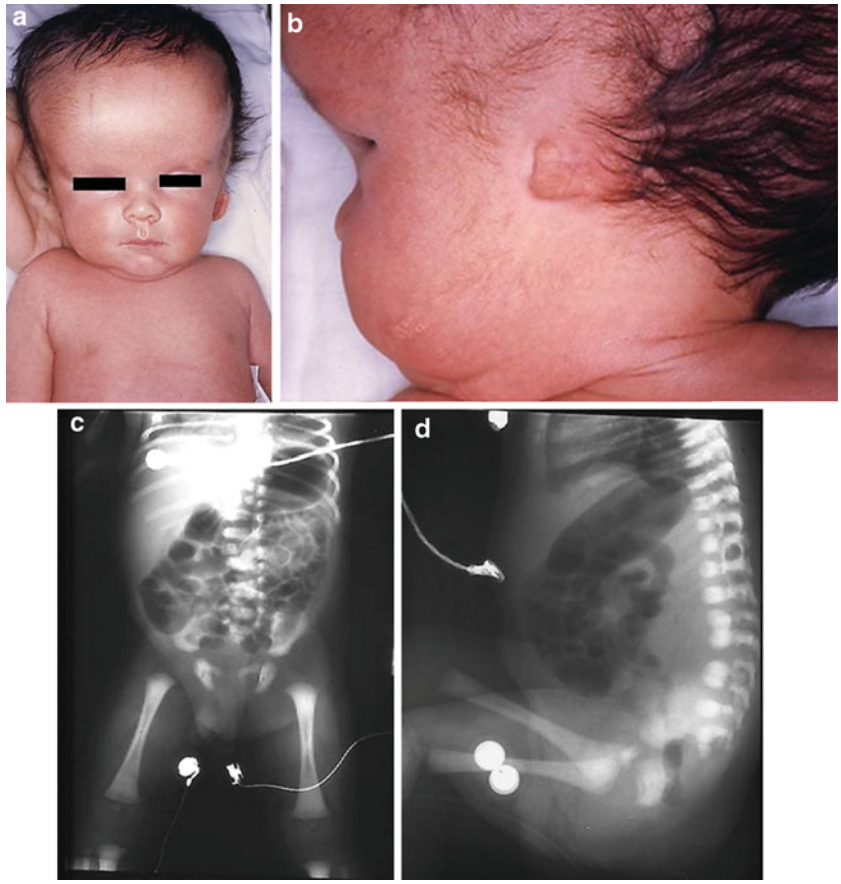

Fig. 2 (**a**–**d**) A newborn with diabetic embryopathy showing a large head due to hydrocephalus, depressed nasal bridge, short nose, micrognathia, microtia, right club hand, hemivertebrae, and caudal dysgenesis

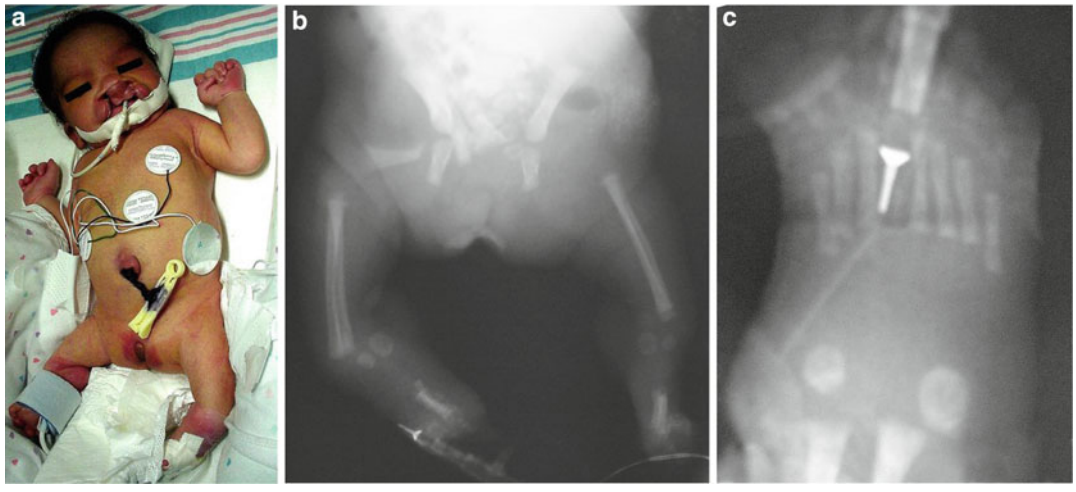

Fig. 3 (**a**–**c**) A newborn with diabetic embryopathy showing cleft lip/palate, caudal regression, femoral hypoplasia, and polydactyly

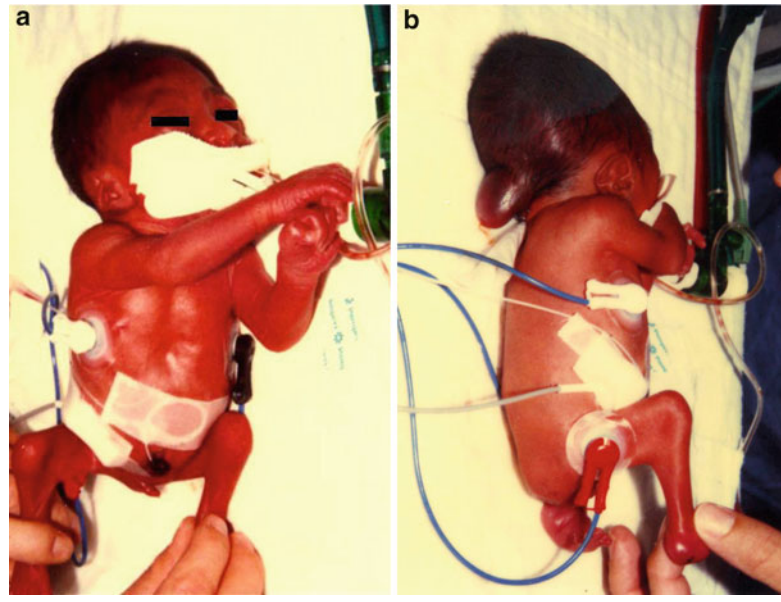

Fig. 4 (**a**, **b**) An infant born to the diabetic mother showing cystic hygroma with multiple contractures and multiple pterygia

Down Syndrome

Contents

In 1866, Down (1866) described clinical characteristics of the syndrome that now bears his name. In 1959, Lejeune et al. (1959) and Jacobs et al. (1959) independently determined that Down syndrome is caused by trisomy 21.

Down syndrome is by far the most common, the best known chromosome disorder in humans and the most common cause of intellectual disability (Peterson and Mikkelsen 2000). Mental retardation, dysmorphic facial features, and other distinctive phenotypic traits characterize the syndrome. Frequency is estimated to be 1 in 800 live births. Approximately 6,000 children are born with Down syndrome annually in the USA (Canfield et al. 2006). Major reviews of pathogenesis, epidemiology, clinical aspects, cytogenetics/nondisjunction, hematology/immunology, neurology, and social aspects are available (American Journal of Medical Genetics 1990).

Synonyms and Related Disorders

Trisomy 21 Syndrome

Genetics/Basic Defects

1. Caused by an extra chromosome 21
    1. Affect almost every organ system
    2. Result in a wide spectrum of phenotypic consequences
        1. Life-threatening complications
        2. Significant alteration of life course (e.g., mental retardation)
        3. Dysmorphic physical features
        4. Decreased prenatal viability
        5. Increased prenatal and postnatal morbidity
2. Typical physical phenotype due to an extra copy of the proximal part of 21q22.3
    1. Mental retardation
    2. Characteristic facial features
    3. Hand anomalies
    4. Congenital heart defects
3. 21q22.1-q22.3 region containing the gene (s) responsible for the congenital heart disease observed in Down syndrome (Korenberg et al. 1992)
4. Down syndrome critical region (DSCR): the region from 21q22.1 to 21q22.3 (McCormick et al. 1989; Rahmani et al. 1989; Opitz and Gilbert-Barness 1990)

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5. DCR-1: a region with the largest number of associated features, including facial and hand phenotypes and mental retardation
6. Types of trisomy 21
    1. Full trisomy 21 (94%)
    2. Mosaicism (2.4%)
    3. Translocations (3.3%)
        1. De novo (75%)
        2. Familial translocation (25%)
    4. Isochromosome 21
7. Origin of nondisjunction: maternal nondisjunction in the first meiotic division (75%, most common)
8. Well-documented risk factor for maternal meiotic nondisjunction: advanced maternal age (Roitzen and Patterson 2003)
9. Down syndrome due to translocation occurs independent of maternal age and may be inherited from either parent (Tolmie 2002)
10. Majority of mosaic cases result from a trisomic zygote with mitotic loss of one chromosome 21

Clinical Features

1. Growth and development
    1. Short stature
    2. Hypotonia which improves with age
    3. Moderate-to-severe mental retardation with IQ range of 20–85 (mean IQ is approximately 50)
    4. Articulatory problems
    5. Sleep apnea occurring when inspiratory airflow from the upper airway to the lungs is impeded for 10 s or more, often resulting in hypoxemia or hypercarbia
    6. Seizure disorder (5–10%)
        1. Infantile spasms (most common type of seizures seen in infancy)
        2. Tonic-clonic seizures (most commonly seen in older patients)
    7. Visual and hearing impairments in addition to the presence of mental retardation further limiting the child's overall function and may prevent the child from participating in significant learning processes and obtaining appropriate language development and interpersonal skills
    8. Obesity during adolescence
    9. Premature aging
        1. Decrease in skin tone
        2. Early graying or loss of hair
        3. Hypogonadism
        4. Cataracts
        5. Hearing loss (Roitzen et al. 1993)
        6. Age-related increase in hypothyroidism
        7. Seizures
        8. Neoplasms
        9. Degenerative vascular disease
        10. Loss of adaptive abilities
        11. Increased risk of senile dementia of Alzheimer type (Zigman et al. 1996)
2. Behavior
    1. Natural spontaneity
    2. Genuine warmth
    3. Cheerfulness
    4. Gentleness
    5. Patience
    6. Tolerance
    7. Anxiety
    8. Stubbornness
3. Psychiatric disorders
    1. Prevalence among children (17.6%)
    2. Prevalence among adults (27.1%)
    3. Children and adolescents at a higher risk for
        1. Autism
        2. Attention deficit hyperactivity disorder
        3. Conduct disorder
        4. Obsessive-compulsive disorder
        5. Tourette syndrome
        6. Depressive disorder during the transition from adolescence to adulthood
4. Skull
    1. Brachycephaly
    2. Microcephaly
    3. Sloping forehead
    4. Vertical creases on the forehead when crying ("Woolley" sign, named after the late mentor, Dr. Woolley)
    5. Flat occiput
    6. Large fontanels with late closure

7. Patent metopic suture
8. Absence of frontal and sphenoid sinuses
9. Hypoplasia of the maxillary sinuses

5. Eyes
   1. Upslanting palpebral fissures
   2. Bilateral epicanthal folds
   3. Brushfield spots (speckled iris)
   4. Refractive errors (50%)
   5. Strabismus (44%)
   6. Nystagmus (20%)
   7. Blepharitis (33%)
   8. Conjunctivitis
   9. Tearing from stenotic nasolacrimal ducts
   10. Congenital cataracts (3%)
   11. Pseudopapilledema
   12. Spasm nutans
   13. Acquired lens opacity (30–60%)
   14. Keratoconus
6. Nose
   1. Hypoplastic nasal bone
   2. Flat nasal bridge
7. Mouth
   1. Open mouth
   2. Tendency of tongue protrusion
   3. Fissured and furrowed tongue
   4. Mouth breathing
   5. Drooling
   6. Chapped lower lip
   7. Angular cheilitis
8. Teeth
   1. Partial anodontia (50%)
   2. Tooth agenesis
   3. Malformed teeth
   4. Delayed eruption
   5. Microdontia (35–50%) in both the primary and secondary dentitions
   6. Hypoplastic and hypocalcified teeth
   7. Malocclusion
   8. Taurodontism (0.54–5.6%)
   9. Increased periodontal destruction
9. Ears
   1. Small.
   2. Overfolded helix.
   3. Chronic otitis media.
   4. Hearing loss common. Between 66% and 89% of children have hearing loss of greater than 15–20 dB in at least one ear by auditory brainstem response.
10. Neck
    1. Atlantoaxial instability (14%) resulting from laxity of transverse ligaments that ordinarily hold the odontoid process close to the anterior arch of the atlas
    2. Laxity causing backward displacement of the odontoid process, leading to spinal cord compression
11. Chest
    1. Narrow chest
    2. Decreased internipple distance (Chen et al. 1974)
12. Congenital heart defects
    1. Common (40–50%).
    2. Frequently seen in hospitalized Down syndrome patients (62%).
    3. Common cause of death in the first 2 years of life.
    4. Endocardial cushion defect/atrioventricular canal (43%, most common type): About 70% of all endocardial cushion defects are associated with Down syndrome.
    5. Ventricular septal defect (32%).
    6. Secundum atrial septal defect (10%).
    7. Tetralogy of Fallot (6%).
    8. Isolated patent ductus arteriosus (4%).
    9. Multiple cardiac defects (30%). The most common associated lesions are patent ductus arteriosus (16%) and pulmonic stenosis (9%).
13. Abdomen
    1. Diastasis recti
    2. Umbilical hernia
14. Gastrointestinal (12%)
    1. Duodenal atresia or stenosis
    2. Hirschsprung disease (less than 1%)
    3. TE fistula
    4. Meckel diverticulum
    5. Imperforate anus
    6. Omphalocele
15. Genitourinary
    1. Renal malformations
    2. Hypospadias
    3. Micropenis
    4. Cryptorchidism

16. Musculoskeletal anomalies (Arumugam et al. 2015).
    1. Atlantoaxial (and atlantooccipital) instability (American Academy of Pediatrics Committee on Sports Medicine and Fitness 1995)
        1. Occurring in approximately 15% of individuals (<21 years old).
        2. Mildest asymptomatic form.
        3. Severe symptomatic subluxation or dislocation at the atlantoaxial joint may injure the spinal cord (cervical myelopathy) (1–2%). Neurologic manifestations include:
            1. Easy fatigability
            2. Difficulties in walking
            3. Abnormal gait
            4. Neck pain
            5. Limited neck mobility
            6. Torticollis (head tilt)
            7. Incoordination and clumsiness
            8. Sensory deficits
            9. Spasticity
            10. Hyperreflexia
            11. Clonus
            12. Extensor-plantar reflex
            13. Other upper motor neuron and posterior column signs and symptoms
            14. Rarely progressing to paraplegia, hemiplegia, quadriplegia, or death
    2. Short and broad hands
    3. Brachydactyly
    4. Clinodactyly of the fifth fingers with a single flexion crease (20%)
    5. Hyperextensible finger joints
    6. Increased space between the great toe and the second toe
    7. Acetabular dysplasia leading to pain, difficulty in gait, and subluxation of the hip joint
    8. Acetabular retroversion: the most common cause of posterior subluxation/dislocation of the hip in patients with DS
    9. Dislocation/subluxation of the patella, deformities such as genu valgum, pes planus, metatarsus primus varus, all of which have been attributed to ligament laxity (Galli et al. 2014)
17. Endocrine
    1. Thyroid disease
        1. Primarily autoimmune disorder with a lifetime prevalence of 13–63%
        2. Congenital hypothyroidism: about 28 times more common among infants with Down syndrome than in the general population with an incidence of 1% detected by newborn screening
            1. 0.7% permanent congenital hypothyroidism
            2. 0.3% transient congenital hypothyroidism
        3. Hypothyroidism in 16–20% of young patients
    2. Diabetes
    3. Decreased fertility
        1. Almost invariably infertile in males
        2. Decreased fertility in females
18. Hematologic
    1. Neonatal leukemoid reactions (i.e., pseudoleukemia) are common. To distinguish this from true leukemia is frequently a diagnostic challenge.
    2. 10- to 15-fold increased risk of developing leukemia in children with Down syndrome. Approximately 1 in 150 patients develops leukemia.
    3. Uniquely predisposed to clonal disorders affecting the megakaryocyte lineage in children with Down syndrome.
        1. Transient myeloproliferative disorder (also known as transient leukemia)
            1. Resolves spontaneously in most cases
            2. Develops acute megakaryoblastic leukemia in up to 30% of cases
        2. Acute megakaryoblastic leukemia
    4. An increased risk of hepatitis B carrier status if previously institutionalized
19. Immunodeficiency: Patients have about 12-fold increased risk of developing infectious diseases, especially pneumonia, secondary to impaired cellular immunity.

20. Upper airway obstruction
    1. Causes
        1. Large tonsils and adenoids
        2. Lingual tonsils
        3. Choanal stenosis
        4. Glossoptosis
    2. Consequences
        1. Serous otitis media
        2. Alveolar hypoventilation
        3. Arterial hypoxemia
        4. Cerebral hypoxia
        5. Pulmonary artery hypertension
        6. Cor pulmonale
        7. Heart failure
21. Skin
    1. Cutis marmorata
    2. Thickened nuchal folds
    3. Xerosis
    4. Localized hyperkeratotic lesions
    5. Elastosis serpiginosa
    6. Alopecia areata (up to 10%)
    7. Vitiligo
    8. Folliculitis
    9. Abscess formation
    10. Recurrent skin infections
22. Dermatoglyphics
    1. Distal axial triradius in the palms
    2. Transverse palmar creases
    3. A single flexion crease in the fifth finger
    4. Ulnar loops (often 10) in the digital patterns
    5. A pattern present in hypothenar and interdigital III regions
23. Significant health problems observed in adults with Down syndrome (Van Allen et al. 1999).
    1. Untreated congenital heart anomalies (15.8%)
    2. Acquired cardiac disease (15.8%)
    3. Pulmonary hypertension (7.8%)
    4. Recurrent respiratory infections/aspiration leading to chronic pulmonary interstitial changes (30%)
    5. Presenile dementia/Alzheimer-type disease (42%)
    6. Adult-onset epilepsy (36.8%)
    7. Osteoarthritic degeneration of the spine (31.6%)
    8. Osteoporosis with resultant fractures of the long bones or vertebral bodies (55%)
    9. Untreated atlantooccipital instability (7.9%)
    10. Acquired sensory deficits
        1. Loss of vision due to early onset of adult cataracts (50%)
        2. Recurrent keratitis (21%)
        3. Keratoconus (15.8%)
        4. Significant hearing loss (25%)
    11. Behavioral problems (50%)
    12. Loss of cognitive abilities and onset of symptoms of Alzheimer disease (group 1: 5.5%; group 2: 75%)
24. Prognosis
    1. Life expectancy
        1. Approximately 75% of conceptuses die in embryonic or fetal stage
        2. Approximately 85% of infants survive up to 1 year
        3. About 50% can be expected to live beyond the age 50 years
    2. Mobility and mortality
        1. Children with DS are at increased risk of leukemia and testicular cancer (Roitzen and Patterson 2003)
        2. Presence of congenital heart disease (most significant factor that determines survival)
        3. Esophageal atresia with or without TE fistula, Hirschsprung disease, duodenal atresia, infection, and leukemia adding to mortality
        4. Higher mortality rate later in life secondary to premature aging
        5. Most common causes of mortality in Down syndrome (Arumugam et al. 2015)
            1. Respiratory diseases (pneumonia)
            2. Congenital heart diseases
            3. Circulatory disorders
            4. Dementia

3. Phenotype of mosaic individuals: depends on the frequency and distribution of trisomic cells, with typical Down syndrome as the worst phenotype

Diagnostic Investigations

1. Serum triple screen.
    1. Alpha-fetoprotein
    2. Unconjugated estriol
    3. Human chorionic gonadotrophin
2. Common techniques used for diagnosis of Down's syndrome (Asim et al. 2015).
    1. Cytogenetic analysis
        1. Clinical diagnosis should be confirmed with cytogenetic studies.
        2. Karyotyping is essential for determination of recurrence risk: free trisomy 21 (93–96%), Robertsonian translocation (2–5%), reciprocal translocation (<1%), isochromosome (<1%), mosaicism (2–4%).
        3. In translocation or isochromosome Down syndrome, karyotyping of the parents and other relatives is required for proper genetic counseling.
        4. Giemsa banding (G-banding): performed on fetal cells at metaphase stage on amniocytes (grown in vitro) or CVS.
    2. Interphase fluorescence in situ hybridization (FISH)
        1. Involves hybridization of selected chromosome specific DNA sequences that have been labeled with fluorescent dye to chromosome preparation that can be visualized under microscope
        2. Used for rapid diagnosis
        3. Successfully applied to both prenatal diagnosis and diagnosis in the newborn period
    3. Quantitative fluorescent-polymerase chain reaction (QF-PCR)
        1. Involves amplification and detection of short tandem repeat using fluorescently labeled primers
        2. Highly reliable and reproducible
        3. Easily detects maternal contamination
        4. Can give diagnosis within 24 h
    4. Paralogous sequence quantification (PSQ)
        1. A PCR based method for detection of targeted chromosome number abnormalities, based on the use of paralogous genes
        2. Can handle 30–40 samples in a day and report result in less than 48 h
    5. Multiplex probe ligation assay (MLPA)
        1. Based on hybridization and PCR method
        2. Very short time for diagnosis (2–4 days)
    6. Next generation sequencing (NGS)
        1. Clonally amplified DNA templates are sequenced in a massively parallel shot gun sequencing
        2. Current time for sample processing, sequencing, and data interpretation in experienced hands: 5–8 days
3. Extraction of fetal cells from maternal circulation: After fetal nucleated red blood cells have been sorted using different cell transferrin and glycophorin-A receptors on the cell surface, interphase FISH can determine chromosome constitution. Chromosome-specific probes for X, Y, 13, 18, and 21 permit diagnosis. The FISH finding should be confirmed by standard cytogenetic techniques.
4. Thyroid function tests (Hardy et al. 2004): TSH and T4 should be obtained at birth and annually thereafter.
5. Measurement of IgG.
    1. Used to identify deficiency of IgG subclasses 2 and 4
    2. A significant correlation between decreased IgG subclass 4 and bacterial infections
    3. Cellular immunity deficits documented in individuals with gingivitis and periodontal disease
6. Skeletal radiography.
    1. Craniofacial anomalies include
        1. Brachycephalic microcephaly
        2. Hypoplastic facial bones and sinuses

2. Cervical spine X-rays (lateral flexion and extension views).
3. Required to measure the atlantodens distance for excluding atlantoaxial instability at 3 years of age.
4. Used prior to anesthesia if there are signs suggesting spinal cord compression.
5. Reduced iliac and acetabular angles in the young infant.
6. Short hands with shortened digits and clinodactyly due to hypoplastic middle phalanx of the fifth finger.

7. Echocardiography (Al-Biltagi 2013): This test should be performed on all infants with Down syndrome for identification of congenital heart disease, regardless of findings on physical examination.
8. Auditory brainstem response (ABR), also known as brainstem auditory evoked response (BAER), to demonstrate hearing loss. Evaluation of ABR in 47 unselected children with Down syndrome, aged between 2 months and 3 1/2 years, demonstrated some degree of hearing loss in 66% of the children examined (28% unilateral, 38% bilateral).
9. Speech evaluation.
10. Pediatric vision screening for ophthalmologic disorders.
11. Modified Denver Developmental Screening Test chart for noninstitutionalized children for assessing the developmental milestones (Chen and Woolley 1978).
12. Growth charts available for children with Down syndrome (Cronk et al. 1988).

Genetic Counseling

1. Recurrence risk (Chen 2015)
   1. Patient's sib
      1. Nondisjunction type: about 1% for younger women and approximates the age-related risk for older women (Nussbaum et al. 2004)
      2. De novo Robertsonian translocation type: 2–3%
   2. Familial Robertsonian translocation type
      1. Theoretical recurrence risk for a Robertsonian carrier parent to have a live-born Down syndrome offspring: 1 in 3
      2. The actual risks to future offspring depend on parental sex:
         1. Mother with rob(Dq;21q): 10–11%
         2. Father with rob(Dq;21q): 2.4%
         3. Mother with rob(21q;22q): 14%
         4. Father with rob(21q;22q): 1–2%
   3. A carrier parent with a 21q21q translocation or isochromosome: a 100% recurrence risk
   4. Gonadal mosaicism postulated for having more than one trisomic child in the family with apparently normal parents
   5. Patient's offspring
      1. Affected individuals rarely reproduce
      2. Females with trisomy 21: About 15–30% are fertile and have a 50% risk of having an affected child
      3. Males with trisomy 21: no evidence of fathering a child
2. Prenatal screening
   1. Advanced maternal age.
      1. The first prenatal diagnosis of Down syndrome made in 1968
      2. Gradual introduction of screening women on the basis of advanced maternal age with amniocentesis into medical practice
   2. Maternal serum biochemical markers (Rose 1996).
      1. Low maternal serum alpha-fetoprotein (MSAFP) shown to be associated with Down syndrome in 1983.
      2. Later, elevated human chorionic gonadotropin (hCG) and low unconjugated estriol (uE3) found to be the additional markers for Down syndrome.
      3. By 1988, the three biochemical markers, together with maternal age, were accepted as a method of prenatal screening for Down syndrome in the general population.
      4. Estimated detection rate when ultrasound is used to estimate gestational

age: 20% when using only the MSAFP test, 59% using the double test (MSAFP and hCG), and 69% using the triple test (MSAFP, hCG, uE3). The false positive rate is 5%. Other factors for adjustment are maternal age and weight, insulin-dependent diabetes mellitus, multiple pregnancy, ethnic origin, previous Down syndrome pregnancy, and first or repeat test in a pregnancy. A positive screening test suggests only an increased risk for having a Down syndrome fetus and that definitive testing by amniocentesis with chromosome analysis is indicated.

3. First-trimester free beta-hCG and pregnancy-associated plasma protein A retrospective screening study (Krantz et al. 1996) achieved rates as high as those associated with MSAFP, hCG, or uE3 in the second trimester.
4. First-∪trimester screening for Down syndrome using nuchal translucency, maternal serum pregnancy-associated plasma protein A, free-β human chorionic gonadotrophin, placental growth factor, and α-fetoprotein (Huang et al. 2015).

3. Prenatal diagnosis (rose 1996)
   1. Ultrasonography.
      1. Nuchal fold thickening identifies 75% of Down syndrome fetuses
      2. Shortened humerus or femur length detects 31% of cases
      3. Cystic hygroma
      4. Duodenal atresia or stenosis (double-bubble sign)
      5. Echogenic intracardiac focus
         1. Endocardial cushion defect with atrial and ventricular septal defects
         2. Abnormal mitral and tricuspid valves
      6. Hyperechogenic bowel
      7. Renal pyelectasis
      8. Slightly shortened femora
      9. Wider lateral flare of the iliac bones
      10. Other subtle sonographic signs
      1. Short ears
      2. Hypoplasia of the middle phalanx of the 5th fingers (clinodactyly)
      3. Choroid plexus cyst
      4. Delayed fusion of the amnion and chorion
      5. Simian crease of the hand
      6. Separation of the great toe ("sandal gap foot")
   2. Amniocentesis, CVS, or fetal blood sampling.
      1. FISH analysis of interphase cells or metaphase spreads
      2. Chromosome analysis
   3. Extraction of fetal cells from maternal circulation: Noninvasive prenatal testing using cell-free fetal DNA has very high sensitivity and specificity for Down syndrome, with slightly lower sensitivity for Edwards and Patau syndrome. However, it is not 100% accurate and should not be used as a final diagnosis for positive cases (Taylor-Phillips et al. 2016).
   4. Preimplantation diagnosis.
4. Management (Pueschel 1990; Carey 1992; Roitzen and Patterson 2003; Baum et al. 2008)
   1. Health supervision for children with Down syndrome (American Academy of Pediatrics Committee on Genetics 2001)
   2. Medical care
      1. Early intervention programs (Hines and Bennett 1996)
         1. Physical therapy
         2. Occupational therapy
         3. Speech therapy
         4. Special education programs
      2. Eye evaluation and management (Miyazaki 2014)
         1. Visual acuity
         2. Refractive errors
         3. Strabismus
         4. Amblyopia
      3. Hearing evaluation and management
      4. Thyroid hormone for hypothyroidism
      5. Medical management of congenital heart defects
         1. Digitalis and diuretics usually required

    2. Subacute bacterial endocarditis prophylaxis
6. Prompt treatment of respiratory tract infections and otitis media
7. Pneumococcal and influenza vaccines for children with chronic cardiac and respiratory disease
8. Anticonvulsants for seizures
9. Provide pharmacologic agents, behavioral therapy, and psychotherapy for behavioral/psychiatric disorders
10. Treat skin disorders
    1. Weight reduction
    2. Proper hygiene
    3. Frequent baths
    4. Application of antibiotic ointment
    5. Systemic antibiotics therapy
11. Prevent dental caries and periodontal disease
    1. Appropriate dental hygiene
    2. Fluoride treatments
    3. Good dietary habits
    4. Restorative care
12. Prevention of obesity
13. Monitor celiac disease
14. Vigilance
    1. Arthritis
    2. Atlantoaxial subluxation
    3. Diabetes mellitus
    4. Leukemia
    5. Obstructive sleep apnea
    6. Seizures
15. Megadoses of vitamins and minerals supplemented with zinc and/or selenium: have not shown benefits in a number of well-controlled studies
16. Transition from childhood to adulthood: to live well-adjusted and happy adult lives (Pueschel 1996)

3. Surgical care
    1. Presence of Down syndrome alone does not adversely affect the outcome of surgery in the absence of pulmonary hypertension.
    2. Timely surgery of cardiac anomalies necessary to prevent serious complications.
    3. Prompt surgical repair of the following gastrointestinal anomalies:
        1. TE fistula
        2. Pyloric stenosis
        3. Duodenal atresia
        4. Annular pancreas
        5. Aganglionic megacolon
        6. Imperforate anus
    4. Adenotonsillectomies may be required for obstructive sleep apnea.
    5. Surgical intervention may be necessary to reduce the atlantoaxial subluxation and to stabilize the upper segment of the cervical spine if neurologic deficits are significant.
    6. Extract congenital cataracts, which occur in about 3% of children, soon after birth with subsequent correction with glasses or contact lenses to assure adequate vision.
    7. Anesthetic airway management (Lin 1998).
        1. Adequate evaluation of the airway and neurological status
        2. Cervical spine radiography (flexion and extension views) when any neurologic deficits suggest spinal cord compression
        3. Avoid hyperextension of the head during laryngoscopy and intubation
        4. Prescribe anticholinergics to control airway hypersecretion
        5. Aware of other airway complications (subglottic stenosis and obstructive apnea resulting from a relatively large tongue, enlarged adenoids, and midfacial hypoplasia)
4. Prenatal treatment of Down syndrome (Guedj et al. 2014)
    1. To date, only EGCG has shown promising results in improving learning/memory in young adults affected with Down syndrome. These results are being confirmed in a multicenter larger study.
    2. Adult therapies, even if they prove to be successful, will only partially improve brain development and cognition in Down syndrome due to the fact that

there is a permanent loss of neuronal progenitors during fetal life.

3. This reduction of neurogenesis and synaptogenesis can potentially be rescued by administering safe and effective molecules to pregnant women as soon as a diagnosis of trisomy 21 is made.

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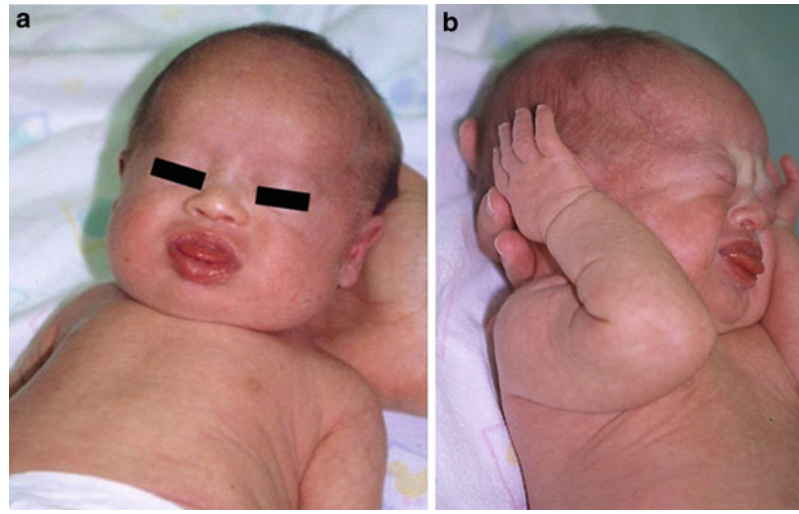


Fig. 1 (**a**, **b**) An infant with Down syndrome showing sloping forehead, upslanting palpebral fissures, "Woolley" sign, flat nasal bridge, small mouth, protruding tongue, narrow chest, and decreased internipple distance

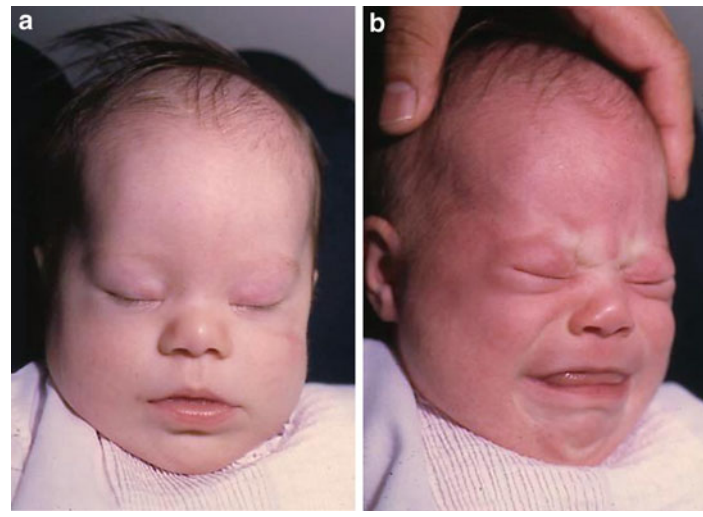


Fig. 2 (**a**, **b**) An infant with Down syndrome showing microcephaly, sloping forehead, upslanting palpebral fissure, and "Woolley" sign

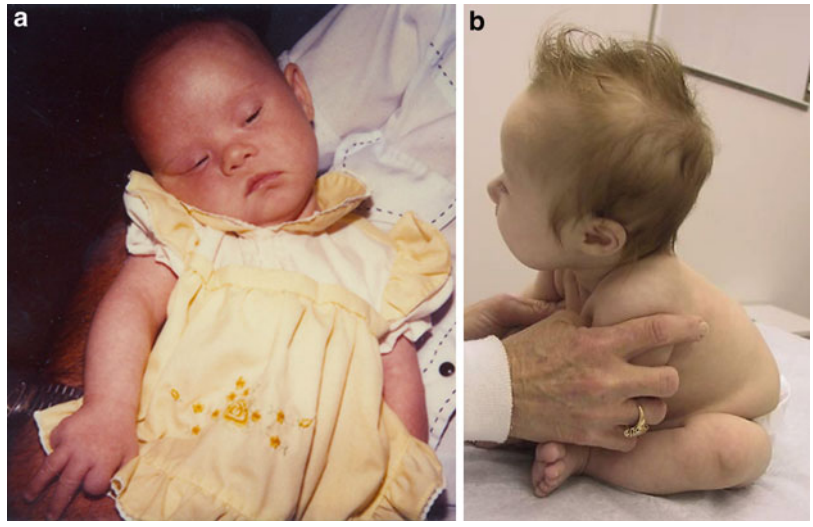


Fig. 3 (**a**, **b**) Two infants with Down syndrome showing severe hypotonia in the neck and back (gibbus)

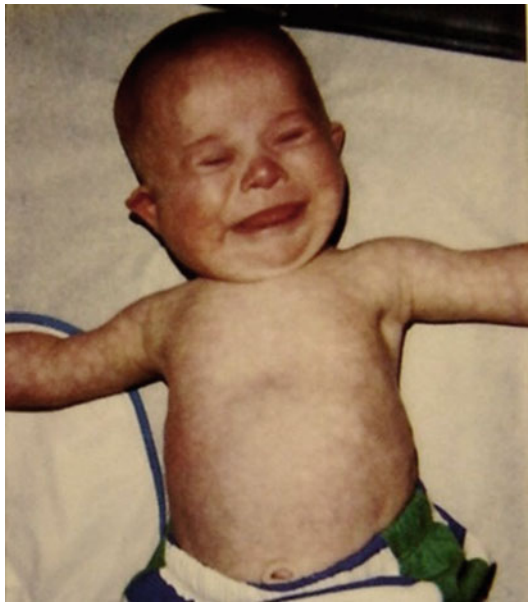


Fig. 4 An infant with trisomy 21 showing typical facial features and cutis marmorata

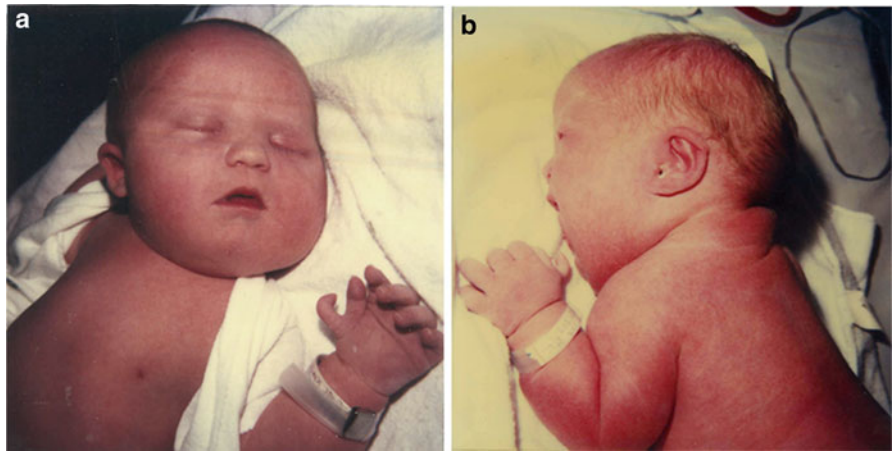
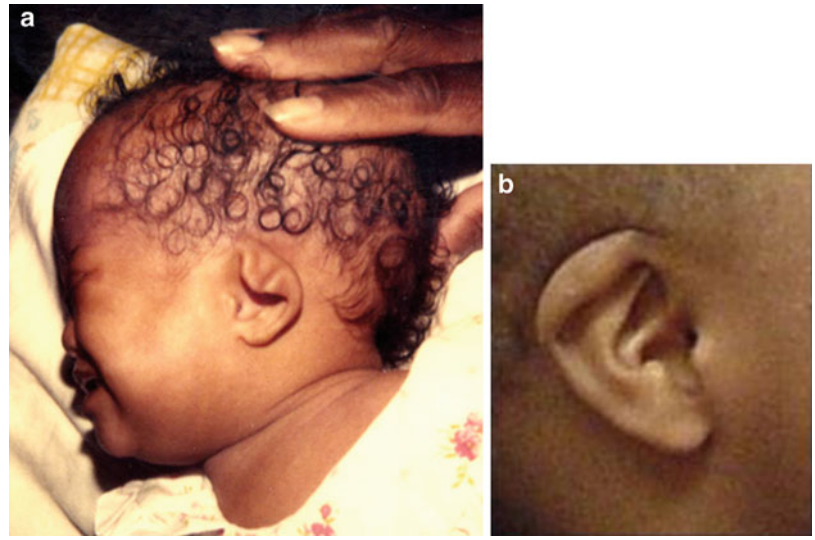


Fig. 5 (**a**, **b**) An infant with Down syndrome showing lymphedema in the cheeks and thickened nuchal fold

Fig. 6 (**a**, **b**) Two children with Down syndrome showing Brushfield spots of the iris

Fig. 7 (**a**, **b**) Two infants with Down syndrome showing typical small ear with overfolded helix



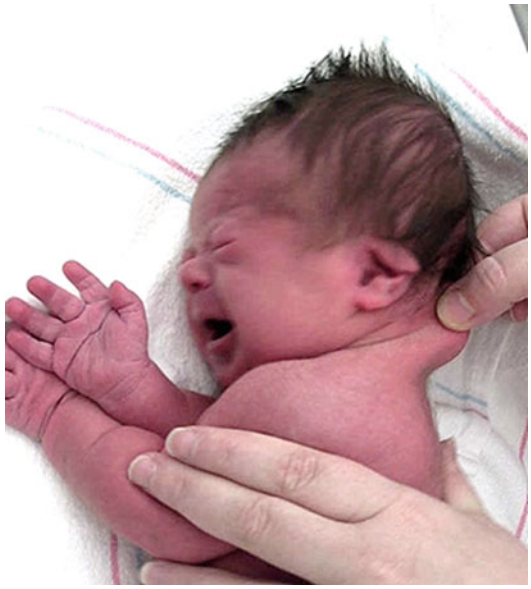


Fig. 8 A neonate with trisomy 21 showing thickened nuchal fold, typical ear, and a transverse palmar crease on the right palm

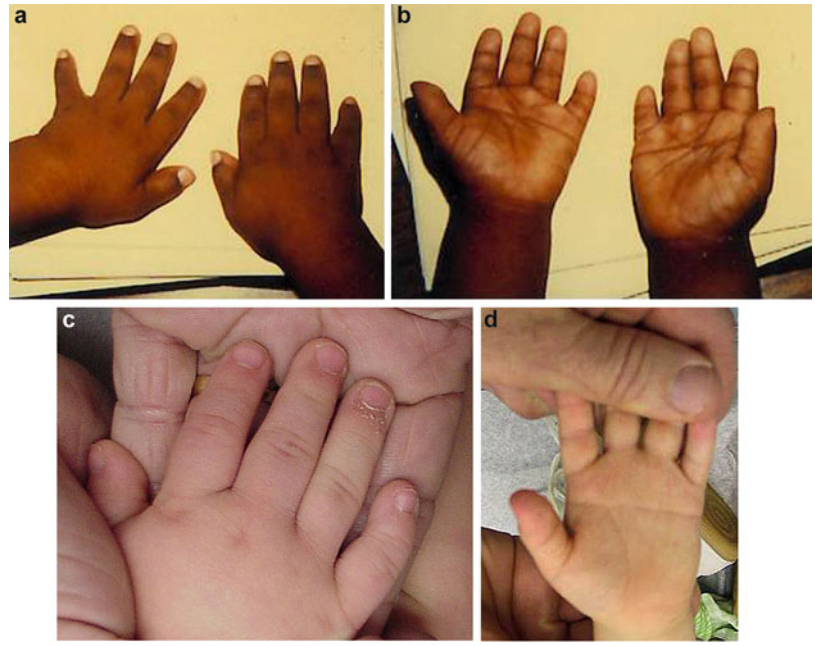


Fig. 9 (**a**–**d**) An infant with Down syndrome showing small hands, small fingers, clinodactyly of the 5th finger with a single crease, and transverse palmar creases

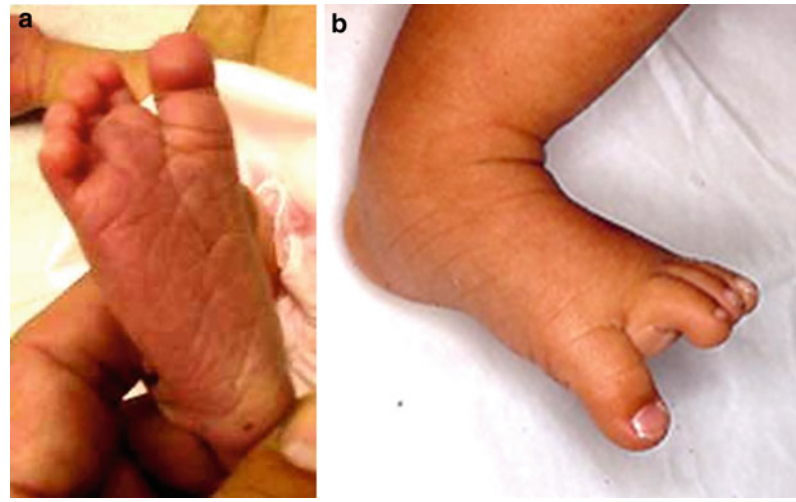


Fig. 10 (**a**, **b**) Two infants with Down syndrome showing a widened space between the first and the second toes ("sandal gap" foot)

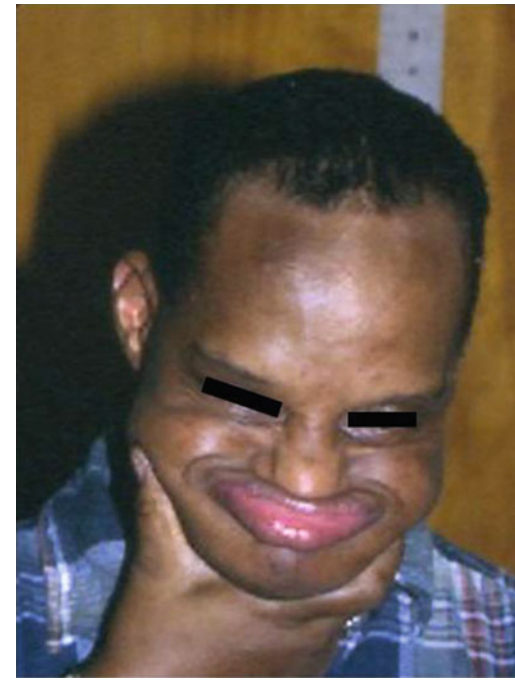


Fig. 11 An adult patient with Down syndrome showing upslanting palpebral fissure and severe midfacial hypoplasia

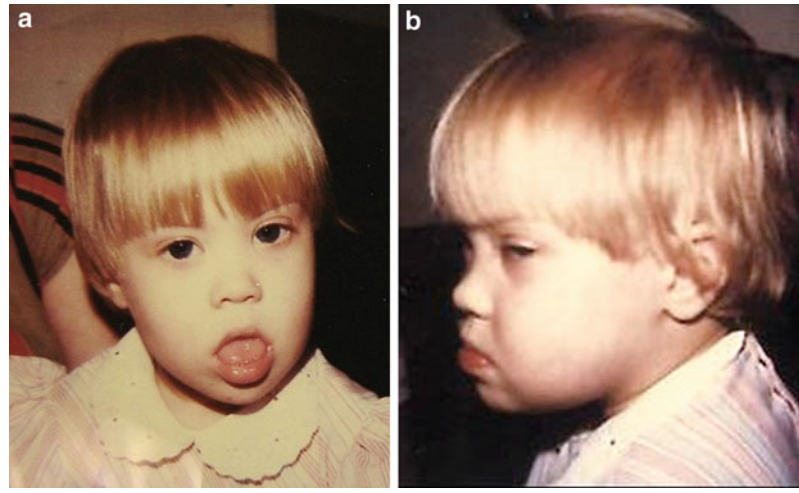


Fig. 12 (**a**, **b**) A girl with mosaic trisomy 21 showing typical Down syndrome phenotype

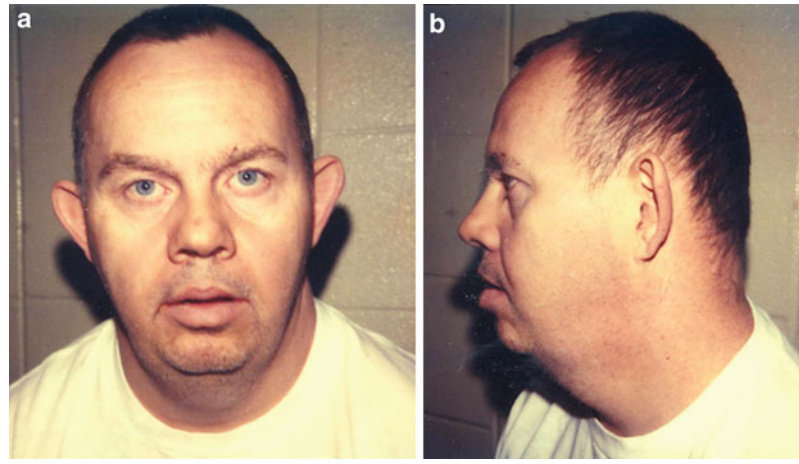


Fig. 13 (**a**, **b**) An adult patient with mosaic trisomy 21 showing relatively mild phenotype

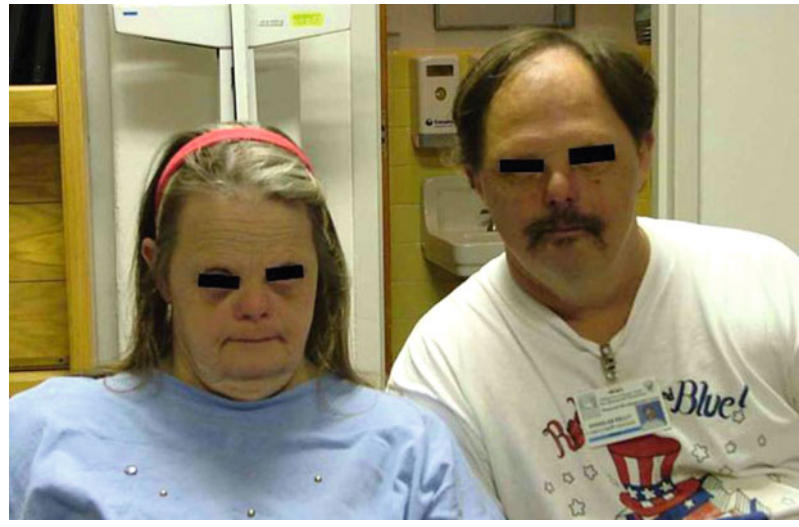


Fig. 14 A brother and a sister with nondisjunction type of trisomy 21

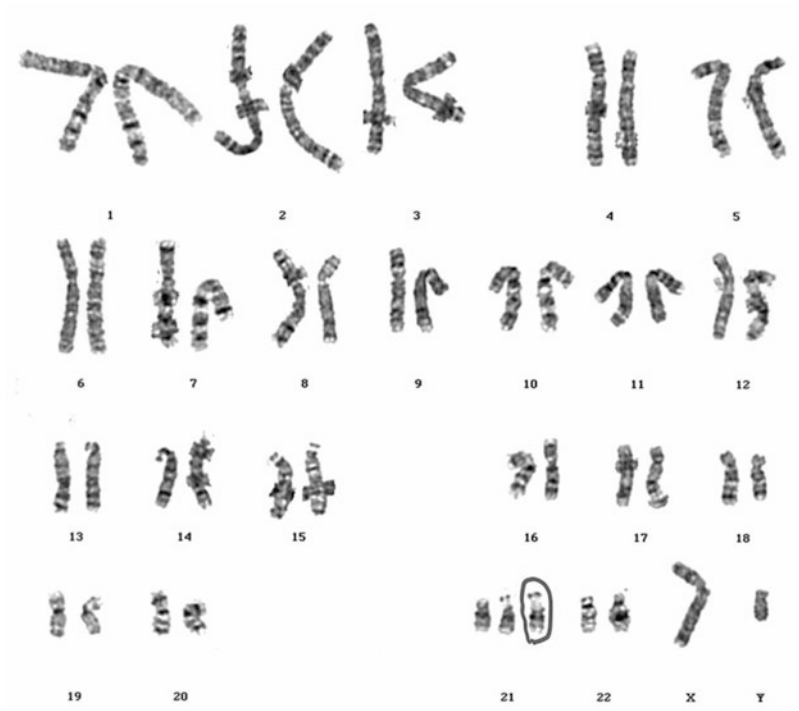


Fig. 15 A G-banded karyotype showing trisomy 21

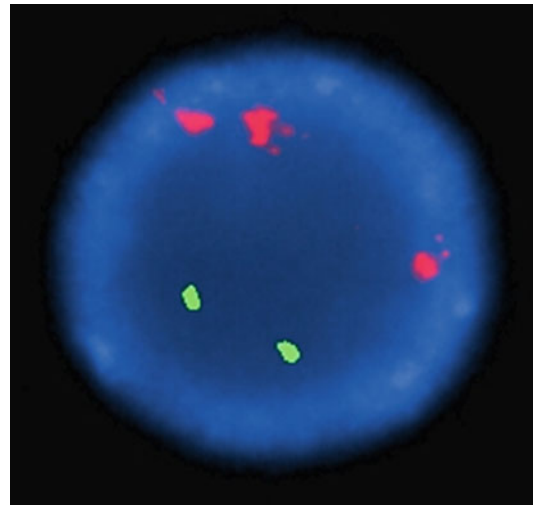


Fig. 16 FISH using a probe cocktail for chromosomes 13 (*green*) and 21 (*orange*) on interphase cells. Three copies of the orange/chromosome 21 signal are seen with only two copies of the green signal/chromosome 13 (AneuVysion LSI 13/21, Vysis/Abbott)

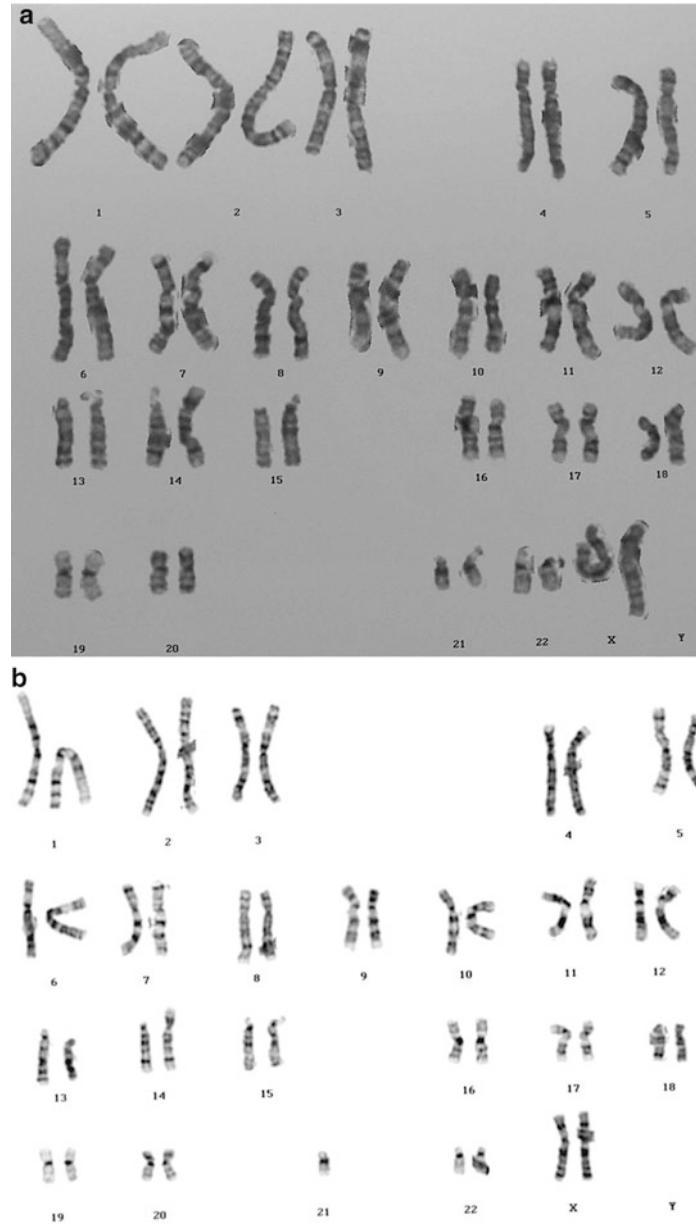


Fig. 17 (**a**, **b**) G-banded karyotypes showing t (14q;21q) trisomy 21 (**a**) and carrier (**b**)

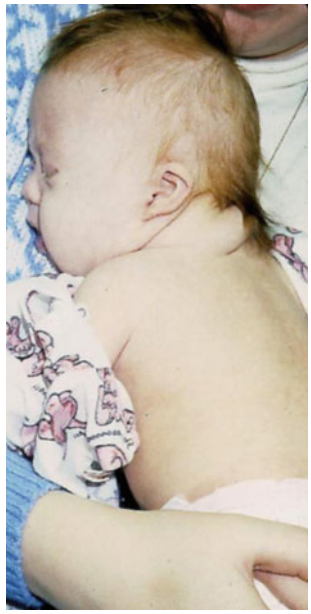


Fig. 18 A neonate with i(21q) trisomy 21 showing typical Down syndrome phenotype including thickened nuchal folds

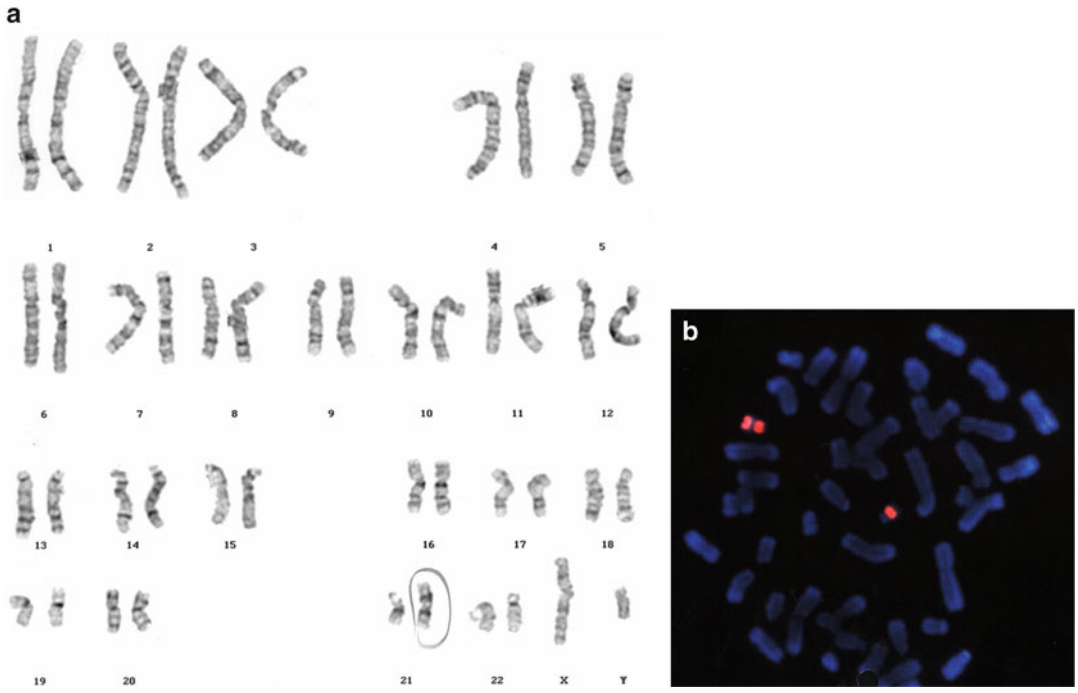


Fig. 19 A G-banded karyotype (**a**) and FISH (**b**) showing i(21q) trisomy 21

Duncan Syndrome

Contents

In 1975, Purtilo et al. (1975) reported the Duncan pedigree in which 6 of 18 males died of a lymphoproliferative disorder. The boys, aged between 2 and 19 years, exhibited a progressive combined variable immunodeficiency disease characterized by benign or malignant proliferation of lymphocytes, histiocytosis, and alterations in concentrations of serum immunoglobulins. This condition is now known as Duncan syndrome or X-linked lymphoproliferative syndrome (XLP) which is a rare T and NK cell immune deficiency which most frequently presents as fulminant infectious mononucleosis following infection with the Epstein-Barr virus (EBV) in most affected boys, leading to death in 50% of the cases.

Synonyms and Related Disorders

X-Linked Lymphoproliferative Disease

Genetics/Basic Defects

1. An X-linked recessive disorder.
2. The gene causing XLP, identified and described in 1998 (Coffey et al. 1998), was termed *SH2D1A* or SAP [signaling lymphocyte activation molecule (SLAM)-associated protein]. The gene encodes a protein which interacts with the SLAM (or CD150, a T-cell surface marker, and self-ligand) and several related receptors (Sayos et al. 1998; Morra et al. 2001; Latour and Veillette 2003).
3. In XLP patients who lack functional SAP, the SLAM family receptors may not signal properly. This property likely contributes to the phenotypes of XLP, including fulminant infectious mononucleosis, lymphoma, and hypogammaglobulinemia (Nichols et al. 2005).
4. Macro- and microdeletion observed in the *SH2D1A* gene of XLP patients or their established B-cell line (Sumegi et al. 2000).
5. XLP is known to be caused by mutation of either of two genes (Filipovich et al. 2013).
   1. *SH2D1A*, encoding SH2 domain protein-containing protein 1A/SLAM-associated protein (SAP); this disorder is sometimes referred to as XLP1.
   2. *XIAP* (also known as *BIRC4*), encoding baculoviral IAP repeat-containing protein

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4 (X-linked inhibitor of apoptosis; XIAP); this disorder is sometimes referred to as XLP2.

6. The immune response of XLP patients against EBV:
    1. Not efficient for the control of EBV expansion (in contrary to the coordinated immune response to EBV seen in normal individuals).
    2. Exhibit a dysregulated response characterized by an excessive accumulation of activated CD8+ T cells, natural killer (NK) cells, and macrophages and by the inability to control acute EBV infection.

Clinical Features

1. Diverse phenotype in affected boys.
2. Fulminant infectious mononucleosis (FIM) with virus-associated hemophagocytic syndrome (VAHS) (Gaspar et al. 2002).
    1. The most common and most dramatic manifestation of XLP with the worst prognosis (over 90% mortality).
    2. Clinically well until EBV infection, leading to a dysregulated and exaggerated immune response with proliferation of cytotoxic T cells, EBV-infected B cells, and macrophages in tissues throughout the body.
    3. Clinically manifests as pronounced lymph-adenopathy and hepatosplenomegaly, resulting in extensive parenchymal damage with accompanying dysregulated cytokine release.
        1. Most prominent in the liver, causing fulminant hepatitis and hepatic necrosis (Sullivan and Woda 1989), and in the bone marrow, leading to profound marrow hypoplasia.
        2. Infiltration in other tissues.
            1. Spleen (white pulp necrosis).
            2. Brain (perivascular mononuclear cell infiltrates).
            3. Heart (mononuclear cell myocarditis).
            4. Kidney (mild interstitial nephritis).
            5. Postmortem hemophagocytosis observed in various tissue in 90% of XLP boys presenting with FIM.
3. Dysgammaglobulinemia (Gaspar et al. 2002).
    1. Extensive necrosis and lymphoid depletion throughout the lymphoreticular system that follows acute EBV infection.
    2. Abnormal immunoglobulin (Ig) production after EBV infection: ranging from decreased levels of IgG to panhypogammaglobulinemia.
    3. Humoral dysfunction may accompany cellular T and natural killer (NK) defects in more severe cases.
4. Malignant lymphoma (Harrington et al. 1987; Gaspar et al. 2002).
    1. Found in approximately one third of boys with XLP, with B-cell lymphoma being the most common lymphoproliferative disorder observed.
    2. Median age: 4–6 years.
    3. Extranodal lesions: approximately 75% in ileocecal region and a smaller number in central nervous system, liver, and kidneys.
    4. Almost all the lymphomas were of B-cell origin but tumors with a T-cell phenotype have also been described.
    5. Lymphomas can be histologically classified as:
        1. Burkitt's lymphomas (53% of all B-cell lymphomas).
        2. Immunoblastic lymphomas (12% of all cases).
        3. Small cleaved or mixed cell lymphomas (12%).
        4. Unclassifiable lymphomas (5% of all cases) (Harrington et al. 1987).
        5. Four cases of Hodgkin's disease were reported to the XLP registry.
    6. Features of lymphomas in XLP: similar to those seen in other primary immunodeficiencies.

1. Extranodal involvement.
2. High-grade histology.
3. Evidence of clonality.
4. Gene rearrangements.

7. Poor survival rate (35%).
8. Remission can often be achieved with the use of standard pediatric lymphoma chemotherapy protocols but there is a high rate of relapse or development of the other manifestations of XLP.

5. Other clinical manifestations (Gaspar et al. 2002).
   1. Aplastic anemia can arise as a complication of fulminant infectious mononucleosis (Purtilo et al. 1982) with hemophagocytosis, leading to marrow aplasia. However, 3% of all cases can present initially as aplastic anemia.
   2. Lymphoid vasculitis.
      1. Another uncommon but well-described complication of XLP.
      2. Histological features: arterial wall destruction with aneurismal dilatation.
   3. Accompanied by various degrees of hemophagocytic lymphohistiocytosis.
6. Phenotype is likely determined by a number of factors, including the SAP mutation, and environmental and infectious factors on a background of disease modifier genes, as seen in other primary immunodeficiencies.
7. XLP without EBV infection: at least 10% of cases of XLP are driven without EBV infection.
8. Posttransplant lymphoproliferative disorder (PTLD) (Ho et al. 1988; Boyle et al. 1997).
   1. Primary EBV infection after transplantation: the major risk factor for the development of PTLD.
   2. Estimated to occur in 2–5% of all transplant recipients.
   3. More common in children since many children are EBV-naive at the time of transplant.
   4. Frequency of EBV infection in pediatric liver recipients: 63%.
   5. 3 clinical types of lymphoproliferative syndrome.
      1. The first type: self-limited mononucleosis-like syndrome.
      2. The second type: begins similarly, but then progresses over the next 2 months to widespread lymphoproliferation in internal organs and death.
      3. The third type: an extranodal intestinal monoclonal B cell lymphoma, occurring late after primary infection.
   6. Mortality rates reported for children who develop PTLD: high and range from 36% to 69%.
9. Males with XIAP deficiency (XLP2) (Filipovich et al. 2013).
   1. Typically present with hemophagocytic lymphohistiocytosis (HLH) (often without EBV infection), recurrent episodes of HLH, splenomegaly, and gastrointestinal disease and may be better described as having an X-linked form of familial hemophagocytic lymphohistiocytosis rather than XLP (Marsh et al. 2010).
   2. To date, neither lymphoproliferative disease (Pachlopnik Schmid et al. 2011) nor common variable immunodeficiency (CVID) has been reported in males with XIAP deficiency (Salzer et al. 2008).
   3. Of note, some males with pathogenic variants in XIAP are asymptomatic and their long-term prognosis is not known.
10. Diagnostic criteria for XLP (Conley et al. 1999).
    1. Definitive: male patients with a mutation in SAP.
       1. Lymphoma/Hodgkin's disease.
       2. Fatal EBV infection.
       3. Immunodeficiency.
       4. Aplastic anemia or lymphohistiocytic disorder.
    2. Probable.
       1. Male patients experiencing lymphoma/Hodgkin's disease, immunodeficiency,

plastic anemia or lymphohistiocytic disorder, resulting in death, following acute EBV infection.
2. Maternal cousins, uncles, or nephews with a history of similar diagnoses, following acute EBV infection.
3. Possible: male patients with lymphoma/Hodgkin's disease, immunodeficiency, plastic anemia, or lymphohistiocytic disorder, resulting in death, following acute EBV infection.

Diagnostic Investigations

1. Identification of SAP as the defective gene in XLP now allows unambiguous diagnosis of the condition.
2. Screen all male patients with common variable immunodeficiency (CVID) since some patients previously labeled as having CVID have been shown to have mutations in the SAP gene.
3. Prior to an encounter with EBV: no uniform abnormalities are observed on laboratory testing of individuals with XLP. Some individuals may have:
   1. Decreased numbers of lymphocyte subsets including decreased T cells, B cells, and NK cells.
   2. Variably decreased NK cell function.
   3. Dysgammaglobulinemia, most frequently manifest by low serum concentration of IgG with elevated serum concentration of IgM and/or IgA.
4. Evidence of acute EBV infections supported by:
   1. Heterophil antibodies on monospot testing.
   2. EBV detection by polymerase chain reaction (PCR).
   3. Detection of EBV-specific IgM antibodies.
   4. Atypical lymphocytosis on peripheral blood smear.
5. Specific tests suggesting the diagnosis of XLP in males with severe EBV infections:
   1. Markedly elevated liver transaminases.
   2. Inverted CD4:CD8 ratio in peripheral blood.
   3. Liver biopsy consistent with widespread necrosis during severe EBV infection.
   4. Bone marrow biopsy with evidence of hemophagocytosis during severe EBV infection.
   5. Positive EBV viral capsid antigen (VCA) titer, but negative Epstein-Barr virus nuclear antigen (EBNA) titer.
6. Molecular genetic testing (Filipovich et al. 2013): clinically available.
   1. Sequence analysis and deletion/duplication analysis of *SH2D1A*.
      1. Sequence analysis of the entire coding region of *SH2D1A* and exon/intron boundaries identifies nucleotide substitutions, small deletions, small insertions, small insertions/deletions, and small inversions.
      2. PCR-based sequencing can detect about 97% of *SH2D1A* mutations in affected males who have two or more maternally related family members with an XLP phenotype and about 75% of mutations in obligate carrier females.
      3. Large deletions account for about 25% of mutations in families with XLP.
      4. Because males have one X chromosome, the absence of amplification of a region of a gene under stringent laboratory conditions implies that a large deletion or rearrangement is present, and because females have two X chromosomes, amplification of a region occurs even in the presence of a large deletion because of the contribution of the second X chromosome; thus, PCR-based sequencing does not accurately detect a large deletion.
   2. Sequence analysis and deletion/duplication analysis of *XIAP*.
7. Carrier detection of at-risk female relatives: available on a clinical basis when the mutation has been identified in the proband or family relative.
8. Postmortem PTLD histology (Collins et al. 2001).
   1. Lymphoma.
   2. Hyperplasia.

3. Combined lymphoma and hyperplasia.
4. EBER1 messenger RNA detected in B-cell PTLD.

Genetic Counseling

1. Recurrence risk (Filipovich et al. 2013).
    1. Patient's sib: The risk to sibs depends upon the carrier status of the mother.
        1. Mother is a carrier: The chance of transmitting the disease-causing mutation in each pregnancy is 50%.
        2. Male sibs who inherit the mutation will be affected.
        3. Female sibs who inherit the mutation will be carriers but asymptomatic and have no immunologic or biochemical markers of the disorder.
        4. Presence of germline mosaicism of the mother: Even if the disease-causing mutation has not been identified in DNA extracted from the mother's leukocytes, her offspring are still at increased risk.
    2. Patient's offspring.
        1. Affected males will likely live to reproduce in the near-future following bone marrow transplantation and that the chemotherapy regimen used prior to BMT will not render them infertile.
        2. Males will pass the disease-causing mutation to all of their daughters and none of their sons.
3. Prenatal diagnosis (Filipovich et al. 2013).
    1. Fetal karyotyping to determine male fetus (46,XY).
    2. DNA extracted from fetal cells by amniocentesis or CVS analyzed for known gene mutation (SH2DA1 or XIAP pathogenic variant).
3. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the pathogenic variant has been identified (Filipovich et al. 2013).
4. Management (Gaspar et al. 2002; Seiter 2015).
    1. All identified males receive immunoglobulin replacement to prevent bacterial and viral infections.
    2. Allogeneic hematopoietic stem cell transplantation (HSCT): the only definitive cure for XLP and prevention of EBV and non-EBV complications at present.
    3. Treatment is difficult during the acute FIM phase of XLP, as demonstrated by the high mortality rate.
        1. Treatment using antivirals (acyclovir/ganciclovir/foscarnet), high-dose immunoglobulin, immunosuppressive agents, and IFN-a and IFN-c have been disappointing.
        2. The high rate of hemophagocytosis associated with XLP has led to the use of antihistiocytic regimes with etoposide such as HLH-94 (Henter et al. 1997), for the treatment of boys with XLP, shown to induce long-term remission or to stabilize the patient prior to allogeneic HSCT.
        3. Etoposide has also been included in the conditioning regime in combination with busulphan and cyclophosphamide for some patients.
    4. Regular immunoglobulin replacement to prevent recurrent infection and additional bacterial prophylaxis in patients developing hypogammaglobulinemia postviral infection. This may not prevent subsequent development of malignant lymphoma or aplastic anemia. Patients with lymphoma have been treated according to standard chemotherapy protocols but there is a high rate of relapse and patients may also develop other phenotypes of XLP.
    5. Anti-CD20 rituximab: Preemptive use of B-cell-directed therapy may reduce the morbidity and mortality of primary EBV infection in X-linked lymphoproliferative disease (XLP)-affected individuals (Milone et al. 2005).

6. Successful bone marrow transplantation in a boy with X-linked lymphoproliferative syndrome and acute severe infectious mononucleosis (Pracher et al. 1994).
7. Autologous lymphokine-activated killer cell infusion: effective for treatment of EBV+ organ transplant recipients (Nalesnik et al. 1997).
8. Allogeneic stem cell transplantation.
    1. Currently only cure for XLP (Gross et al. 1996).
    2. Should be recommended in both symptomatic and asymptomatic XLP patients (Lankester et al. 2005).
9. Prospect of gene therapy as a future treatment option with the identification of the XLP gene.
    1. Recent success of gene therapy for the treatment of human severe combined immunodeficiency (SCID)-X1 disease offers hope for other immunodeficient conditions (Cavazzana-Calvo et al. 2000).
    2. Gene therapy for XLP is attractive in that the cellular defects are primarily confined to T and NK cells, both of which are readily accessible and can be efficiently transduced.

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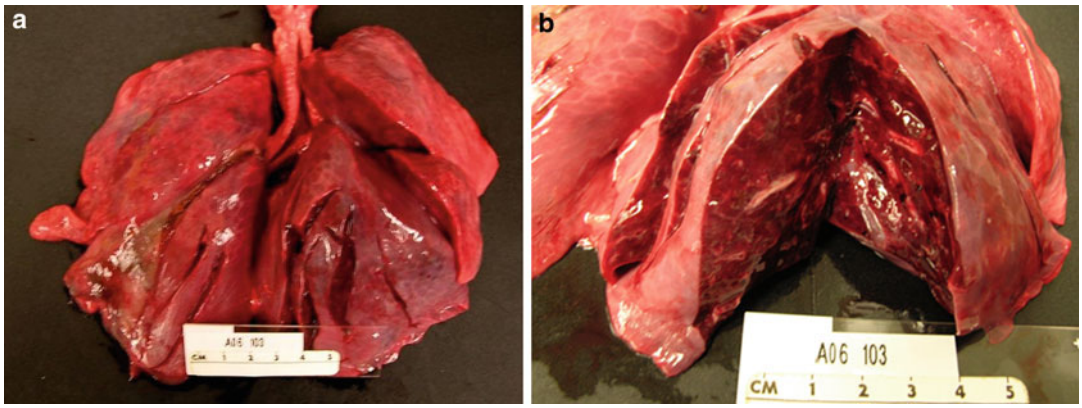

Fig. 1 (**a**, **b**) The deceased patient was a 4-year-old boy complained of fever, anemia, neutropenia, thrombocytopenia, and lymphadenopathy. He was noted to have cervical, axillary, and inguinal lymphadenopathy and hepatosplenomegaly. DNA analysis revealed a nonsense mutation, 172 C > T (Q56X), in the coding sequence of *SH12D1A* gene which confirmed the diagnosis of X-linked lymphoproliferative disease. A maternal first cousin is also affected with Duncan disease. On necropsy, both lungs appeared congested and the cut surface of both lungs was dark and airless with diffuse atelectasis

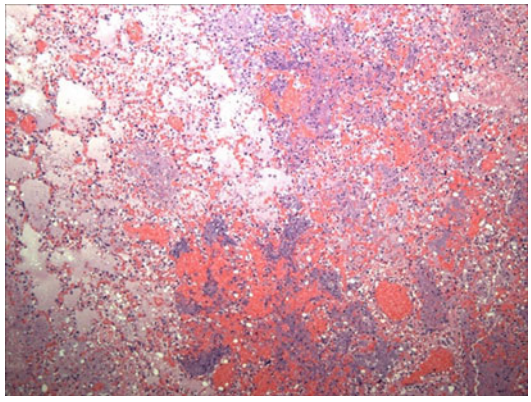

Fig. 2 Microscopic examination of the lungs showed congestion, hemorrhage, and edema with extensive gram-negative bacterial growth

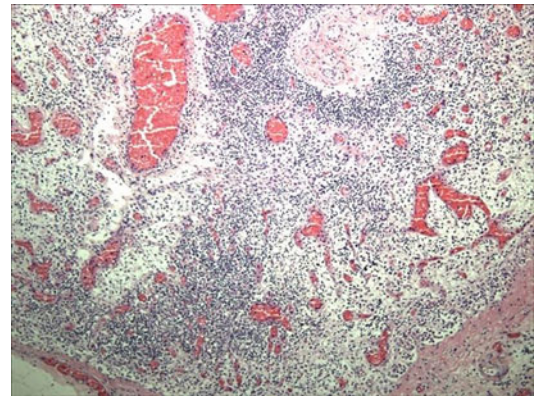

Fig. 3 The microscopic examination of the lymph nodes showed absence of germinal centers, depletion of the lymphocytes, sinus histiocytosis, and vascular congestion

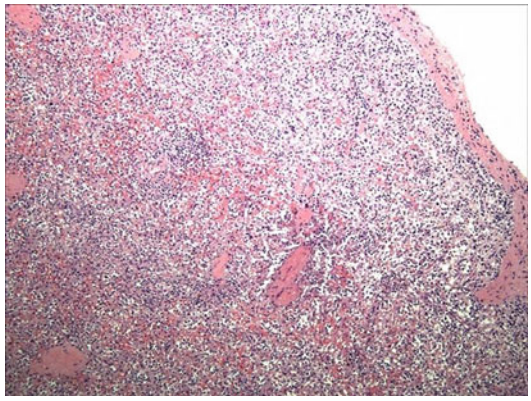

Fig. 4 Microscopic examination of the spleen showed lymphocyte depletion and rare megakaryocytes

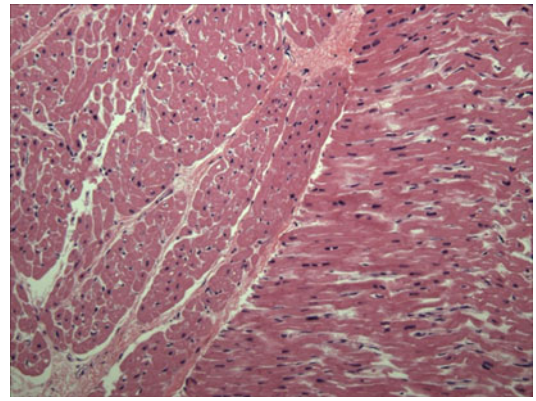

Fig. 6 Nuclei of heart muscles were enlarged, consistent with moderate hypertrophy

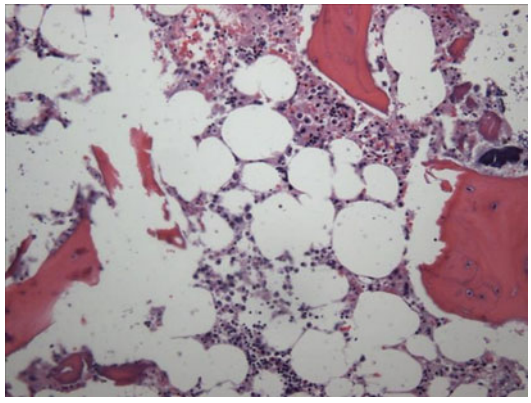

Fig. 5 Bone marrow was hypocellular with fat to cell ratio of 90:10 and very few mature lymphocytes

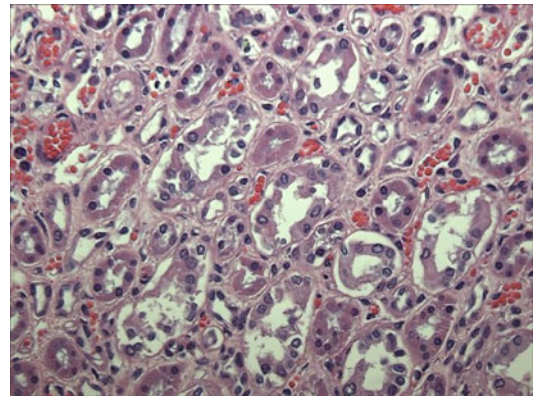

Fig. 7 Proximal tubules of the kidney were necrotic, consistent with ischemic changes

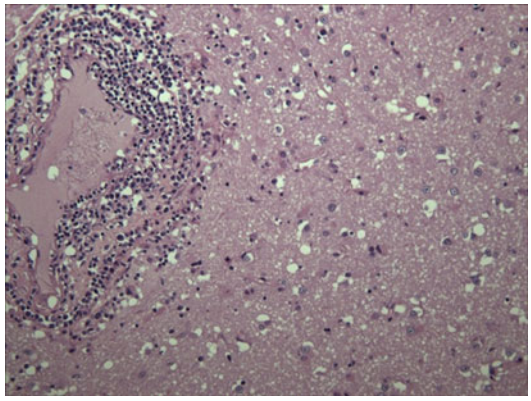

Fig. 8 The brain showed intense perivascular and mild patchy parenchymal infiltration with atypical reactive lymphocytes

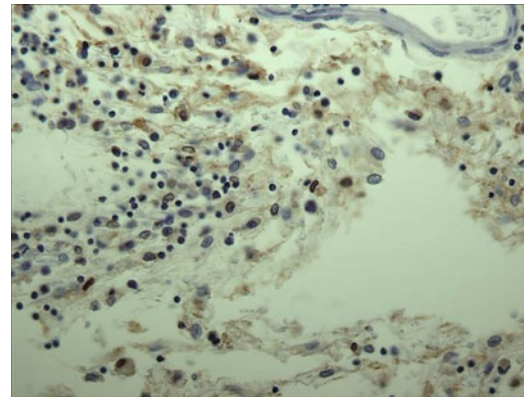

Fig. 10 Some cells in the infiltrate were positive for EB virus by FISH analysis

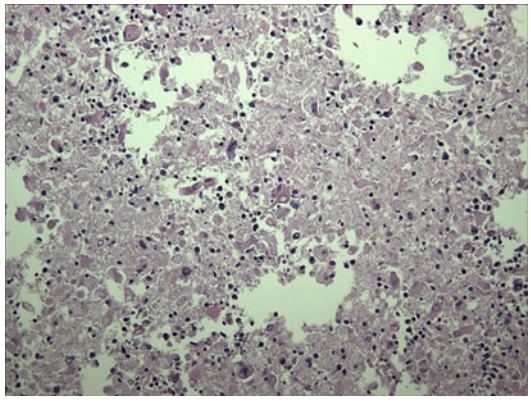

Fig. 9 The liquefied areas of the brain contained numerous foamy macrophages and the surrounding tissue contained numerous gemistocytes (active gliosis) in the RSFG, left corpus striatum, brain stem, and cerebellum

Dyschondrosteosis

Contents

Dyschondrosteosis is an autosomal dominant form of mesomelic dysplasia, first described by Leri and Weill in 1929. Langer mesomelic dysplasia, also called mesomelic dwarfism of the hypoplastic ulna, fibula, and mandible type (Langer 1967), is a more severe form (homozygous state) of Leri-Weill dyschondrosteosis.

Synonyms and Related Disorders

Langer mesomelic dysplasia; Leri-Weill syndrome (LWS)

Genetics/Basic Defects

1. Inheritance
    1. Dyschondrosteosis: autosomal dominant inheritance (Lichtenstein et al. 1980)
    2. Langer mesomelic dysplasia: pseudoautosomal dominant inheritance (Shears et al. 2002)
    3. The pseudoautosomal region 1 is a known recombination "hot spot" in male meiosis. Published genetic maps indicate high recombination frequency of ~40% for *SHOX* (short stature homeobox-containing) in male meiosis leading to pseudoautosomal inheritance. (Evers et al. 2011)
    4. Compound heterozygous deletions in pseudoautosomal region 1: reported in an infant with mild manifestations of Langer mesomelic dysplasia (Tsuchiya et al. 2014).
2. Molecular basis (Zinn et al. 2002)
    1. Caused by mutations and deletion of *SHOX* (short stature homeobox-containing) gene (Belin et al. 1998; Huber et al. 2001)
        1. The *SHOX* gene is mapped to Xp22.3 based on the observation of unbalanced translocation involving the pseudoautosomal region of the short arm of the X and Y chromosomes (PAR1) (Yp11.3) in dyschondrosteosis patients and of some degree of Madelung deformity in Turner syndrome patients (Guichet et al. 1997)
        2. The Xp22.3 region encompasses the pseudoautosomal *SHOX* gene, which encodes isoforms of a homeo-domain transcription factor expressed in developing human limbs

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. The gene in the Xp22.3 region escapes X-inactivation in females and participates in obligate recombination during male meiosis. Consequently, dyschondrosteosis segregates as an apparently "autosomal" dominant disorder
4. Duplications of cis-regulatory DNA elements can result in a SHOX-related phenotype (Bunyan et al. 2015)
5. 67% of mutations observed in patients with bilateral Madelung deformity (Flanagan et al. 2002)

2. In usual circumstances, *SHOX* is present in two identical copies (Binder and Rappold 2015)
   1. In females, one copy is present on each X chromosome
   2. In males, one copy is present on the X chromosome and one copy – sometimes called *SHOX(Y)* – is present on the Y chromosome
3. Haploinsufficiency of the *SHOX* gene implicated in the following disorders (Rao et al. 1997; Rappold et al. 2002; Binder 2011; Binder and Rappold 2015):
   1. Turner syndrome: *SHOX* is haploinsufficient in females with 45,X Turner syndrome, accounting for approximately 2/3 of the characteristic growth deficit
   2. Idiopathic short stature: Observation that a point mutation that cosegregates with idiopathic short stature suggests that *SHOX* haploinsufficiency may also cause growth failure in the patients with normal karyotype. *SHOX* mutations have been found in 2–3% of patients with idiopathic short stature
   3. Leri-Weill dyschondrosteosis (Palka et al. 2000) (including homozygous form of Langer mesomelic dysplasia)
   4. 45,X male: Loss of the *SHOX* gene associated with Leri-Weill dyschondrosteosis (Stuppia et al. 1999)
4. Identification of large-scale deletions or mutations in the *SHOX* gene in the majority of the cases
5. *SHOX* mutations: causative for mesomelic growth retardation, Madelung deformity in Leri-Weill dyschondrosteosis, and Langer mesomelic dysplasia (Barca-Tierno et al. 2012)
6. Leri-Weill syndrome as a part of contiguous gene syndrome with deletion of Xp22.3

3. Langer mesomelic dwarfism
   1. A homozygous state of dyschondrosteosis gene (Espiritu et al. 1975a, b; Fryns and Van den Berghe 1979; Kunze and Klemm 1980)
   2. Caused by deletion of both *SHOX* alleles (complete *SHOX* deficiency)
   3. Also associated with compound heterozygous mutations and deletions of the *SHOX* gene, mapped to the pseudoautosomal region 1 (PAR1) of the sex chromosomes Xp22.33 and Y11.32 or the downstream PAR1 where SHOX enhance elements are located
      1. A compound heterozygote with a deletion in the 3′ *SHOX* flanking region in one allele and the loss of the entire *SHOX* gene in the other has been described with a "mild" Langer mesomelic dysplasia phenotype (Fukami et al. 2005)
      2. Detection of two different deletions in a proband with clinical features of Langer mesomelic dysplasia in the pseudoautosomal 1 region (PAR1) of the X and Y chromosomes: a *SHOX* encompassing deletion inherited from his father and a downstream PAR1 deletion not including *SHOX* inherited from his mother (Campos-Barros et al. 2007)

Clinical Features

1. Dyschondrosteosis (LWS) (Carter and Currey 1974; Dawe et al. 1982)
   1. Phenotypic inter- and intrafamilial heterogeneity is a frequent finding in LWS (Schiller et al. 2000)
   2. Mesomelic dwarfism (disproportionate short stature) (Felman and Kirkpatrick 1970)

3. Phenotypic inter- and intrafamilial heterogeneity, a frequent finding
4. Much more common and less severe than Langer mesomelic dysplasia
5. Females more commonly and more severely affected (more severe Madelung deformity) than males (Ross et al. 2001)
6. Intelligence: normal
7. Limbs
    1. Mesomelia (disproportionate forelimb shortening)
        1. Shortened forearms
        2. Shortened forelegs
    2. A Madelung deformity of the forearms and wrists (Anton et al. 1938; Herdman et al. 1966; Felman and Kirkpatrick 1969; Beals and Lovrien 1976) secondary to bowing of the radius and dorsal subluxations of the distal ulna
    3. Reduced radiocarpal motion
    4. Limited elbow and wrist pronation and supernation
    5. Genu varum

2. Langer mesomelic dysplasia
    1. The homozygous form of Leri-Weill syndrome (Espiritu et al. 1975a, b)
    2. Severe disproportionate short stature with marked mesomelic and rhizomelic limb shortening
    3. Parents of some children with Langer mesomelic dysplasia have features of the more common dominantly inherited mesomelic skeletal dysplasia Leri-Weill dyschondrosteosis (Balci et al. 1999)
    4. Intelligence: normal
    5. Limb malformations
        1. Aplasia or severe hypoplasia of the ulna and fibula
        2. Thickened and curved radius and tibia
    6. Hypoplasia of the mandible
    7. A variable degree of Madelung deformity and mesomelic shortening in both parents
3. Prognosis
    1. Minimal disability from the Madelung deformities of the wrists
    2. Secondary arthrosis of the radiocarpal joint
    3. Osteoarthritis of the large joints
    4. Langer mesomelic dysplasia: much more severe phenotype than dyschondrosteosis
4. Skeletal dysplasias associated with Madelung deformity (Lamberti and Light 2014)
    1. Dyschondrosteosis: the most important skeletal dysplasia associated with Madelung deformity
    2. Multiple hereditary osteochondromatosis
    3. Ollier disease
    4. Achondroplasia
    5. Multiple epiphyseal dysplasias
    6. Mucopolysaccharidoses (e.g., Hurler and Morquio syndromes)

Diagnostic Investigations

1. Radiography (Langer 1965; Carter and Currey 1974)
    1. Mesomelic dysplasia
    2. Madelung deformity of the wrists
        1. Short forearm
        2. Bowed radius
        3. Bowed ulna
        4. Premature fusion of the ulnar half of the radial epiphysis
        5. A V-shaped deformity of the wrist with slanting at the distal radial contour and dorsal dislocation of the ulna
        6. Wedging of the carpal bones between the deformed radius and protruding ulna, resulting in a triangular configuration with the lunate at the apex
        7. Cubitus valgus
    3. Coxa valga
    4. Lateral subluxation of the patella
    5. Short tibia
    6. Exostosis of the proximal medial tibia
    7. Langer mesomelic dysplasia
        1. Aplasia or severe hypoplasia of the ulna and fibula
        2. Thickened and curved radius and tibia
2. Cytogenetic analysis (Binder and Rappold 2015)
    1. Rare patients with Leri-Weill dyschondrosteosis

1. A contiguous gene syndrome caused by deletion in distal Xp22.3 (Ballabio et al. 1989; Spranger et al. 1999)
2. An unbalanced X;Y translocation (Shears et al. 1998; Calabrese et al. 1999)
3. Complex sex chromosome abnormalities (Wei et al. 2001)

2. Submicroscopic deletions of SHOX causing the SHOX-related haploinsufficiency disorders: not usually detectable by G-banded karyotyping

3. Molecular genetic analysis (Schiller et al. 2000)
   1. *SHOX* deletions detected by FISH analysis using cosmid probe for *SHOX*
   2. Southern blot and SSCP analysis
   3. Long range PCR and sequencing
   4. MLPA for PAR1 deletions
   5. High-resolution melting (HRM), dHPLC, and/or DNA sequencing for point mutations, small deletions, and insertions of *SHOX*

Genetic Counseling

1. Recurrence risk
   1. Patient's sibs
      1. Leri-Weill dyschondrosteosis
         1. Neither parent is affected: not increased
         2. One parent is affected with Leri-Weill dyschondrosteosis: 50% affected with Leri-Weill dyschondrosteosis and 50% unaffected
         3. Two parents are affected with Leri-Weill dyschondrosteosis: 50% affected with Leri-Weill dyschondrosteosis, 25% affected with Langer mesomelic dysplasia, and 25% risk of having neither conditions
      2. Langer mesomelic dysplasia (both parents with Leri-Weill dyschondrosteosis): 50% affected with Leri-Weill dyschondrosteosis, 25% affected with Langer mesomelic dysplasia, and 25% unaffected
   2. Patient's offspring
      1. Leri-Weill dyschondrosteosis
         1. Spouse is normal: 50% affected and 50% unaffected
         2. Spouse is affected with Leri-Weill dyschondrosteosis: 50% affected with dyschondrosteosis, 25% affected with Langer mesomelic dysplasia, and 25% having neither condition
      2. Langer mesomelic dysplasia
         1. Spouse is normal: All children will be affected with Leri-Weill dyschondrosteosis
         2. Spouse is affected with Leri-Weill dyschondrosteosis: 50% affected with Langer mesomelic dysplasia and 50% affected with Leri-Weill dyschondrosteosis
   2. Prenatal diagnosis possible for at-risk families
      1. Prenatal ultrasonography of skeletal features compatible with mesomelic dwarfism
      2. Molecular analysis of previously identified disease-causing *SHOX* mutations in the proband or a parent from the fetal DNA obtained from amniocentesis or CVS
      3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified
3. Management (Lamberti and Light 2014; Kozin and Zlotolow 2015)
   1. Medical therapy of Madelung deformity
      1. May be helpful in skeletally mature individuals with Madelung deformity who have mild-to-moderate short-term wrist pain
      2. Splints to relieve joint pain
      3. Decrease manual activity levels to manage symptoms without surgery
   2. Surgical therapy of Madelung deformity
      1. Primary goals: pain relief and cosmetic improvement of Madelung deformity

1. Minimal improvement of range of motion, especially in pronation and supination
2. Release of the Vickers ligament alone or in combination with an osteotomy
2. Radial dome osteotomy
3. Radioulnar length adjustment
4. Ulnar shortening osteotomy
3. Tibial osteotomy and lengthening combined with epiphysiodesis of the distal fibular epiphysis for the tibiofibular disproportion
4. Ongoing clinical trial with growth hormone therapy in patients with short stature due to *SHOX* mutations

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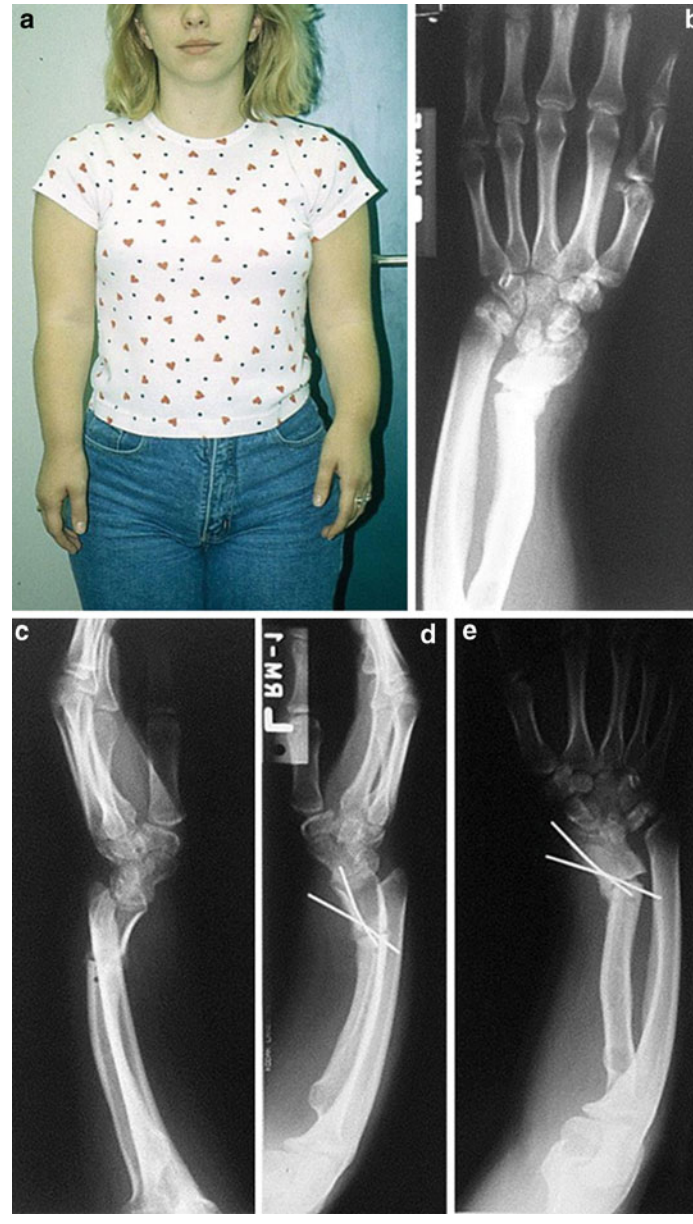

Fig. 1 A young lady with Leri-Weill syndrome (**a**) showing disproportionate short stature, short forearms and legs, and Madelung deformity of the wrists. Radiographs (**b**–**e**) illustrate typical Madelung deformity (curved radius and ulna with triangular configuration) corrected by surgery

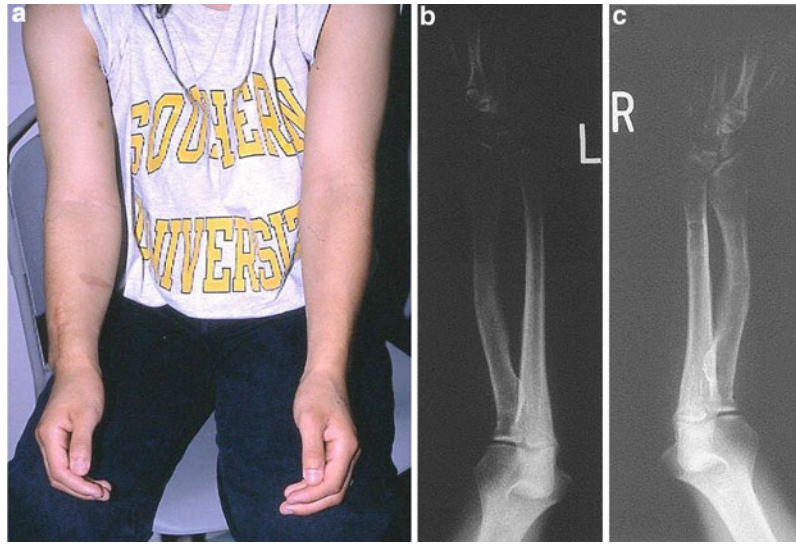

Fig. 2 A young lady with Leri-Weill syndrome with short forearms and Madelung deformity (**a**) demonstrated by radiographs (**b**, **c**)

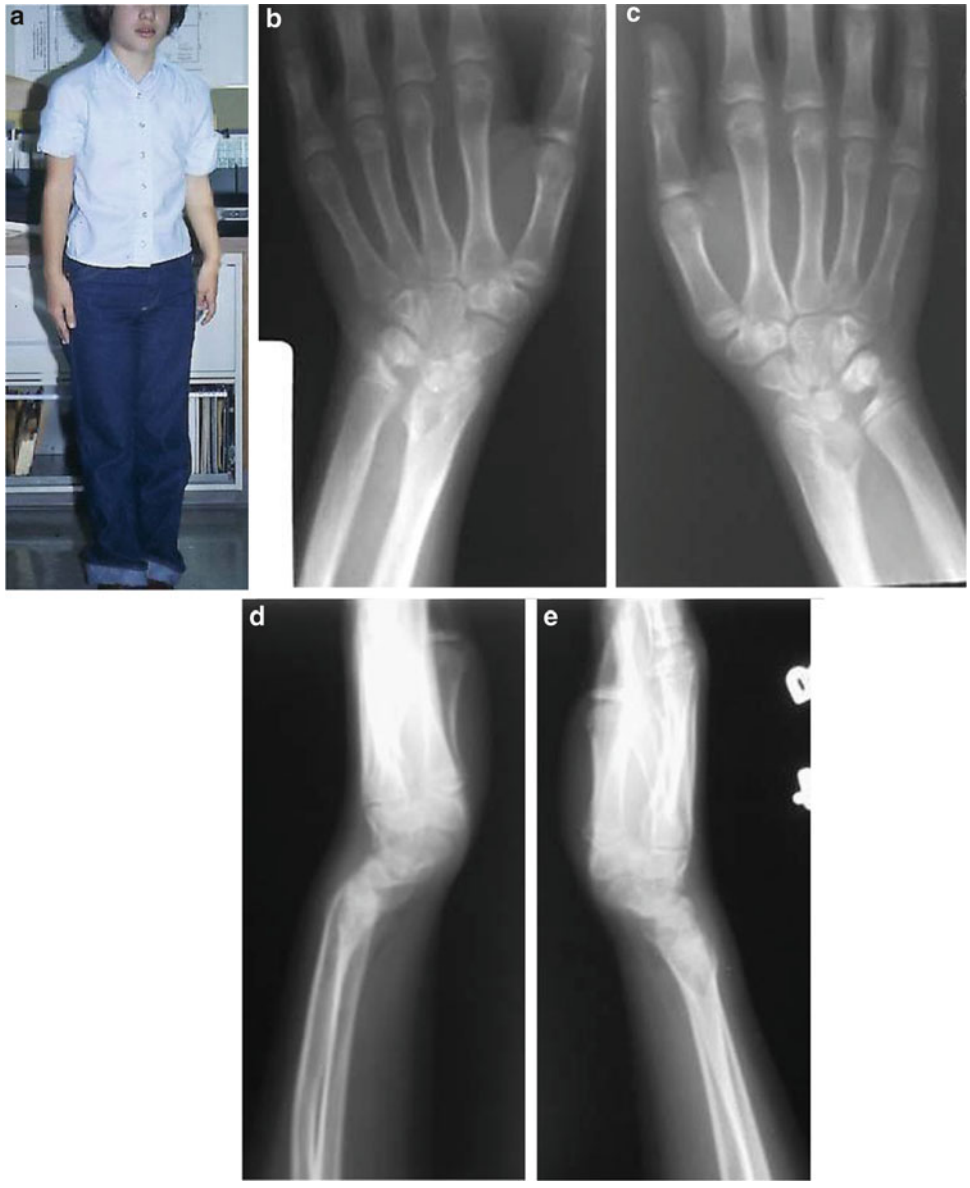

Fig. 3 A young lady with Leri-Weill syndrome showing disproportionate short stature, short forearms and legs, and Madelung deformity (**a**) illustrated by radiographs (**b**–**e**)

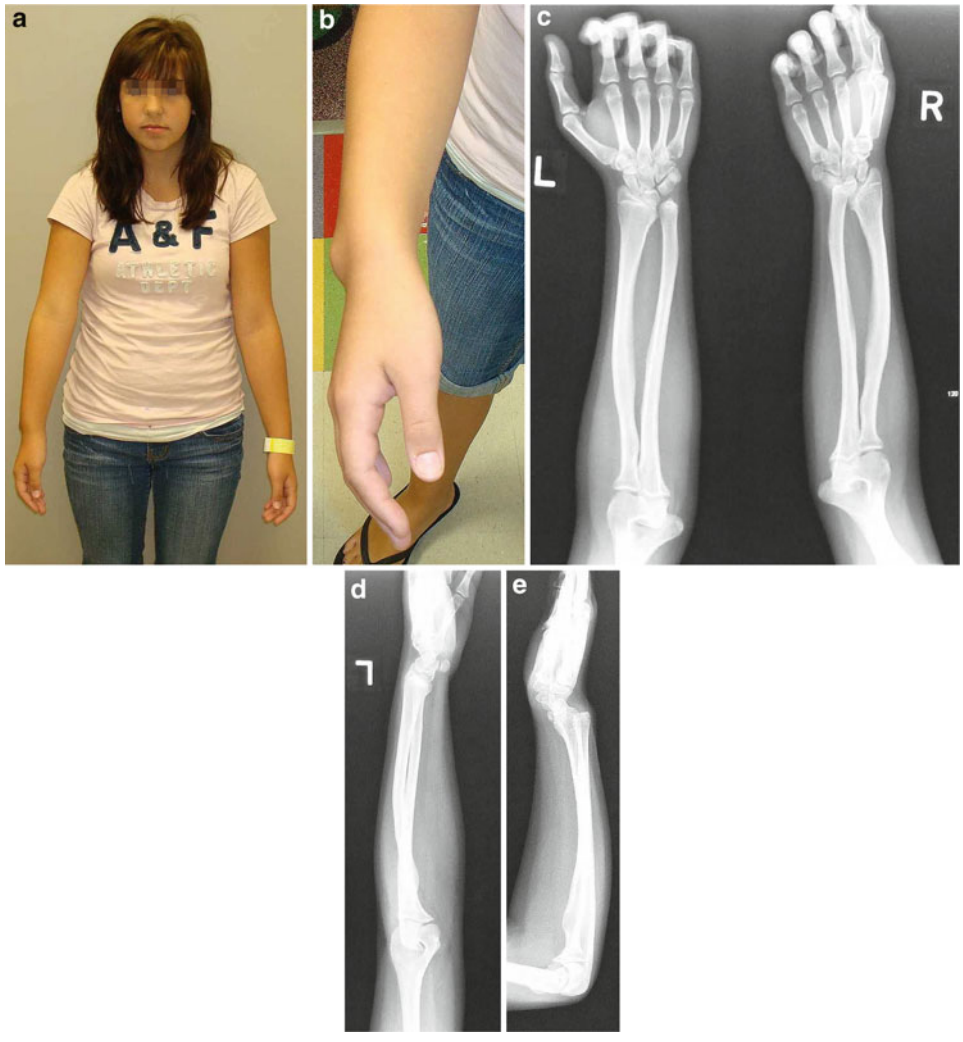

Fig. 4 A 14-year-old girl with Leri-Weill syndrome showing disproportionate short stature, short forearms and legs, and Madelung deformity of the wrists (**a**, **b**). Radiographs (**c**–**e**) illustrate typical Madelung deformity (curved radius and ulna with triangular configuration)

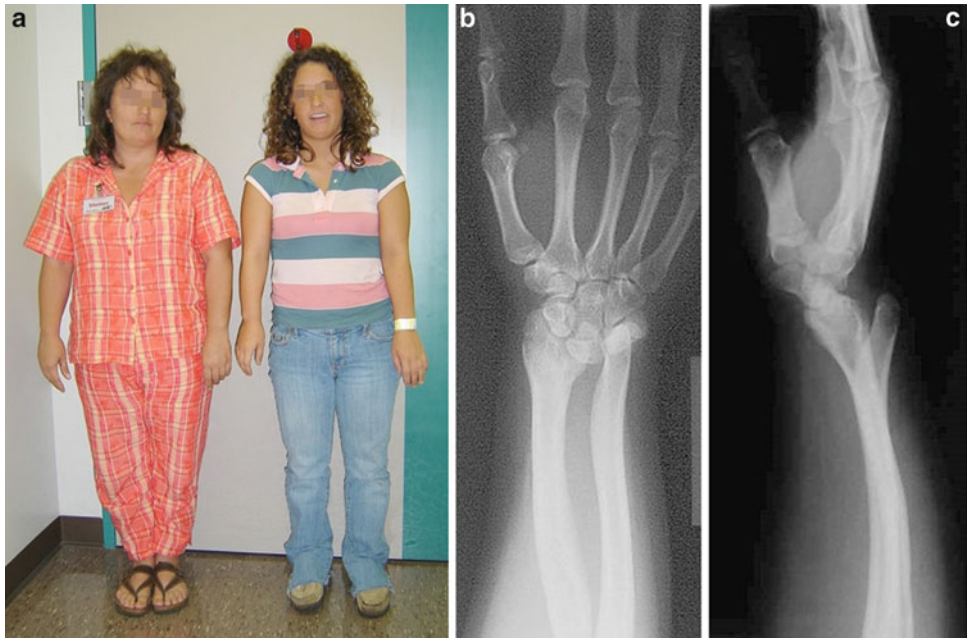

Fig. 5 Mother and daughter with Leri-Weill syndrome with typical phenotype (**a**) and wrist radiographs (**b**, **c**)

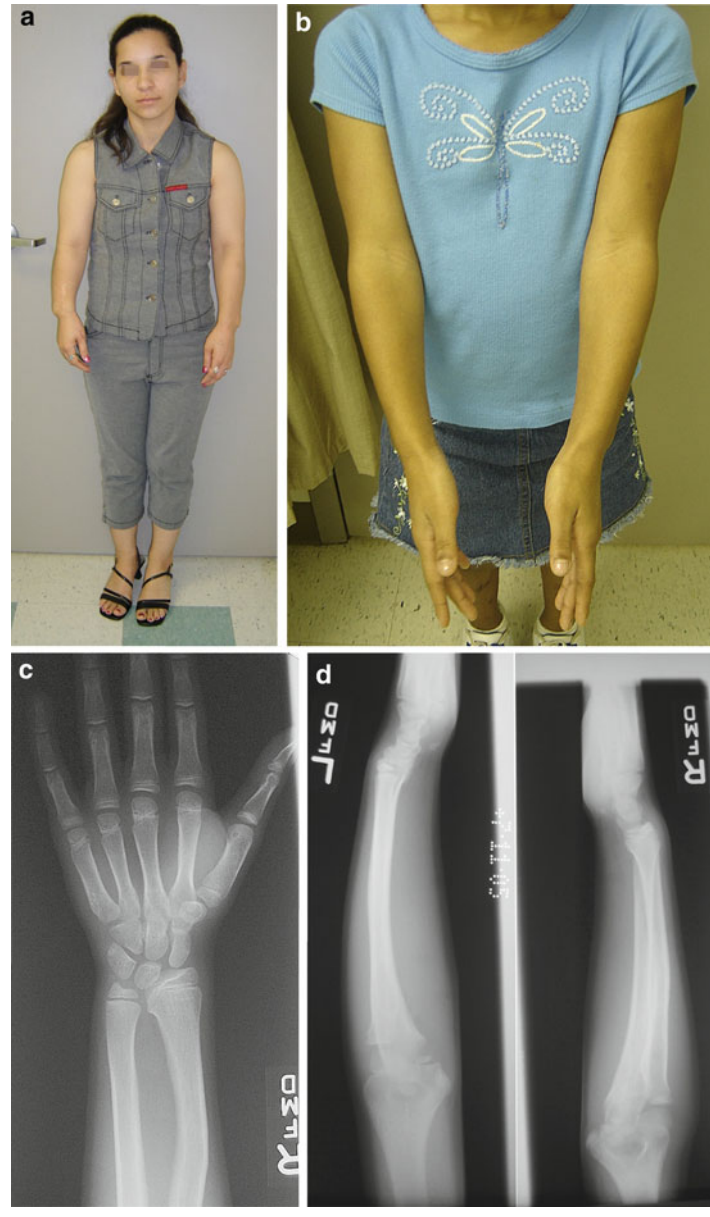

Fig. 6 Another mother (**a**) and daughter (**b**) with Leri-Weill syndrome and forearm radiographs of the daughter (**c, d**)

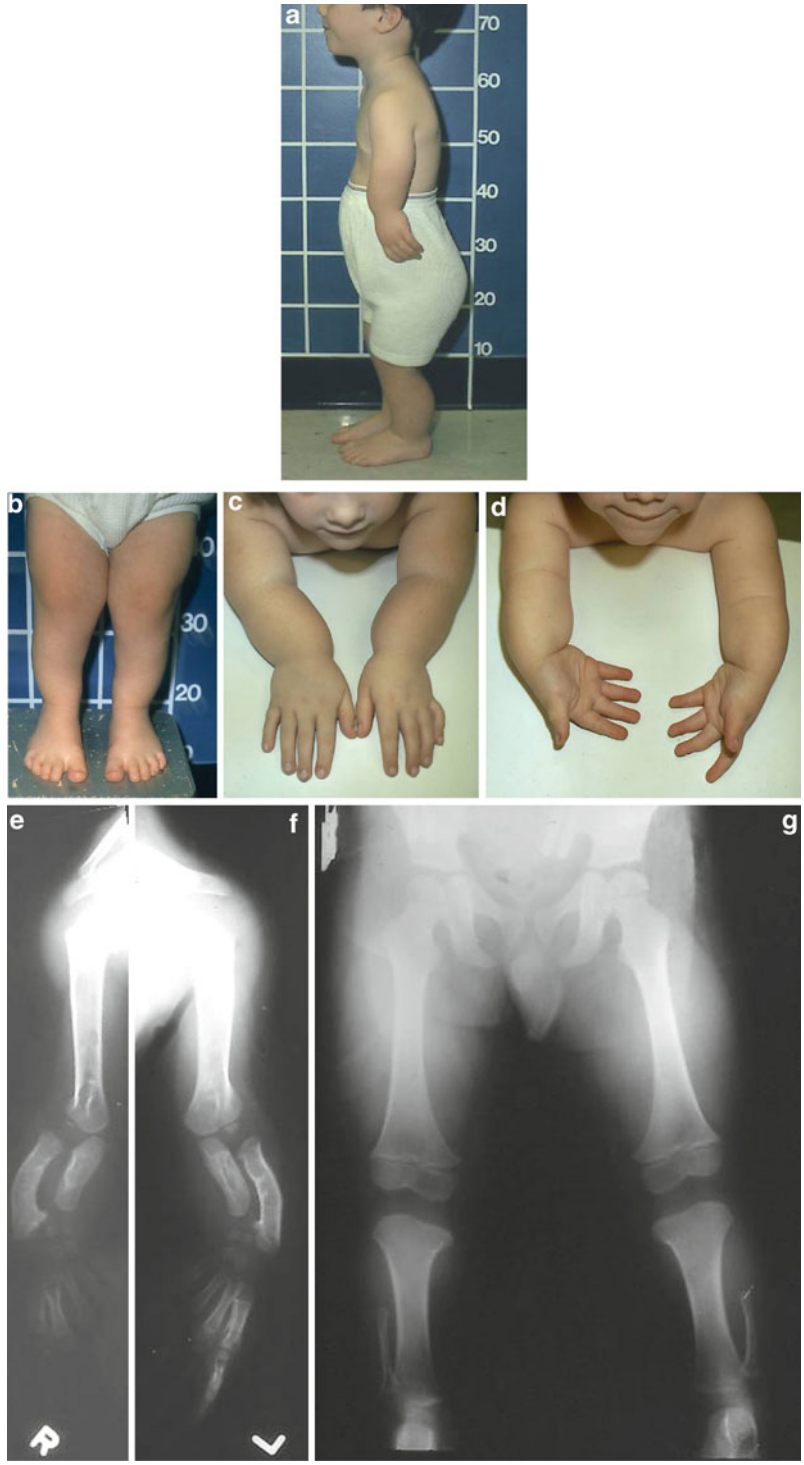

Fig. 7 (continued)

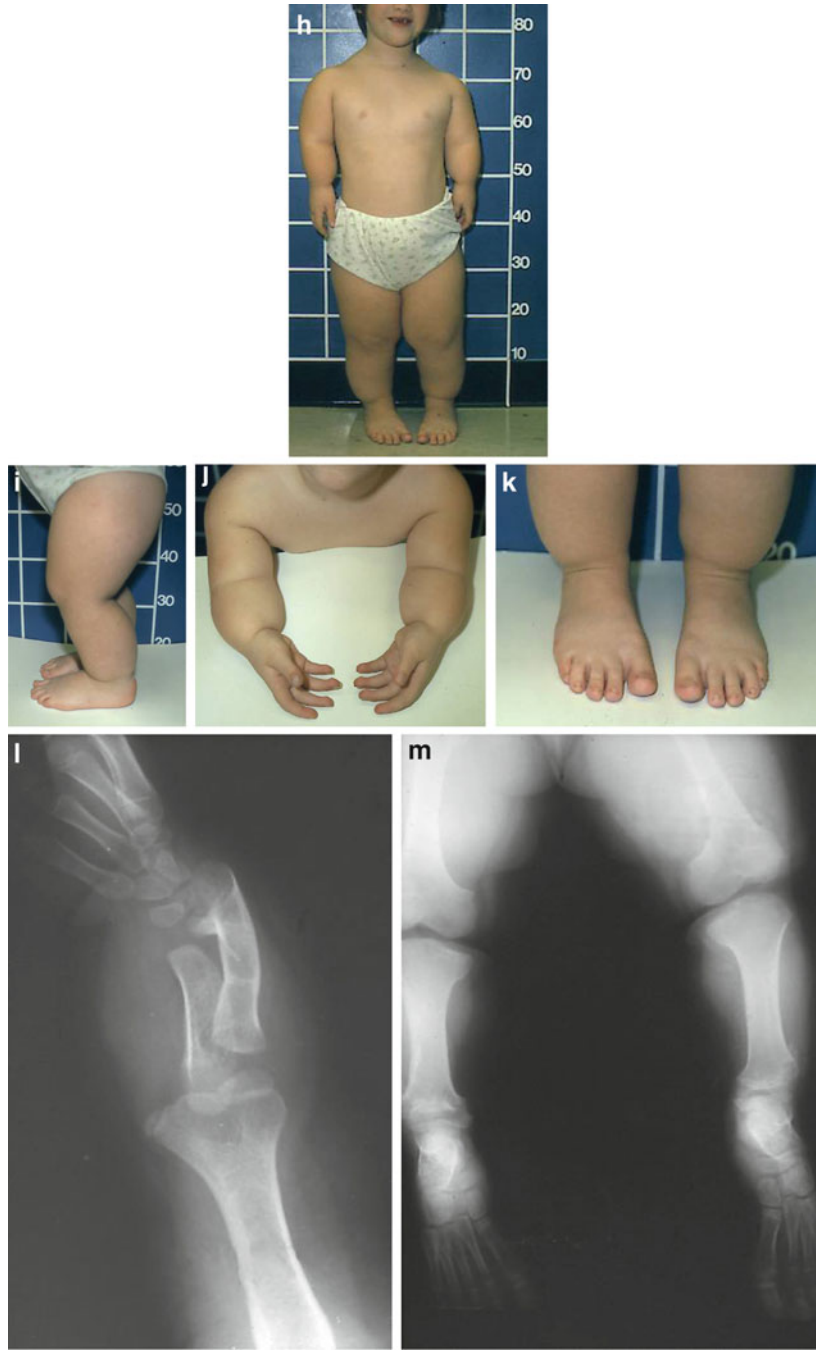

Fig. 7 Two sibs with Langer mesomelic dysplasia (**a**–**d**; **g**–**j**) showing severe mesomelic dwarfism, Madelung deformities, and radiographic features (**e, f**; **k**, **l**, **m**) of bowed and foreshortened radius and ulna, hypoplastic/aplastic fibula, and short and thick tibia. Both parents have dyschondrosteosis (Espiritu et al. 1975a, b)

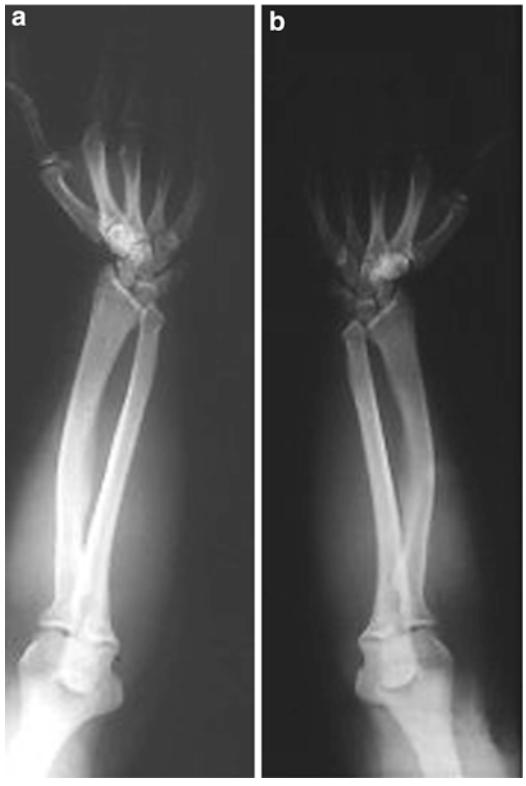

Fig. 8 (**a**, **b**) Radiograph of the mother of the above two children showing typical Madelung deformity

Dysmelia

Contents

Dysmelia is a widely accepted term used to define a group of malformations in which there is hypoplasia, and partial or total aplasia of the tubular bones of the extremities, ranging from isolated peripheral hypoplasia to complete loss of the extremity. The condition is commonly known as limb deficiency or limb reduction defect. The prevalence rate for all types of limb deficiency is 0.69 per 1,000 (McGuirk et al. 2001).

Synonyms and Related Disorders

Amelia; Congenital limb deficiency/reduction; Ectromelia (ectrodactyly); Phocomelia; Thalidomide embryopathy

Genetics/Basic Defects

1. Causes: heterogeneous
   1. Known syndromes
      1. Holt-Oram syndrome (please see the chapter of "Holt-Oram Syndrome")
      2. Fanconi anemia (please see the chapter of "Fanconi Anemia")
      3. Split hand and foot malformation (SHFM) (Gurrieri and Everman 2013)
         1. This rare condition: affects 1 in 8,500–25,000 newborns
         2. Extremely complex because of its variability in clinical presentation, irregularities in its inheritance pattern, and the heterogeneity of molecular genetic alterations
         3. Caused by duplications in the 10q24.3 region (Vergult et al. 2013)
      4. Nonsyndromal SHFM caused by a 10q24 microduplication containing *FBXW4* gene
      5. Syndromal SHFM (occurs with extra-limb manifestations)
         1. EEC syndrome (most common) (please see the chapter "► Ectrodactyly-Ectodermal Dysplasia-Clefting (EEC) Syndrome")
         2. Limb-mammary syndrome
         3. ADULT (Acro-Dermato-Ungual-Lacrimal-Tooth) syndrome
         4. Rapp-Hodgkin syndrome
         5. AEC (ankyloblepharon-ectodermal dysplasia-clefting) syndrome (also called Hay-Wells syndrome), EEM syndrome
         6. Acro-cardio-facial syndrome

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_73

7. Karsch-Neugebauer syndrome
6. Thrombocytopenia-absent radius (TAR) syndrome (please see the chapter of "Thrombocytopenia-Absent Radius Syndrome")

2. Chromosome abnormalities
3. Teratogens
   1. Thalidomide (Tseng et al. 1996; Radomsky and Levine 2001)
      1. Probably the most potent primate teratogen known
      2. Between one in every two to one in every ten fetuses exposed at the critical development period were affected (Newman 1986)
      3. A hypnosedative drug, introduced and marketed as Contergan in Germany in the 1950s
      4. Promoted as a safe sedative and was found to be useful as an antiemetic during pregnancy, resulting in its widespread use throughout Europe in late 1960
      5. Has been used in the past few decades in a variety of dermatologic conditions (e.g., erythema nodosum leprosum, prurigo nodularis, actinic prurigo, discoid lupus erythematosus, aphthous stomatitis, Behcet syndrome, and graft-versus-host disease)
      6. Side effects: teratogenicity and peripheral neuropathy
      7. Producing a symmetrical pattern of deficiency (or polydactyly) on the preaxial side of both arms and legs
   2. Misoprostol (prostaglandin E1 analog)
      1. Asymmetrical digit loss
      2. Constriction rings
      3. Syndactyly
4. Fetal constraint/in utero limb compression (Graham et al. 1980; Graham 1986)
   1. Ectopic tubal gestation
   2. Uterine structural anomalies
   3. A large uterine fibroid
   4. Early amnion rupture
5. Vascular disruption
   1. Early chorionic villous sampling
      1. The risk for transverse deficiencies, especially of the central digits in the hand, is increased with chorionic villus sampling, particularly when performed before 10 weeks of gestation (Brumback et al. 2000; golden et al. 2003)
      2. Unilateral upper limb reduction (Boyd et al. 1990)
      3. Symmetrical digit loss
      4. Constriction rings
      5. Syndactyly
   2. Dilation and curettage
   3. Exposure to ergotamine
   4. Trauma to the abdomen and placenta
   5. Intrauterine thrombosis causing intrauterine vascular deficiency of the upper limb (Armstrong and Page 1997)
      1. Emboli from closure of ductus arteriosus, placenta, umbilical arteries
      2. Prematurity
      3. Maternal diabetes (venous thrombosis)
      4. Dehydration
      5. Polycythemia
      6. Protein C, S, and antithrombin III deficiencies
      7. Sepsis
      8. Congenital heart disease
      9. Musculoelastic ridge within a vessel
   6. Fetal vascular occlusive disease (Hoyme et al. 1982)
      1. Occlusion of the brachial artery secondary to embolization from the placental vascular thrombi
      2. A massive thrombus occluding the brachial artery secondary to hypovolemia and hypoperfusion associated with fetal blood loss during placental abruption
6. Vascular abnormalities such as cavernous hemangioma at the site of limb deficiency (Hall 1992)

7. A candidate gene for radial ray deficiencies: detected in the 7p22.1 deletion including the *RAC1* gene (Vergult et al. 2013)
8. Duplications of *BHLHA9*: associated with ectrodactyly and tibia hemimelia inherited in non-Mendelian fashion (Klopocki et al. 2012)
9. Unknown causes

2. The pattern of malformation in dysmelia (Henkel and Willert 1969)
   1. A diminution of skeletal material
   2. Disturbance of maturation of remaining skeletal elements
   3. Relationship of the malformed extremities to each other
3. A diminution of skeletal material: common to all malformations of dysmelia
   1. Reduction tendencies of individual bones: The reduction of the skeletal material of the individual bone follows a certain direction and sequence:
      1. Thumb: The reduction tendency of the thumb directs from proximal to distal
         1. Hypoplastic tubular bones of the thumb and the first metacarpal in the mildest cases
         2. Reduction of skeletal material beginning at the base of the first metacarpal in the more severe cases
         3. The shaft of the thumb becomes aplastic with increasing severity
         4. The last remnant of the first metacarpal is its head, followed by defective proximal phalanx.
         5. Preservation of the terminal phalanx until, in total aplasia, all bones of the thumb disappear
      2. Big toe and first metatarsal: the reduction tendency same as the thumb
      3. Radius and tibia: The reduction tendency directs from distal to proximal:
         1. Hypoplasia: the mildest degree of malformation of the radius or the tibia
         2. A defect seen in the distal part of the metaphysis with increasing severity, extending in a proximal direction with more severe deformities
         3. The head disappears last, before the radius or tibia becomes totally aplastic.
      4. Humerus and femur: The reduction tendency directs from proximal to distal:
         1. Hypoplastic: the mildest cases of the axial form of ectromelia.
         2. A defect of bone at the proximal end (just distal to the head of the humerus or in the region of the neck and the trochanter in the femur) in more pronounced cases.
         3. Distal epiphysis represents the last part of the humerus or the femur until it disappears in total aplasia.
   2. Reduction tendency of the limb as a whole:
      1. Upper limb
         1. Mild manifestations of the deformity restricted to the radial ray of the hand.
         2. With increasing severity, the radius becomes involved and only after the radius is either completely absent or its remnants have fused with ulna is the humerus affected.
      2. Lower limb
         1. Impairment of the tibia and the tibial ray in mild cases.
         2. The tibia need not be totally absent and its remnants need not be fused before the femur shows signs of reduction.
         3. The isolated malformations of the femur have been observed without impairment of the distal part of the limb.
      3. Coincidental impairment of the shoulder and pelvic girdles with the reduction of the limb mass
         1. The degree of the impairment dependents on the severity of the humeral or femoral defect.
         2. Most pronounced in phocomelia and amelia.

4. Reduction of the hand and fingers
    1. Strictly dependent on the severity of the defect of the skeleton of the arm.
    2. A decrease in the number of remaining fingers as the defect of the skeleton of the arm increases.
    3. Radial hypoplasia: All fingers may be present; their number is reduced to four or even three in the axial types and very often to one in phocomelia.
    4. The reduction of the hand starting at the thumb and progressing from the radial to the ulnar side, so that with increasing severity of the arm deficiency, the index, middle, and ring fingers are absent.
5. Reduction of foot in dysmelia
    1. Reduction progresses from the tibial to the fibular rays.
    2. Isolated malformations of the tibial ray: extremely rare in dysmelia.

3. The axis of malformation in dysmelia:
    1. Combination of the humerus, radius, and radial ray of the hand in an axis of malformation within the skeleton of the upper extremity, sparing the ulnar.
    2. Same combination seen in the lower extremity, where the axis is formed by the femur, the tibia, and the tibial ray of the foot, sparing the fibula.
    3. In the short axial types, the ulna or the fibula is the only long bone of the extremity that still exists.
4. Fusion of the adjacent bones:
    1. The skeletal elements undergoing fusion: always hypoplastic or partially aplastic.
    2. Fusion occurring in parallel bones (carpals, tarsals, metacarpals, metatarsals, radius, and ulna) or in bones arranged longitudinally (phalanges, humerus, and ulna).
    3. Tendency toward synostosis in the lower extremity appears to be limited to the bones of the foot.

4. Disturbance of maturation of remaining skeletal elements
    1. Retardation of cartilage ossification in bones not directly involved in the defect.
    2. Ossification centers far away from the part directly involved tend to ossify in a delayed manner.
5. Relationship of the malformed extremities to each other
    1. Bilateral and symmetrical in manifestation in most cases of amelia.
    2. Presence of lower limbs is observed in most patients with dysmelia of the upper extremity, even if the arms are phocomelic or amelic.

Clinical Features

1. Classification of dysmelia (Henkel and Willert 1969)
    1. Ectromelia:
        1. Definition: used to include those dysmelia in which the radius and the tibia with their peripheral rays and the humerus or the femur are involved.
        2. Classification (Henkel and Willert 1969): There is a need to subdivide into the distal, axial, and proximal forms of ectromelia because there are differences in manifestation and severity of skeletal abnormality and in some cases synostosis occurs as well as reduction.
            1. Distal form of ectromelia
            2. Axial form of ectromelia
            3. Proximal form of ectromelia
    2. Phocomelia:
        1. Definitions
            1. Used to include those dysmelia in which no remnants of long bones are seen between the limb girdle and the peripheral part (hands and foot)
            2. Used to describe the congenital anomaly in which a limb is represented by a flipper-like appendage
        2. Classification (Frantz and O'Rahilly 1961)

1. Type I: complete phocomelia (hand or digits attached directly to trunk)
2. Type II: proximal phocomelia (forearm bones between hand and trunk)
3. Type III: distal phocomelia (hand attached directly to humerus)

3. Unclassifiable limbs (Tytherleigh-Strong and Hooper 2003)
1. Type A: an abnormal humerus with an abnormal single forearm bone
2. Type B: an abnormal humerus with an abnormal radius and ulna
3. Type C: an abnormal humerus fused to a forearm bone or bones

3. Amelia: used to include the most severe degree of dysmelia in which there is total loss of an extremity

2. Distal form of ectromelia
1. Confined to the distal part of the extremity
2. Involving the radial ray of the hand and the radius only
1. Thumb type: the mildest degree of dysmelia, affecting the first ray of the hand only with the following two different manifestations:
1. Triphalangism of the thumb
2. Hypoplasia of the thumb
2. Radial type: sparing the ulnar
1. Hypoplasia of the radius
2. Hypoplasia of the radius with radioulnar synostosis
3. Partial aplasia of the radius
4. Partial aplasia of the radius with radioulnar synostosis
5. Total aplasia of the radius

3. Involving the tibial ray of the foot and the tibia only
1. Big toe type
1. Triphalangism of the big toe
2. Duplication of the big toe
2. Tibial type: sparing the fibula
1. Hypoplasia of the tibia
2. Partial aplasia of the tibia
3. Total aplasia of the tibia

3. Axial form of ectromelia
1. Involvement of the distal as well as the proximal part of the limb
1. Involving the radius, the radial ray of the hand, and the humerus
1. Sparing the ulnar
2. The malformed radius: hypoplastic, partly aplastic, or totally aplastic
3. The remnants of the radius in partial aplasia: regularly fused with the ulna, presenting as radioulnar synostosis
2. Involving the tibia, the tibial ray of the foot, and the femur
1. Sparing the fibula
2. The remnant of the tibia not showing tendency toward synostosis

2. Radial longitudinal/ray deficiency (RLD) (Bauer et al. 2013)
1. Most often bilateral, although the extent of involvement is usually asymmetric
2. Severity: ranges from mild thumb hypoplasia to complete absence of the radius, radial carpus, and thumb
3. Selected syndromes with radial ray deficiencies (Wilcox et al. 2015)
1. Thrombocytopenia absent radius syndrome
2. Holt-Oram syndrome
3. Vertebral defects, anal atresia, cardiac malformations, tracheoesophageal fistula, esophageal atresia, renal anomalies, and limb anomalies (VACTERL) association
4. Fanconi anemia
5. Radial ray deficiency, X-linked
6. Radial aplasia, X-linked
7. Radial ray hypoplasia with choanal atresia
8. Radial aplasia with cleft lip/palate
9. Radial hypoplasia, triphalangeal thumbs, hypospadias, and maxillary distema
10. Trisomy 18
11. Others

3. Ulnar longitudinal deficiency (Bauer et al. 2013)
1. Occurs far less often than RLD, at a rate of about 1 in 25,000 live births.
2. A sporadic, noninherited condition.

3. Unlike RLD, it is not associated with systemic conditions, but it has a strong association with other musculoskeletal conditions.
    1. Proximal femoral focal deficiency
    2. Postaxial lower extremity deficiency (fibular deficiency)
    3. Congenital scoliosis
    4. Hand and finger differences
    5. Upper limb involvement: most commonly unilateral
    6. Entire involved limb: usually hypoplastic.
    7. Elbow is abnormal or fused in most cases
4. Tibial hemimelia (please see the chapter of "Tibial Hemimelia")
5. Fibular hemimelia (please see the chapter of "Fibular Hemimelia")
6. The different degrees of reduction of the humerus or the femur leading to the upper and lower limb types:
    1. Upper limb type
        1. Long axial type of the arm: hypoplasia or partial aplasia of the humerus with partial aplasia of the radius and radioulnar synostosis or with total aplasia of the radius
        2. Intermediate axial type of the arm: subtotal aplasia of the humerus with partial aplasia of the radius and radioulnar synostosis or with total aplasia of the radius
        3. Short axial type of the arm: total aplasia of the humerus with partial aplasia of the radius and radioulnar synostosis or with total aplasia of the radius
    2. Lower limb type
        1. Long axial type of the leg: hypoplasia or partial aplasia of the femur with partial or total aplasia of the tibia
        2. Intermediate axial type of the leg: subtotal aplasia of the femur with partial or total aplasia of the tibia
        3. Short axial type of the leg: total aplasia of the femur with partial or total aplasia of the tibia
    3. Lower limb deficiency associated with other organ system defects (Le and Scott-Wyard 2015)
        1. Tibial deficiency: deafness, ectrodactyly or polydactyly of the hands, craniofacial abnormalities
        2. Femoral hypoplasia-unusual facies syndrome (please see the chapter of "Femoral Hypoplasia: Unusual Facies Syndrome"): bilateral femoral deficiency, facial abnormalities including micrognathia and cleft palate, hypoplasia or synostosis of the upper extremity, vertebral abnormalities, congenital heart disease, and polydactyly
        3. Roberts or SC phocomelia syndrome (please see the chapter of "Roberts Syndrome"): bilateral symmetric tetraphocomelia, thumb aplasia, syndactyly, elbow and knee flexion contractures, mental retardation, cleft lip/palate, micrognathia, hypotelorism, cryptorchidism, and cardiac defects
        4. Sacral agenesis: hemipelvectomy or hip disarticulation and is often associated with neurogenic bowel and bladder
4. Proximal form of ectromelia
    1. Can be found only in the lower limb
    2. No parallel defect in the upper limb
    3. Only involves the proximal part of the lower limb, the femur (proximal focal femoral deficiency) (Bedoya et al. 2015), which can display all different degrees of reduction, leading to the following subtypes:
        1. Long proximal type: hypoplasia of the femur, coxa vara or partial aplasia of the femur without impairment of the distal part of the limb
        2. Intermediate proximal type: subtotal aplasia of the femur without impairment of the distal part of the limb
        3. Short proximal type: total aplasia of the femur without impairment of the distal part of the limb

5. Phocomelia
    1. Absent humerus, radius, and ulna or femur, tibia, and fibula
    2. Remainder of the extremity
        1. Consisting of a malformed hand formed by one, two, or three ulnar finger rays and ulnar parts of the carpus or of a similarly affected foot
        2. Directly attached to a hypoplastic shoulder girdle or to a misshapen pelvis
6. Amelia
    1. The most severe form of dysmelia
    2. Total absence of the arm or the leg
    3. Shoulder girdles: hypoplastic in the absence of the arms
    4. Pelvis: deformed in a box-like shape in the absence of the legs
7. Selected syndromes with multiple limb deficiencies (Wilcox et al. 2015)
    1. Acheiropody: hypoplasia/aplasia of the radius, ulna, tibia, fibula, and distal humerus and aplasia of hands and feet
    2. Acromesomelic dysplasia, Hunter-Thompson type: hypoplastic ulna, tibia, fibula, small fingers and toes
    3. Amelia, autosomal recessive
        1. All limbs absent
        2. May have defects in other organs
    4. Anonychia-onchodystrophy with hypoplasia or absence of distal phalanges (Cooks syndrome)
        1. Triphalangeal thumb, hypoplasia/aplasia of distal phalanges
        2. Nail dysplasia or anonychia
    5. Aprosencephaly
        1. Oligodactyly, radiohumeral fusion
        2. Brain and craniofacial malformations
    6. Brachial amelia, cleft lip, holoprosencephaly
        1. Upper limb amelia, femoral, fibular hypoplasia, oligodactyly
        2. Cleft lip, holoprosencephaly, omphalocele, congenital heart disease
    7. CHARGE syndrome
        1. Can have a variety of limb deficiencies
        2. Ocular coloboma, congenital heart disease, choanal atresia, retarded growth and development, genital anomalies, ear anomalies, and deafness
    8. Faciocardiomelic dysplasia
        1. Radial, ulnar, tibial, fibular, digital hypoplasia
        2. Micrognathia, macroglossia, microstomia, congenital heart disease
    9. Grebe dysplasia: radial, ulnar, tibial, fibular hypoplasia, small fingers and toes, polydactyly
    10. Hanhart syndrome (hypoglossia-hypodactylia)
        1. Variable hypoplasia/aplasia of any segment
        2. Hypoglossia, hypoplastic mandible
    11. Laryngeal atresia, encephalocele, limb deformities
        1. Radial, ulnar, tibial hypoplasia, oligodactyly
        2. Laryngeal atresia, encephalocele, renal anomalies
    12. Mesomelic dysplasia, Kantaputra type: ulna > radial, fibula > tibia hypoplasia
    13. Mesomelic dysplasia, Langer type
        1. Radial, ulnar, fibula > tibia hypoplasia
        2. Micrognathia
    14. Microgastria-limb reduction defects association
        1. Hypoplasia of the upper limb
        2. Microgastria, hypoplastic lungs, genitourinary anomalies
    15. Nievergelt mesomelic dysplasia: hypoplasia of the radius, ulna, tibia, fibula
    16. Orofacial digital syndrome type 10
        1. Radial and fibular hypoplasia, oligodactyly, preaxial polydactyly
        2. Dysmorphic facies, oral frenula
    17. Roberts syndrome (SC phocomelia)
        1. Humeral, radial, ulnar, femoral, tibial, fibular hypoplasia/aplasia; upper extremities more severely affected than lower; may have tetraphocomelia, oligosyndactyly
        2. Cleft lip/palate, congenital heart disease, microcephaly, intellectual disability
    18. Rodriguez acrofacial dysostosis
        1. Radial, ulnar, humeral, fibular hypoplasia/aplasia to phocomelia, oligodactyly

2. Micrognathia, microtia, brain, cardiac, and lung malformations
19. Skeletal defects, genital hypoplasia, mental retardation
    1. Hypoplasia of all segments, hypoplastic clavicle and scapula, oligodactyly
    2. Genital hypoplasia, microcephaly, dysmorphic facies, intellectual disability
20. Tetramelic monodactyly: only 5th digit present
21. Tukel syndrome
    1. Postaxial oligosyndactyly,
    2. Opthalmoplegia

8. Differential diagnosis (Tseng et al. 1996; Radomsky and Levine 2001)
    1. Transverse limb defects
        1. Adam-Oliver syndrome
        2. Amniotic band sequence
        3. Oromandibular limb hypogenesis syndrome
        4. Poland anomaly
        5. Fetuses with homozygous α-thalassemia (Lam et al. 1997)
    2. Preaxial limb defects
        1. Chromosome syndromes
        2. Facio-radial syndromes (e.g., Nager syndrome)
        3. Hemato-radial syndromes
            1. Aase syndrome
            2. Fanconi anemia
            3. TAR syndrome
        4. Holt-Oram syndrome
        5. Poland anomaly
        6. Roberts syndrome
        7. VATER association
    3. Central limb defects
        1. EEC syndrome
        2. Poland anomaly
    4. Postaxial limb defects
        1. Cornelia de Lange syndrome
        2. Facio-ulnar syndromes (e.g., Miller syndrome)
        3. Femur-fibula-ulna complex
        4. Ulnar mammary syndrome
    5. Amniotic band syndrome and other mechanical and constraint problems
        1. Digital constrictions and amputations
        2. Transverse amputations of the distal and proximal limbs, with a normal limb above the amputation
        3. Amelia
    6. Vascular compression, disruption thrombosis, embolization
        1. Transverse amputations
        2. Postaxial and preaxial limb reduction defect
        3. Femoral hypoplasia
        4. Digital amputation or hypoplasia
        5. Poland anomaly
    7. Genetic diseases
        1. Bilateral and unilateral limb reduction defect of preaxial or postaxial type
        2. Ectrodactyly (Nair et al. 2011)
            1. An autosomal dominant ectodermal dysplasia presenting as bilateral congenital malformed hands and feet.
            2. Affects about 1 in 90,000 births with males and females equally as likely to be affected.
            3. Characterized by transverse terminal aphalangia or partial to total absence of the distal segments of fingers.
            4. May involve one or more digits or the full hand and even part of the upper arm. More severe manifestations are hemimelia or amelia.
            5. All these abnormalities are considered to represent various degrees of severity of the same anomaly and may be due to an intrauterine vascular occlusion or insufficiency.
            6. These different forms are connected with a different genetic mutation.
            7. Ectrodactyly type I, the most frequent form, has been found to be a mutation on chromosome 7 in a region that contains two homeobox genes, *DLX5* and *DLX6*.
            8. Usually, this is characterized as the split hand/foot deformity due to the absence of the third digit, with clefting into the proximal portion of the hand or foot and syndactyly of

remaining digits on each side of the cleft. The hand resembles a lobster claw.
3. Monodactyly
4. Limb reduction defects as features of many different genetic disorders, such as absent radius with absence/hypoplasia of the thumb

8. Cytogenetic abnormalities (e.g., del(13q) syndrome and trisomy 18 syndrome) (Christianson and Nelson 1984)
1. Severe limb hypoplasia
2. Polydactyly
3. Absent thumb
4. Absent radius
5. Other multiple congenital anomalies

9. Thalidomide embryopathy (Mongeau et al. 1966; Newman 1986; Brent and Holmes 1988; Radomsky and Levine 2001)
1. Deformities of the upper and lower extremities: grossly symmetric, although opposite limbs are often unequally affected to some degree
1. Phocomelia
2. Amelia
3. Bone hypoplasia
4. Absence of bones
5. Paraxial hemimelia
6. Transverse hemimelia
7. Dyscheiria
8. Dyspodia
2. Malformed external ears
1. Anotia
2. Micropinna
3. Small or absent auditory canals
3. Abnormalities of the eyes
1. Anophthalmia
2. Microphthalmos
3. Coloboma
4. Cataracts
4. Face
1. Hypoplastic nasal bridge
2. Choanal atresia
3. Facial palsy
5. CNS malformations
1. Facial nerve paralysis
2. Deafness
3. Marcus Gunn or jaw-winking phenomenon
4. Crocodile-tear syndrome
5. Seizure disorder
6. Respiratory tract anomalies
1. Laryngeal and tracheal abnormalities
2. Abnormal lobulation of the lungs
7. Cardiovascular anomalies
1. Capillary hemangioma, extending from dorsum of the nose to the philtrum in the midline
2. Congenital heart diseases (conotruncal defects)
8. Gastrointestinal anomalies
1. Upper intestinal atresia
2. Congenital absence of the gall bladder and the appendix
3. Anal stenosis
4. Inguinal hernias
9. Renal anomalies
1. Abnormal rotation of the kidney
2. Pelvic position of the kidneys
3. Horseshoe kidney
4. Hydronephrosis
5. Double ureter
10. Genital anomalies
1. Double vagina
2. Vaginal atresia
3. Rectovaginal fistula
4. Cryptorchidism
11. Other malformations
1. Aglossia
2. Teratoma at the sacral region
3. Fissure of the mandible
12. Mortality: 40% at or shortly after birth

10. Warfarin and diphenylhydantoin
1. Digital hypoplasia
1. Usually mild
2. Can be severe
2. Limb hypoplasia due to chronic exposure throughout gestation, usually very mild

11. Maternal diabetes
1. Femoral hypoplasia
2. Sacral agenesis

Diagnostic Investigations

1. Radiography (Cobben et al. 1994)
    1. Evaluate limb defects
    2. Evaluate nonlimb skeletal defects
2. Diagnostic protocol for preaxial defects
    1. Blood count including thrombocytes
    2. Hb F (electrophoresis)
    3. Urine sediment
    4. Renal sonography
    5. Echocardiography
    6. Chromosome analysis
    7. Audiologic evaluation
    8. Ophthalmologic evaluation

Genetic Counseling

1. Recurrence risk (Cobben et al. 1994)
    1. Patient's sib
        1. Genetic syndromes: depending on the inheritance pattern of the disorder
        2. Chromosome abnormalities: about 1% unless the parent carries a translocation
        3. Environmental factors: not increased unless the mother exposes to the teratogen during pregnancy
        4. Nonsyndromic nonfamilial reduction defects of one limb
            1. Transversal: <1%
            2. Postaxial: <1%
            3. Preaxial: low
            4. Central: low
        5. Nonsyndromic nonfamilial reduction defects of more than one limb
            1. Transversal: probably low
            2. Postaxial: probably low
            3. Preaxial: unknown
            4. Central: unknown
    2. Patient's offspring
        1. Genetic syndromes: depending on the inheritance pattern of the disorder
        2. Chromosome abnormalities: patients usually not surviving to reproduction
        3. Environmental factors: not increased unless patient exposes to the same teratogen during pregnancy
        4. Nonsyndromic nonfamilial reduction defects of one limb
            1. Transversal: <1%
            2. Postaxial: <1%
            3. Preaxial: probably low
            4. Central: probably low
        5. Nonsyndromic nonfamilial reduction defects of more than one limb
            1. Transversal: possibly low
            2. Postaxial: possibly low
            3. Preaxial: unknown
            4. Central: autosomal dominant
2. Prenatal diagnosis
    1. Transvaginal sonography: an important element in the evaluation of any first trimester limb deficiencies
    2. Second trimester ultrasonography to detect limb deficiencies and other associated anomalies (Rijhsinghani et al. 1995; Piper et al. 2015)
    3. Chromosome analysis from amniocentesis or CVS to rule out chromosome anomaly
3. Management
    1. Avoid using teratogenic agents during pregnancy
    2. Management of malformation of the upper extremities
        1. Bilateral upper extremity: amelia and/or phocomelia
            1. Good prosthetic fitting of children based primarily on relating prosthetic function to the functional needs of the patient to be fitted
            2. Satisfactory foot function, a prerequisite to the prosthetic habilitation of the severe bilateral upper limb problem in children
            3. Compensatory prehension patterns developed by the feet, helpful particularly in total toilet care and total dressing and undressing
            4. The combination of the 3 prime functional patterns (self-feeding, toilet care, and total dressing and undressing), plus the acquired secondary functional patterns (writing, control of light switches, ability to open and close doors, ability to

operate radio and television, card-playing, etc.) produces a gratifying level of rehabilitation (Aitken 1964)

2. Upper extremity: paraxial hemimelica
   1. Passive stretching
   2. Application of splints to stabilize the wrists
3. Bilateral transverse hemimelia: fit with standard prostheses with hooks as terminal devices
4. Prosthetic treatment of upper limb deficiency: casting and fitting techniques applicable to transverse forearm loss with myoelectric hand prostheses (Curran and Hambrey 1991)

3. Management of malformation of the lower extremities
   1. Lower extremity bilateral phocomelia (Lamb et al. 1970)
      1. Fit with a special bucket on a pair of short skis to develop balance
      2. Prostheses (McLaurin swivel walker for children) to help walking
   2. A transverse lower limb deficiency: fits with conventional prosthesis (Hirons et al. 1991)
4. Occupational therapy: exercise and other treatment of the upper extremities to increase strength and dexterity to prepare to operate prostheses
5. Prosthetic training of the children
6. Parents' contribution
   1. Observation of the child's training session
   2. Parent to learn to:
      1. Put on and remove prostheses
      2. Care and encourage use of the prostheses
      3. Cleanse the stump
7. Prosthetic devices
   1. Every effort to be made to develop a prosthesis that will compensate for the absence of functions and restore independence to the greatest possible degree
   2. Main objectives
      1. To assist the child to develop a normal body image
      2. To construct a prosthesis based on sound anatomical principles which has an adequate range of motion
      3. To fit the prosthesis early so that, at a few months of age, the child unconsciously accepts it as a part of his body
8. Psychosocial counseling
   1. To assist parents to cope with the situation
   2. To explain the plan of treatment to parents
   3. Overall success of a given family in accepting and adjusting to a congenital deformity: related to its educational level and the usual pattern of behavior of its members under stress

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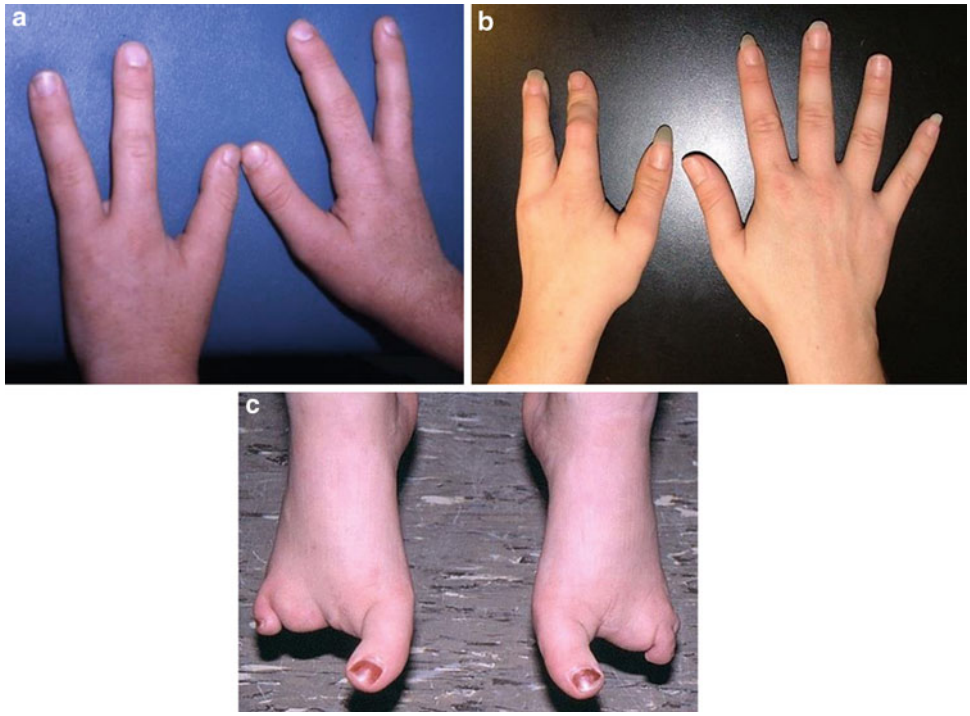

Fig. 1 Ectrodactyly of hands (**a**, **b**) and feet (**c**) in three patients showing symmetric and asymmetric anomalies

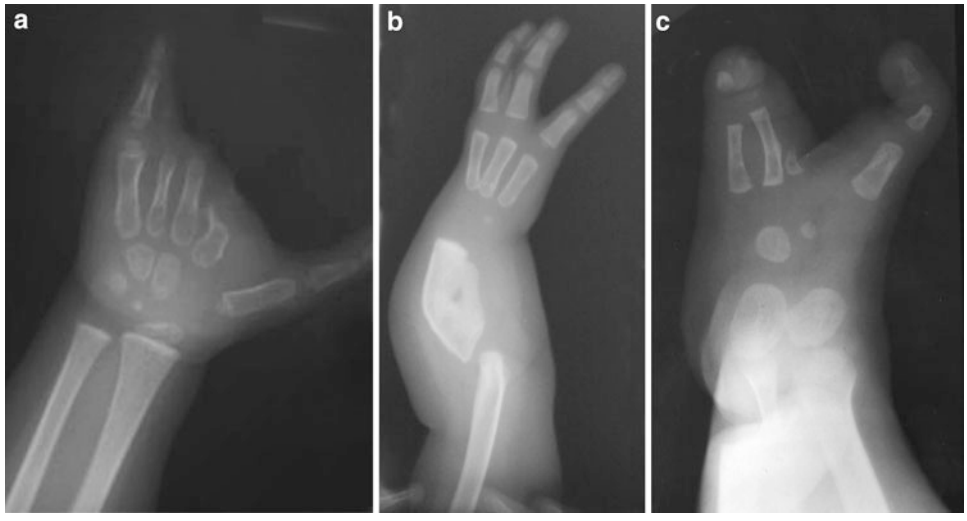

Fig. 2 Radiographs of ectrodactyly (two hands (**a**, **b**) and a foot (**c**)) in three patients showing different types of ectrodactyly

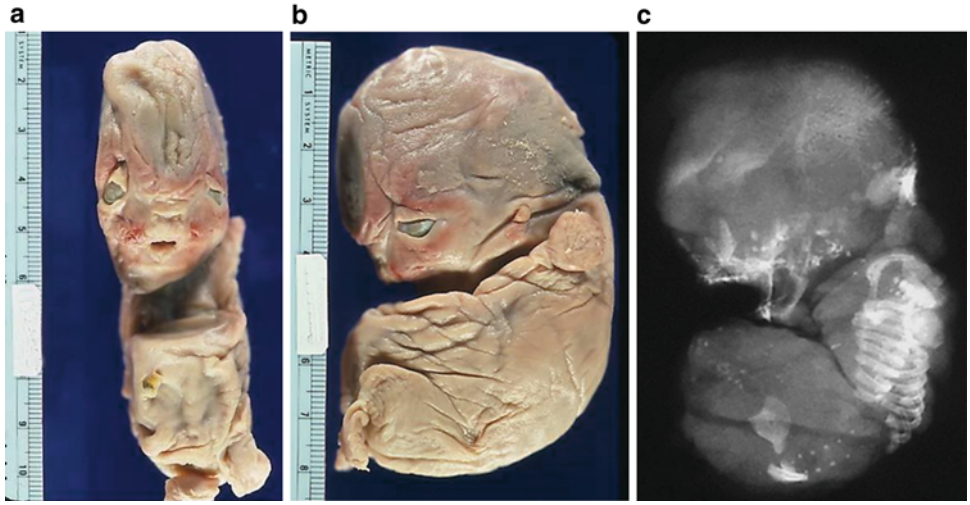

Fig. 3 An embryo with phocomelia showing deficient limbs (**a**, **b**), illustrated by radiograph (**c**)

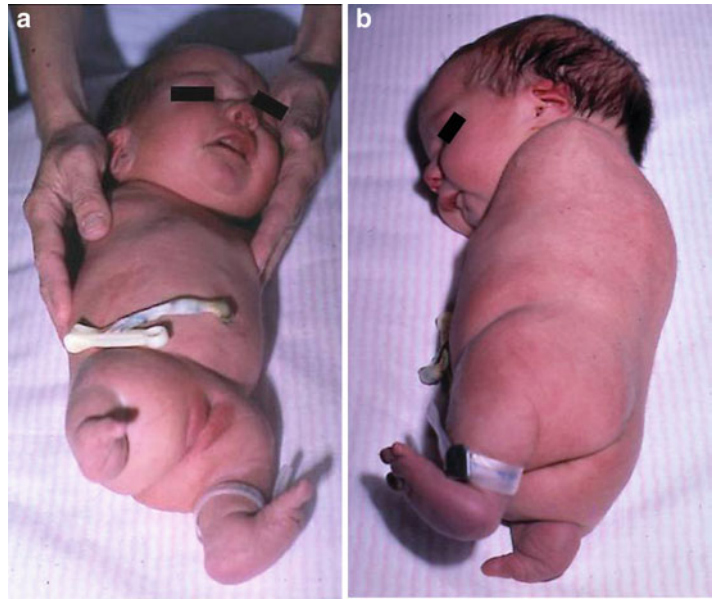

Fig. 4 (**a**, **b**) A neonate with amelia of the upper limbs and reduction malformations of the lower limbs

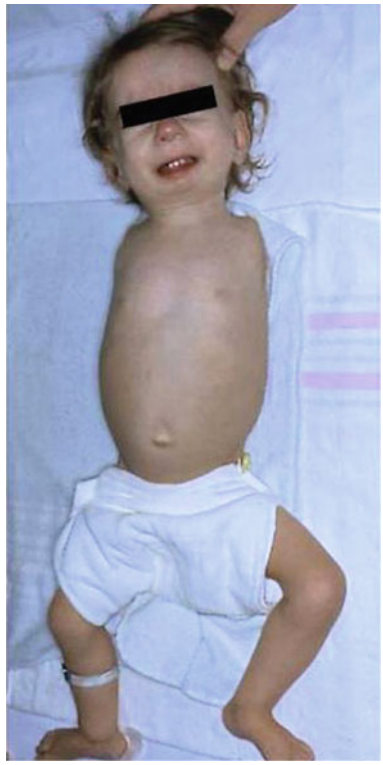

Fig. 5 A child with amelia showing complete absence of upper extremities

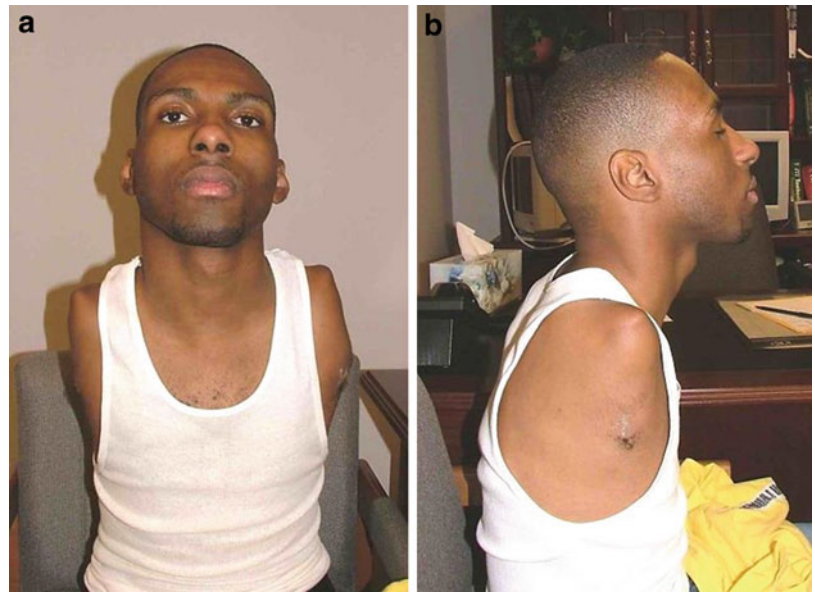

Fig. 6 (**a**, **b**) A patient with amelia of the upper extremities. He is intelligent, uses his chin and shoulder to write, and drives a car by using one foot to turn the driving wheel and one foot to pedal the accelerator and brake

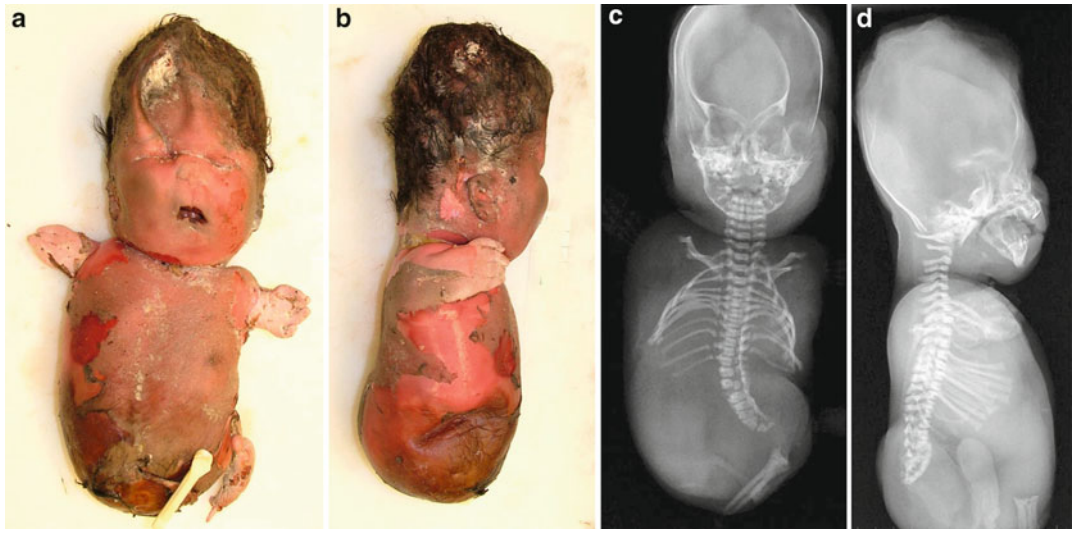

Fig. 7 (**a**–**d**) A macerated stillborn with phocomelia. Her upper extremities consist of hands attached to the shoulders with absence of the long bones. Her left lower extremity consists of a foot attached via thin twisted skin to the pelvic area with absence of the long bones. Right lower extremity was completely absent. There were severe dysplastic vertebrae, fusions of ribs, and absence of pelvic bones. In addition, the infant had blind vagina, absent right kidney, rudimentary left kidney, hypoplastic lungs, and microphthalmia

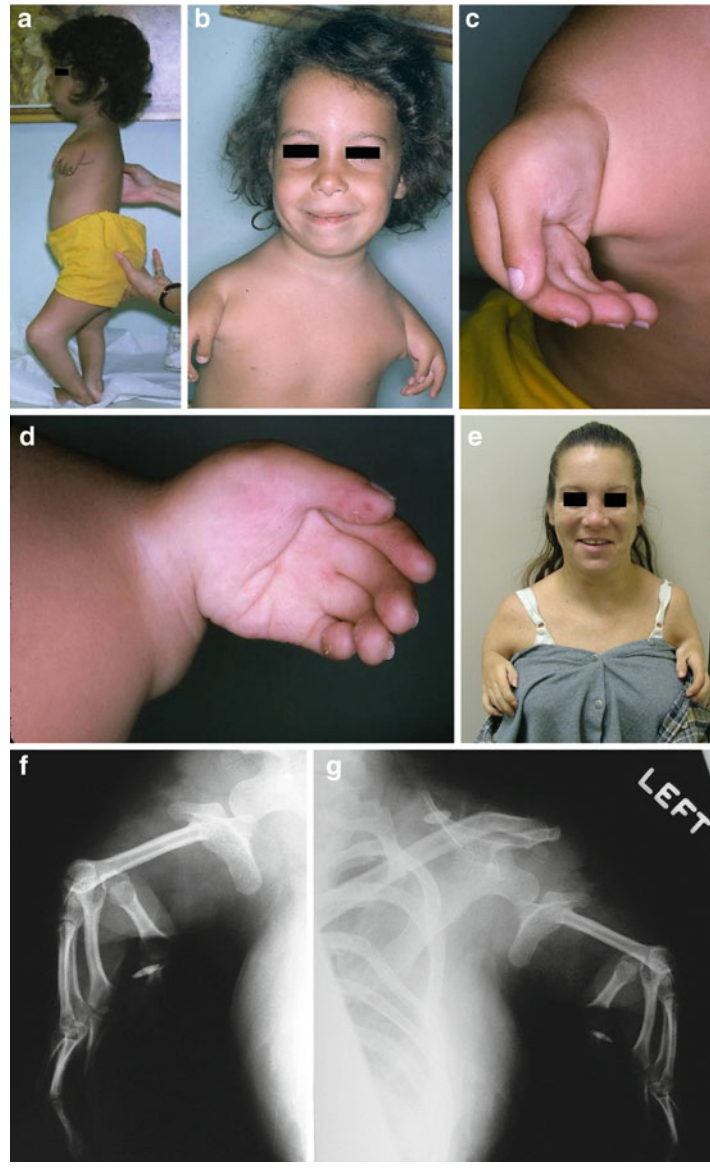

Fig. 8 (**a**–**g**) A girl and a lady with phocomelia showing flipper-like hands, illustrated by radiographs

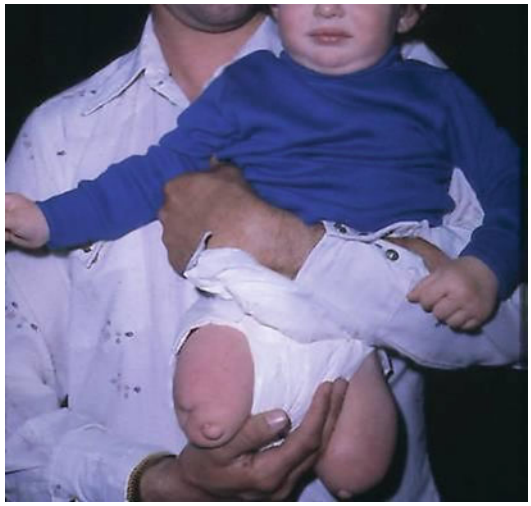

Fig. 9 An infant with transverse reduction of the lower extremities

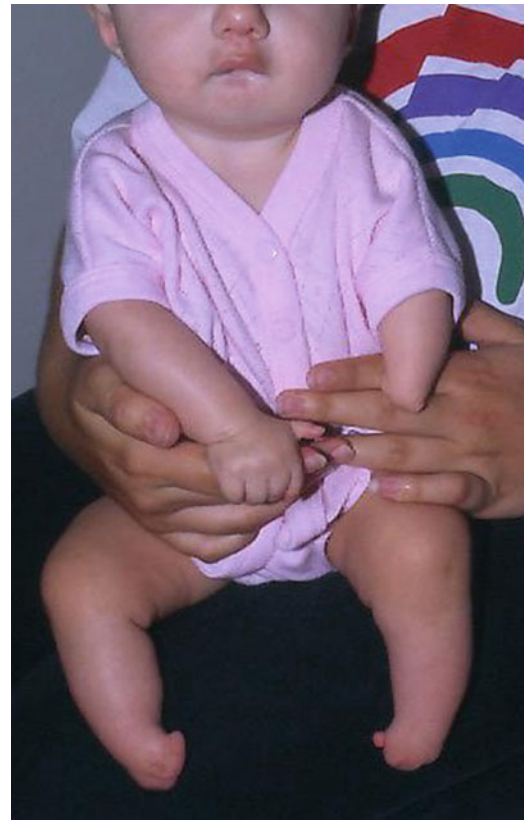

Fig. 10 An infant with unilateral transverse reduction of left upper extremities (intrauterine amputation), constriction ring of the left big toe, and syndactyly of the toes of both feet, secondary to amniotic band syndrome

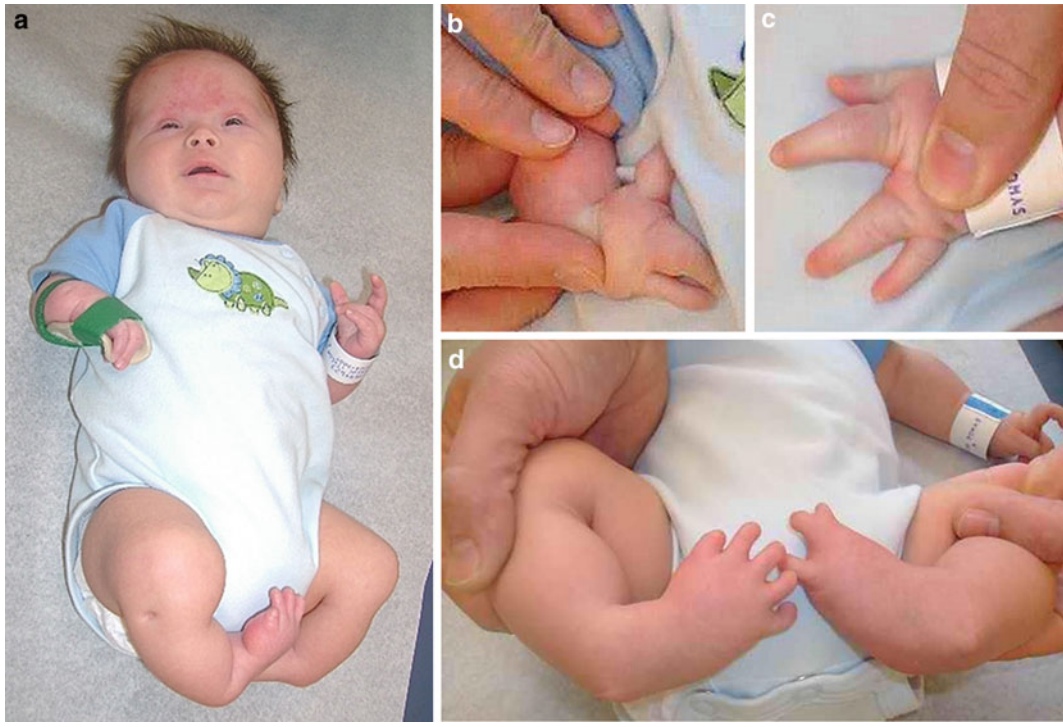

Fig. 11 (**a**–**d**) An infant with reduction malformations of both upper and lower extremities

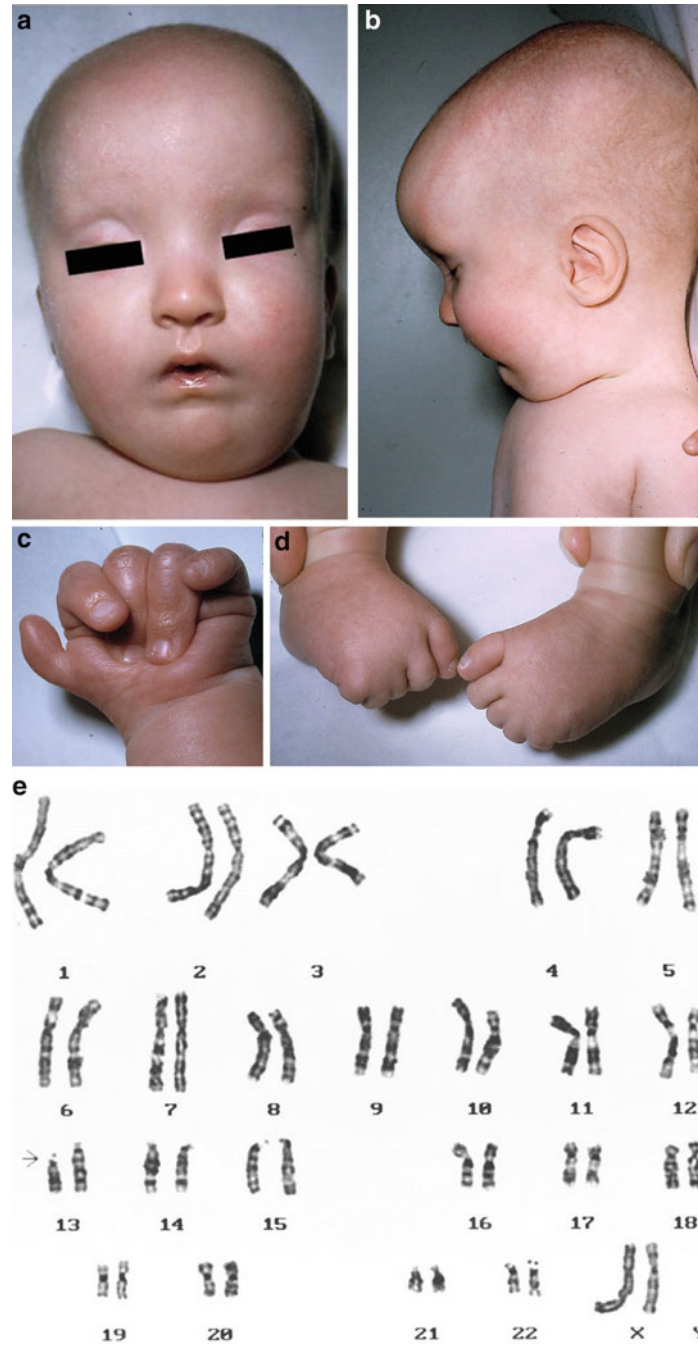

Fig. 12 (**a**–**e**) A neonate with del(13q) syndrome showing hypoplastic thumbs, syndactyly of toes, in addition to multiple congenital anomalies. The karyotype shows the deletion of 13q

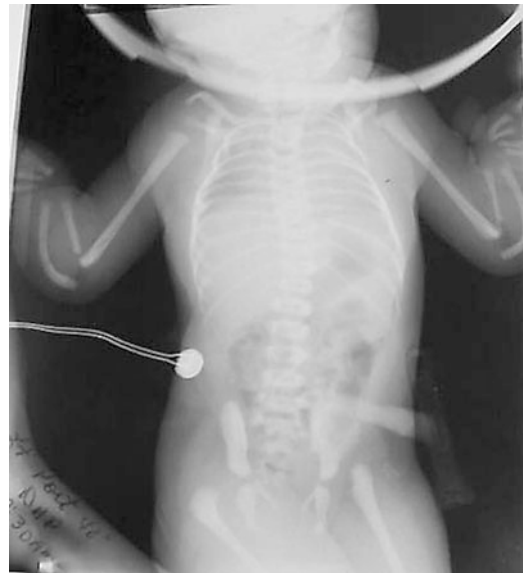

Fig. 13 Radiograph of another neonate with del(13q) syndrome showing limb reduction anomalies of the upper extremities

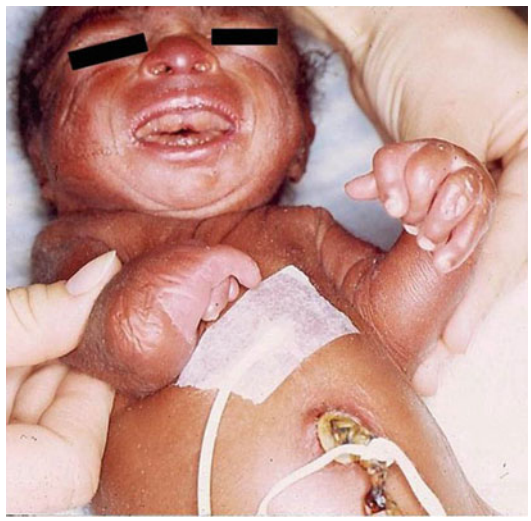

Fig. 14 A neonate with trisomy 18 syndrome showing limb reduction defects of the upper extremities in addition to multiple congenital anomalies

Dysplasia Epiphysealis Hemimelica

Contents

Dysplasia epiphysealis hemimelica (DEH) is a rare osteocartilaginous overgrowth involving one or multiple epiphyses or ossification centers, usually in the lower extremity on one side of the body. In 1926, Mouchet and Belot (1926) described a condition called tarsomegaly, which Trevor, later in 1950 (Trevor 1950), called tarso-epiphyseal aclasis. As the tarsal bones are not the only bones involved, Fairbank in 1956 (Fairbank 1956) used the term dysplasia epiphysealis hemimelica. The term reflects the characteristic hemimelica involvement and typically affects either the medial or the lateral side of the epiphysis, with the medial side affected twice as frequently (Lang and Aztiuz 1997; Kuo et al. 1998; Araujo et al. 2006; Mann et al. 2010). The condition has been referred to as Trevor disease.

Synonyms and Related Disorders

Trevor disease

Genetics/Basic Defects

1. Inheritance
   1. Most cases: sporadic
   2. Autosomal dominant inheritance in rare familial DEH
      1. Epiphyseal osteochondromas with autosomal dominant inheritance and multiple parosteal bone proliferations (DEH) (Fahmy and Pandey 2008)
      2. Dominant carpotarsal osteochondromatosis (DEH)
      3. In a family with seven affected members (Maroteaux et al. 1993)
      4. A single family with seven members affected by different combinations of dysplasia epiphysealis hemimelica, intracapsular chondroma, extraskeletal osteochondroma, and typical osteochondroma (Hensinga et al. 1974)
   3. Male-to-female ratio, 3:1
2. Etiology and pathogenesis
   1. Etiology unknown (Grogan 2015)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. A congenital disorder becoming clinically evident in the course of the development of the epiphyses
3. Basic pathologic process: an abnormal proliferation of cartilage in an epiphysis, similar to osteochondroma

Clinical Features

1. Most frequent presentation: ages 2–14 years (birth to 63 years of age) (Gerscovich and Greenspan 1989)
2. Chief clinical signs
    1. Massive ossification of the hypertrophic cartilaginous areas, and the involved joints undergo rapid degenerative changes (arthrosis) (Bernard et al. 1984)
    2. Unilateral asymmetric bony hard swelling on the extremities: variable severity (Carlson and Wilkinson 1979; Wiedemann et al. 1981)
    3. Cartilage overgrowth: usually found to be limited to one extremity and to half of the affected epiphysis (Kettelkamp et al. 1966)
    4. Rare bilateral lesions reported (Merzoug et al. 2002)
    5. Angular deformity
    6. Usually on the inner or outer aspect of the knee and/or ankle
    7. Regional muscle wasting
    8. Occasional recurrent locking of the joint
    9. With or without pain
    10. With or without restriction of motion
    11. Slow progression
3. Apparent deformity
    1. Varus or valgus deformity depending on the site of involvement
    2. Genu valgum or varum depending on the site of involvement
    3. Flexion contracture
    4. Pes planus
    5. Pes equinus
4. Sites of involvement
    1. Lower extremities, more commonly affected than the upper extremities
        1. Four most common locations of involvement (Rosero et al. 2007)
            1. Talus-calcaneus (22%)
            2. Distal tibia-fibula (22%)
            3. Proximal tibia (11%)
        2. Proximal tibial epiphysis
        3. Tarsal navicular
        4. First cuneiform
        5. Middle and lateral cuneiforms
        6. Metatarsals
        7. Phalanges
    2. Upper extremities: very uncommon involvement (Azouz et al. 1984; Vanhoenacker et al. 1999; Takagi et al. 2000; Rosero et al. 2007)
        1. Carpal bones
            1. Scaphoid
            2. Lunate
            3. Capitate
            4. Hamate
            5. Trapezium
            6. Trapezoid
        2. Metacarpals
        3. Phalanges
        4. Proximal radius
        5. Proximal and distal ulna
        6. Proximal and distal humerus
        7. Glenoid cavity
        8. Coracoid process of the scapula
        9. Extremely rare DEH of the elbow presenting with a symptomatic ulnar nerve compression (Maalouf et al. 2011)
    3. Pelvis
        1. Acetabulum
        2. Pubic bone
        3. Iliac bone
5. Affected limb
    1. May be longer than the unaffected one due to:
        1. The enlargement of several ossification centers
        2. Increased diaphyseal length
    2. May be shorter due to focal early closure of the epiphyseal plate

6. Quiescent following epiphyseal plate fusion
7. Prognosis
    1. Relatively benign condition
    2. Complications do occur (Aydin 2014)
        1. Angular deformity may recur because of the epiphyseal disturbance (Keret et al. 1992)
        2. Loose bodies may be present in the joint: present with acute onset of symptoms such as locking and swelling of patients with DEH (Wheeldon and Altiok 2015)
        3. A fixed deformity may persist
        4. The limb lengths could be different
        5. May develop an early degenerative osteoarthritis due to the joint irregularity
    3. Malignant degeneration has not been reported
8. Classification based on degrees of involvement (Azouz et al. 1985)
    1. Localized form
        1. Usually affecting the bones of the hindfoot or ankle
        2. Also may affect an epiphysis
    2. Classical form
        1. Characteristic hemimelic distribution seen in more than one area in a single lower extremity (two-thirds of the reported cases), particularly:
            1. Talus
            2. Distal femoral epiphyses
            3. Distal tibial epiphyses
        2. Lesion localized to the ankle and foot, called Mouchet and Belot type
    3. Generalized or severe form
        1. Involving a whole lower extremity from the pelvis to the foot or ankle
        2. Involving femoral head, symphysis pubis, or triradiate cartilage of the acetabulum
9. Differential diagnosis with other osteocartilaginous lesions (Douira-Khomsi et al. 2011)
    1. Synovial chondromatosis
    2. Capsular or para-articular chondroma
    3. Myositis ossificans
    4. Tumoral calcinosis
    5. Particularly osteochondroma

Diagnostic Investigations

1. Radiography (Gerscovich and Greenspan 1989; Silverman 1989; Schmidt and Lomasney 1994)
    1. Skeletal survey to look for sites of involvement
    2. Earliest radiographic sign
        1. Appearance of secondary centers of ossification adjacent to an epiphysis
        2. Slow enlargement of these centers eventually merging with each other and then with the epiphysis
    3. Asymmetric hemimelic distribution of overgrowth of one side of epiphysis with irregular contour and ossification
        1. Generally only half or part (either the medial or lateral half) of an epiphysis or ossification center affected
        2. Rarely involving the entire epiphysis
    4. Overgrowth of adjacent bones
    5. Adjacent (probably secondary) metaphyseal and growth plate involvement
        1. Exhibiting widening and streak-like metaphysis (as in Ollier disease)
        2. Spur formation (as in osteochondroma)
    6. Mature lesions showing enlargement of one side of an epiphysis, simulating as osteochondromatous mass or enlargement of one side of an ossification center
    7. Epiphysis irregularly calcified and ossified
    8. Joints usually deformed
    9. Advanced bone age in unaffected epiphyses
    10. Less common findings
        1. Loose bodies in affected joints
        2. Osteochondral fractures
    11. Bilateral involvement extremely rare
2. CT of the lesions
    1. Improving diagnostic accuracy in the growing skeleton
    2. Demonstration of the anatomic relationship of the involved structures
    3. Visualization of the soft tissues, bones, and tumorous mass
    4. Evaluation of the condition of the articular surfaces

3. MRI imaging (Keret et al. 1992; Azouz 1996; Iwasawa et al. 1996; Peduto et al. 1999)
    1. To identify a definite plane of separation between the pathologic osteochondromatous mass and the normal epiphysis
    2. To accurately identify bony and cartilaginous structural abnormalities in multiple planes noninvasively without ionizing radiation
    3. To identify secondary changes in menisci, tendons, ligaments, and muscles
    4. Epiphyseal mass of the knee mostly showed the same signal intensity as normal cartilage but contained low-signal spots corresponding to calcified foci. The cartilaginous cap was depicted as a mottled area of high intensity on a T2-weighted image (Iwasawa et al. 1996)
4. Histopathology
    1. Osteocartilaginous exostosis (with cartilaginous cap) (Kettelkamp et al. 1966) arising from an epiphysis, apophysis, or round bone (Oates)
    2. Nests of cartilage cells showing active proliferation during growth of the lesions
    3. Diminishing amount and activity of the cartilage as the lesions mature
    4. Increased size of lesions in adults showing areas of actively proliferating cartilage
    5. Infrequently with an area of necrosis, presumably caused by inadequate nutrition
    6. Histological findings (Bahk et al. 2010)
        1. Identical to those of osteochondromas
        2. Presence of caps of disorganized hyaline cartilage
        3. Endochondral ossification of varying degrees underlying the caps

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased unless in rare autosomal dominant familial cases
    2. Patient's offspring: not increased unless in rare autosomal dominant familial cases
2. Prenatal diagnosis has not been reported

3. Management
    1. Observation in asymptomatic cases; no cases of malignant transformation has been reported (Kuo et al. 1998)
    2. Dysplasia epiphysealis hemimelica with a painless intra-articular mass should not be excised unless the mass interferes with the joint motion (Luevitoonvechkij et al. 2012)
    3. Surgical excision of the mass or corrective osteotomy generally recommended for the following lesions:
        1. Causing disabling pain
        2. Interfering function
        3. Increasing deformity of the involved joint
    4. Simple excision indicated if the cartilaginous overgrowth is not in the weight-bearing articular surface
    5. Extraarticular osteotomy indicated for correction of varus/valgus deformities if the arthrogram shows the smooth joint surface
    6. Anticipate recurrence of the angular deformity after the corrective osteotomy if the growth plate at the affected joint is open and active

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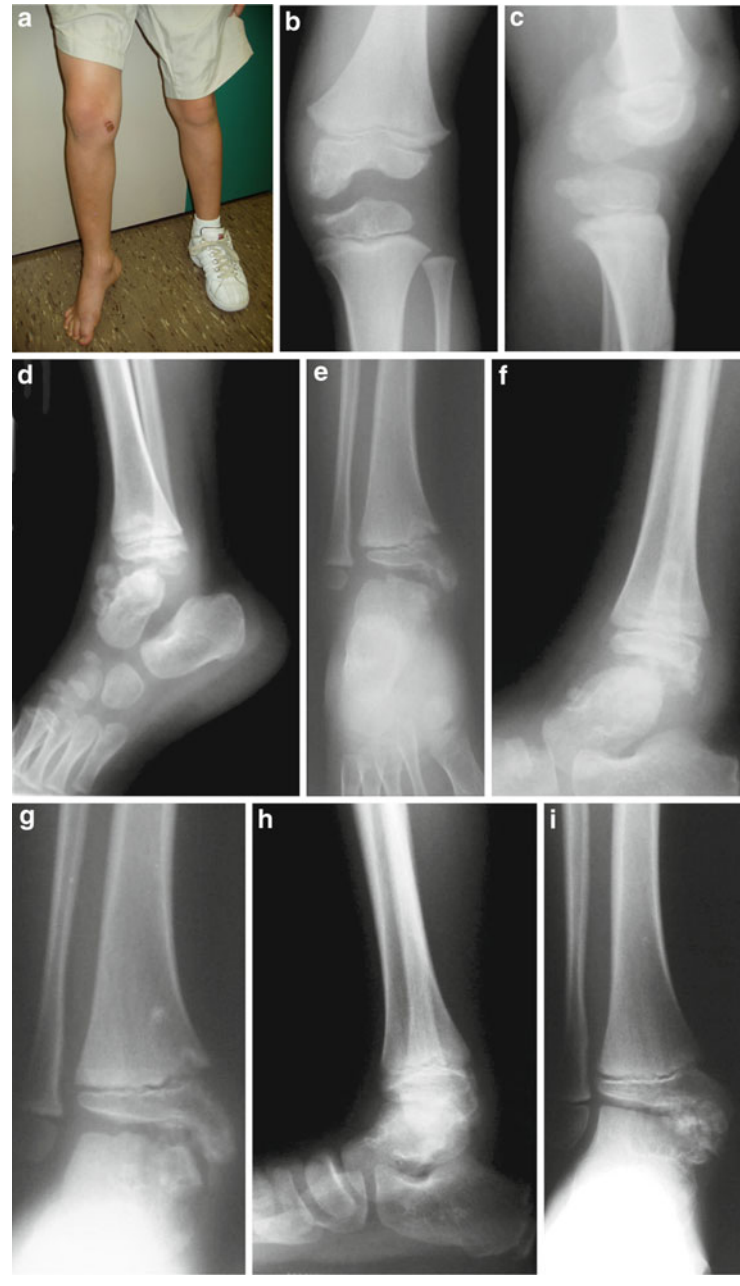

Fig. 1 (**a**–**i**) A 9-year-old boy with dysplasia epiphysealis hemimelica showing hard swellings on the inner sides of the knees and the ankle of the right lower extremities (**a**). The knee radiographs at 9 years of age (**b**, **c**) show the secondary ossification center merged with the medial side of the epiphyses of the distal femur and that of the proximal tibia. The radiographs of ankles at 4 (**d**, **e**), 5 (**f**, **g**), and 9 years (**h**, **i**) of age show irregularly calcified mass extending from medial malleolus of the distal tibia and involvement of the talus. The patient had bony protuberance of the right knee and right ankle without pain or restriction of motion. The age of onset was about 2 years

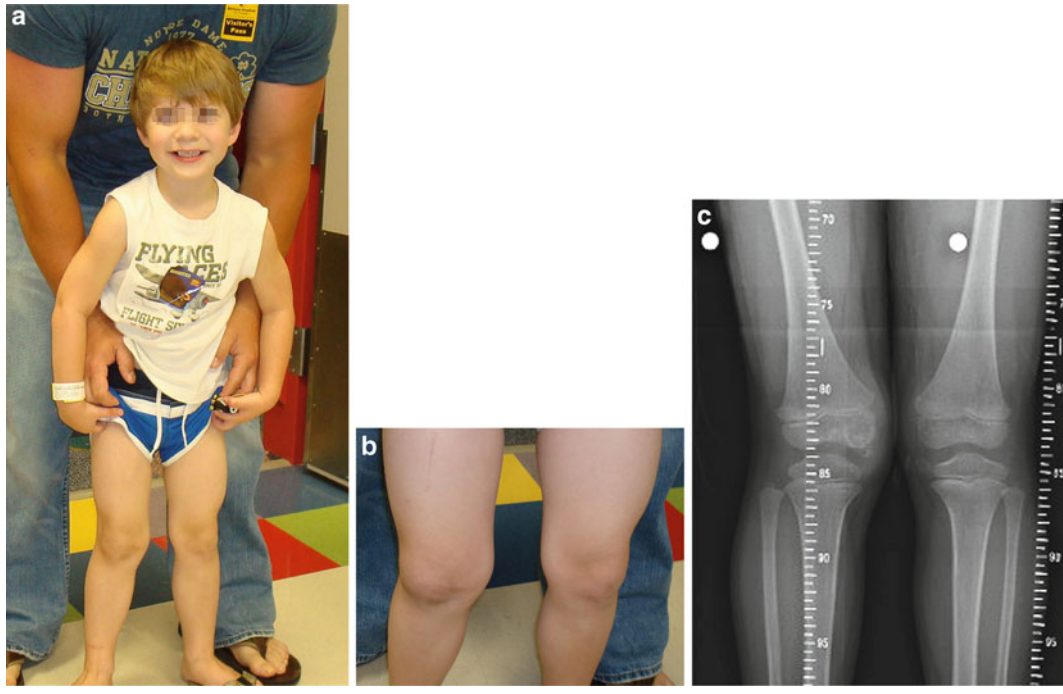

Fig. 2 (**a**–**c**). A 5-year-old boy (**a**) was seen because of swollen right knee with complaint of knee pain and limping. Note the swelling of the medial aspect of the right knee (**b**). The knee radiograph (**c**) shows second ossification center merged with the medial aspect of the epiphysis of the right distal femur

Dystonia

Contents

Dystonia is characterized by sustained, nonsuppressible contractions of agonist and antagonist muscles, resulting in twisting and repetitive movements that typically lead to abnormal postures (Fahn et al. 1998; Friedman and Standaert 2001; Brűggermann and Klein 2010).

Synonyms and Related Disorders

Dystonia (types 1–19); dystonia plus; heredodegenerative dystonia; paroxysmal dystonia; primary (idiopathic) dystonia; secondary dystonia

Genetics/Basic Defects

1. Genetically defined forms of the primary dystonias and dystonia-plus syndromes (Brűggermann and Klein 2010)
    1. Monogenic forms of dystonia have been assigned the acronym DYT according to the gene or gene locus involved
    2. This assortment of clinical rather than heterogeneous dystonias and dyskinesias is represented by a current list of 20 DYTs, in which monogenic forms of dystonia are included in chronological order based on the first appearance in the literature
    3. Although this listing of DYTs can serve as an orientation, it does not represent a logical classification in the strict sense of the word Rather, the monogenic forms can be pragmatically grouped as:
        1. Pure dystonias
            1. Part of the primary forms and thought to occur in the absence of neuropathologic changes
            2. Considered mainly to alter the function of neuronal basal ganglia circuits
        2. Dystonia-plus syndromes: characterized by additional neurologic manifestations, such as parkinsonism and myoclonus (Albanese et al. 2006)
        3. Paroxysmal dyskinesias: typically manifest episodically; dystonia usually is only one of several movement disorders present, and there are no interictal neurologic abnormalities

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. At least 25 different types of dystonia can be distinguished genetically as follows (Müller et al. 1998; Németh 2002; Bhidayasiri 2006; Brűggermann and Klein 2010; Morgante and Klein 2013; Lohmann and Klein 2013; Balint and Bhatia 2014; Klein et al. 2014; Skogseid 2014; Xiao et al. 2014):
    1. Dystonia type 1 (early-onset generalized primary torsion dystonia, Oppenheim dystonia)
        1. Autosomal dominant inheritance with reduced penetrance of about 30–40%
        2. Locus/gene: DYT1/*TOR1A* on chromosome 9q34 (Ozelius et al. 1989)
        3. Mutations
            1. GAG deletion in the *DYT1* gene resulting in loss of glutamic acid residues in the C-terminus of a novel ATP-binding protein, torsin A
            2. 18-base pair deletion resulting in loss of six amino acids (F323-Y328del) in a novel ATP-binding protein, torsin A
    2. Dystonia 2 (autosomal recessive torsion dystonia)
        1. Autosomal recessive inheritance
        2. Locus: *DYT2* (chromosome map unknown)
    3. Dystonia 3 (X-linked dystonia parkinsonism)
        1. X-linked recessive inheritance
        2. Locus/gene: *DYT3*/*TAF1* on chromosome Xq13.1
    4. Dystonia 4 (whispering dysphonia)
        1. Autosomal dominant inheritance
        2. Locus/gene: *DYT4*/*TUBB4A* on chromosome 19 (Hersheson et al. 2013; Lohmann et al. 2013)
    5. Dystonia 5 (dopa-responsive dystonia parkinsonism)
        1. Common autosomal dominant inheritance
            1. Locus/gene: *CYT5a*/*GCH1* (GTP cyclohydrolase 1) on chromosome 14q22.1-q22.2
            2. Caused by mutation in the *guanosine triphosphate cyclohydrolase I* gene, *GCH1*
        2. Rare autosomal recessive form (Segawa syndrome)
            1. Associated with mutations in the tyrosine hydroxylase gene, *TH*
            2. Locus/gene: *DYT5b*/*TH* on chromosome11p15.5
    6. Dystonia 6 (adolescent-onset torsion dystonia of mixed type)
        1. Autosomal dominant inheritance
        2. Locus/gene: *DYT6*/*THAP1* on chromosome 8p21-p22
    7. Dystonia 7 (adult-onset focal torsion dystonia)
        1. Autosomal dominant inheritance
        2. Locus: DYT7 on chromosome 18p
    8. Dystonia 8 (paroxysmal nonkinesigenic dyskinesia)
        1. Autosomal dominant inheritance
        2. Locus/gene: *DYT8*/*MR-1* on chromosome 2q33-q35
    9. Dystonia 9 (paroxysmal choreoathetosis with episodic ataxia and spasticity)
        1. Autosomal dominant inheritance
        2. Locus: *DYT9* on chromosome 1p21-p13.3
    10. Dystonia 10 (paroxysmal kinesigenic choreoathetosis)
        1. Locus/gene: *DYT10*/*PRRT2* on chromosome 16p11.2-q12.1
        2. Autosomal dominant inheritance
    11. Dystonia 11 (myoclonus-dystonia)
        1. Autosomal dominant inheritance
        2. Locus/gene: *DYST11*/*SGCE* on chromosome 7q21
        3. Caused by mutations in the ε-sarcoglycan gene in most families
    12. Dystonia 12 (rapid-onset dystonia parkinsonism)
        1. Autosomal dominant inheritance
        2. Locus/gene: *DYT12*/*ATP1A3* on chromosome 19q13
    13. Dystonia 13 (multifocal/segmental dystonia)
        1. Autosomal dominant inheritance
        2. Locus: *DYT13* on chromosome 1p36.13-36.32 (Valente et al. 2001)
    14. Dystonia 14: recently redefined as *DYT5*

15. Dystonia 15 (myoclonus-dystonia)
    1. Autosomal dominant inheritance
    2. Locus: *DYT15* on chromosome 18p11
16. Dystonia 16 (young-onset dystonia parkinsonism)
    1. Autosomal recessive inheritance
    2. Locus/gene: *DYT16*/*PRKRA* on chromosome 2p
17. Dystonia 17 (autosomal recessive primary torsion dystonia)
    1. Autosomal recessive inheritance
    2. Locus: *DYT17* on chromosome 20pq
18. Dystonia 18 (paroxysmal exertion-induced dyskinesia 2)
    1. Autosomal dominant inheritance
    2. Locus/gene: *DYT18*/*SLC2A1* on chromosome 1p
19. Dystonia 19 (episodic kinesigenic dyskinesia 2)
    1. Autosomal dominant inheritance
    2. Locus: *DYT19* on chromosome 16q
20. Dystonia 20 (paroxysmal nonkinesigenic dyskinesia 2)
    1. Autosomal dominant inheritance
    2. Locus: *DYT20* on chromosome 2q
21. Dystonia 21 (late-onset pure dystonia)
    1. Autosomal dominant inheritance
    2. Locus: *DYT21* on chromosome 2q14.3-q21.3
22. Dystonia 22 (undescribed form of dystonia)
23. Dystonia 23 (adult-onset cranial-cervical dystonia)
    1. Autosomal dominant inheritance
    2. Locus/gene: *DYT23*/*CIZ1* on chromosome 9q
24. Dystonia 24 (adult-onset cranial-cervical dystonia)
    1. Autosomal dominant inheritance
    2. Locus/gene: *DYT24*/*ANO3* on chromosome 11p
25. Dystonia 25 (adult-onset cranial-cervical dystonia)
    1. Autosomal dominant inheritance
    2. Locus/gene: *DYT25*/*GNAL* on chromosome 18p

3. Secondary dystonia (Schlaggar and Mink 2003)
    1. Association with a number of disorders
        1. Hepatolenticular degeneration (Wilson disease)
            1. Dystonia in over a third of the patients
            2. Associated with lesions in the putamen in 80% of cases
        2. Hallervorden-Spatz disease (pantothenate kinase-associated neurodegeneration)
        3. Huntington chorea
        4. Lesch-Nyhan disease
        5. Metachromatic leukodystrophy
        6. Methylmalonic acidemia
        7. Mitochondrial disorders
        8. Ceroid lipofuscinosis
        9. Gangliosidoses
        10. Glutaric aciduria
        11. Ataxia telangiectasia
        12. Niemann-Pick disease type C
        13. Early-onset parkinsonism
        14. Corticobasal degeneration
        15. Certain forms of spinocerebellar ataxia
            1. Spinocerebellar ataxia 3 (Machado-Joseph disease): The severity of the dystonic symptoms is related to the length of the trinucleotide repeat
            2. Spinocerebellar ataxia 17 (caused by mutations in the thymine-adenine-thymine-adenine binding protein: Dystonia may be the presenting sign of the disorder)
        16. Other inherited disorders (Cloud and Jinnah 2010)
    2. Other causes
        1. Psychogenic
        2. Vascular lesions such as carotid occlusive disease and hemorrhagic stroke
        3. Anoxic brain injury (cerebral anoxia/hypoxia): a well-known cause of secondary dystonia
        4. Acute disseminated encephalomyelitis
        5. Trauma
            1. Head trauma: Dystonia is among the most common movement disorders following severe head injury
            2. Peripheral trauma causing segmental dystonia.

6. Both acute and chronic use of dopamine blocking medications and other medications
    1. Haloperidol
    2. Resperidol
    3. Fluphenazine
    4. Thioridazine
    5. Chlorpromazine
    6. Metoclopramide
    7. Phenytoin
    8. Stonatrioran
7. Other acquired and sporadic causes (Cloud and Jinnah 2010)

4. Pathophysiology: a new interpretive hypothesis involving multiple levels of the nervous system
    1. Spinal cord: increased spinal motor neuron excitability in patients with generalized dystonia due to reduced presynaptic inhibition and compromised supraspinal inhibition systems
    2. Basal ganglia: disturbed pattern of basal ganglia output neurons
    3. Thalamus: disorganization of input–output properties and hyperactivity in thalamic neurons in two dystonic cynomolgus monkeys
    4. Somatosensory system: increased temporal discrimination thresholds for tactile stimuli
    5. Sensorimotor integration and motor cortical function
        1. Abnormal somatotopic arrangement of sensorimotor interaction
        2. Abnormal functioning of cortico-subcortical loops causing abnormalities of both intracortical inhibition and cortical excitability
5. Dystonia with unknown etiology

Clinical Features

1. Dystonia describes a symptom that may be part of many disorders with a variety of causes
    1. An abnormal sustained posture that is often writhing or twisting in quality
    2. Can be rapid or slow
    3. Often painful
2. Tremor (a rhythmic and involuntary movement of any body part): a phenotypic motor feature in dystonia (Defazio et al. 2015)
3. Classifications of dystonia
    1. Classification based on distribution of dystonia
        1. Primary/generalized dystonia
            1. Occurs in childhood
            2. Often begins focally in the legs and progresses to a generalized symptom involving the entire body
        2. Focal dystonia
            1. May occur at any age
            2. Typically starts in adulthood
            3. Affects an isolated body area, such as the hand and arm (writer's cramp), neck (cervical dystonia, previously known as spasmodic torticollis), vocal/laryngeal apparatus (dystonic adductor dysphonia or whispering dysphonia), mouth (oromandibular dystonia, musician's cramp), or eyelids (blepharospasm)
            4. Multifocal dystonia (two or more noncontiguous parts affected)
        3. Segmental dystonia
            1. May occur at any age
            2. Typically starts in adulthood
            3. Involves only the right or left side of the body
            4. Cranial (two or more parts of cranial and neck musculature affected)
            5. Axial (neck and trunk affected)
            6. Brachial (one arm and axial, both arms, with or without neck, with or without trunk)
            7. Crural (one leg and trunk, both legs, with or without trunk)
        4. Hemidystonia: affects the ipsilateral arm and leg
        5. Secondary dystonia
            1. Can be generalized, focal, or segmental
            2. Induced by a disease or ingested substance
            3. Can occur at any time
            4. Treated by identifying the underlying medical disorder or substance

2. Classification based on age of onset of dystonia
    1. Early-onset dystonia
        1. Often starts in a limb
        2. Tends to generalize and frequently has a genetic origin
    2. Adult-onset dystonia
        1. Usually spares the lower extremities
        2. Frequently involves cervical or cranial muscles
        3. A tendency to remain focal
        4. Sporadic in most cases
4. Classification of dystonia based on three axes (Albanese et al. 2006; Bhidayasiri 2006)
    1. By cause (etiology)
        1. Primary (or idiopathic): Dystonia is the only clinical sign, and there is no identifiable exogenous cause or other inherited or degenerative disease (autosomal dominant) (e.g., early-onset limb dystonia (*DYT1*), mixed dystonias (*DYT6*, *DYT3*), and late-onset craniocervical dystonia (*DYT7*))
        2. Secondary dystonia
            1. Dystonia plus: Dystonia is a prominent sign but is associated with another movement disorder. There is no evidence of neurodegeneration. (e.g., dopa-responsive dystonia, rapid-onset dystonia parkinsonism, myoclonus-dystonia (*DYT11*))
            2. Heredo-degenerative: Dystonia is a prominent sign, among other neurological features (autosomal dominant, e.g., Huntington disease, spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy; autosomal recessive, e.g., Wilson disease, GM1 and GM2 gangliosidosis, metachromatic leukodystrophy, homocystinuria; X-linked, e.g., X-linked dystonia parkinsonism/lubag)
            3. Paroxysmal: Dystonia occurs in brief episodes with normalcy in between. These disorders are classified as idiopathic (often familial although sporadic cases also occur) and symptomatic due to a variety of causes. Three main forms are known depending on the triggering factor. In paroxysmal kinesigenic dyskinesia (PKD, *DYT9*), attacks are induced by sudden movement, in paroxysmal exercise-induced dystonia (PED) by exercise such as walking or swimming, and in the nonkinesigenic form (PNKD, *DYT8*) by alcohol, coffee, tea, etc. A complicated familial form with PNKD and spasticity (*DYT10*) has also been described
            4. Acquired causes: Dystonia is a symptom of an identified neurological condition, such as a focal brain lesion and exposure to drugs or chemicals (e.g., drug-induced tardive dystonia, dystonia due to stroke, a brain tumor, AV malformations, or demyelination, intracranial *vs.* peripheral trauma, off-period dystonia in Parkinson's disease)
            5. Unknown etiology: Parkinson's disease, corticobasal degeneration, multiple system atrophy, and progressive supranuclear palsy
    2. By age at onset
        1. Early onset (variably defined as £20–30 years): usually starts in a leg or arm and frequently progresses to involve other limbs and the trunk
        2. Late onset: usually starts in the neck (including the larynx), the cranial muscles, or the one arm. Tends to remain localized with restricted progression to adjacent muscles
    3. By distribution
        1. Focal: single body region (e.g., writer's cramp, blepharospasm)
        2. Segmental: contiguous body regions (e.g., cranial and cervical, cervical and upper limb)
        3. Multifocal: noncontiguous body regions (e.g., upper and lower limb, cranial and upper limb)
        4. Generalized: both legs and at least one other body region (usually one or both arms)

5. Hemidystonia: half of the body (usually secondary to a structural lesion in the contralateral basal ganglia)

5. Clinical characteristic in genetically defined forms of dystonia and dystonia-plus syndromes (Klein et al. 1999; Brűggermann and Klein 2010)
   1. Dystonia type 1 (early-onset generalized primary torsion dystonia)
      1. Early-onset torsion dystonia (onset usually childhood)
      2. May present as focal, usually in the limbs
      3. Often generalizes to other body parts as the disease progresses
   2. Dystonia type 2 (autosomal recessive torsion dystonia)
      1. Early onset
      2. Generalized or segmental torsion dystonia
   3. Dystonia type 3 (X-linked dystonia parkinsonism, "lubag") meaning "twist," a local dialect in the island of Panay in the Philippines)
      1. Only described in individuals from the Philippines
      2. Usually males
      3. Onset usually adulthood
      4. Usually generalized dystonia
      5. Parkinsonism (50% of cases) unresponsive to L-dopa
      6. Progressive neurodegenerative syndrome
   4. Dystonia type 4 (whispering dysphonia)
      1. Described in a single large Australian family
      2. Laryngeal and cervical dystonia
      3. Age of onset: 13–37 years
   5. Dystonia type 5 (dopa-responsive dystonia parkinsonism)
      1. Childhood onset of dystonia
      2. Onset of dystonia in a limb, typically a leg, resulting in gait disturbance
      3. Gradual progression to generalized dystonia (usually more pronounced in the legs)
      4. Dystonia with concurrent or subsequent parkinsonism
      5. Diurnal worsening of symptoms
         1. Aggravation of symptoms toward the evening
         2. Alleviation of symptoms in the morning after sleep
      6. A variety of atypical presentations
         1. Generalized hypotonia
         2. Proximal weakness
         3. Gait disturbance
         4. "Atypical cerebral palsy"
      7. A dramatic response to L-dopa
   6. Dystonia type 6 (adolescent-onset torsion dystonia of mixed type)
      1. Described in two Mennonite families
      2. Adolescent onset
      3. Mostly segmental torsion dystonia
      4. Focal or generalized (rare)
      5. Cranial, cervical, or limb dystonia
   7. Dystonia type 7 (adult-onset focal torsion dystonia)
      1. Described in a single German family
      2. Adult-onset focal dystonia
      3. Torticollis
      4. Writer's cramp
      5. Spasmodic dysphonia
      6. Blepharospasm
   8. Dystonia type 8 (paroxysmal dystonic choreoathetosis)
      1. Variable age of onset (early childhood, adolescence, or early adulthood)
      2. Attacks of dystonia/choreoathetosis
      3. Precipitated by stress, hunger, fatigue, alcohol, caffeine, nicotine, and chocolate
   9. Dystonia type 9 (paroxysmal choreoathetosis with episodic ataxia and spasticity)
      1. Age of onset: 2–15 years
      2. Attacks of dystonia, paresthesias, and double vision
      3. Precipitated by exercise, fatigue, stress, and alcohol
      4. Spastic paraplegia between attacks
   10. Dystonia type 10 (paroxysmal kinesigenic choreoathetosis)
      1. Attacks of dystonia/choreoathetosis
      2. Precipitated by sudden unexpected movements
      3. Respond to anticonvulsant therapy

11. Dystonia type 11 (myoclonus-dystonia)
    1. Onset usually in the first or second decade of life
    2. Rapid, jerk-like movements
    3. Responsive to alcohol
    4. Combined with variable degrees of dystonia
12. Dystonia type 12 (rapid-onset dystonia parkinsonism)
    1. Acute or subacute onset (develop over hours or weeks) of generalized dystonia
    2. In combination with parkinsonism
13. Dystonia type 13 (multifocal/segmental dystonia)
    1. Described in a single Italian family
    2. Juvenile or early adult onset of segmental dystonia
    3. With prominent cranial-cervical and upper limb involvement
    4. Some focal dystonia and some generalized dystonia
14. Dystonia type 15 (myoclonus-dystonia)
    1. Described in a single Canadian family
    2. Characterized by jerky movements of the upper limbs, hands, and axial muscles
    3. Myoclonus dystonia and limb dystonia: alcohol responsive
15. Dystonia type 16 (dystonia Parkinsonism)
    1. Recessively inherited form of early-onset generalized dystonia associated with a homozygous missense mutation in the *PRKRA* gene (Camargos et al. 2008)
    2. Described in three Brazilian families, sharing the same P222L mutation, inherited from a common founder
    3. Clinical features
        1. Prominent bulbar involvement with dysphonia, dysarthria, and even dysphagia
        2. Parkinsonism: a less prominent feature (Klein 2008)
16. Dystonia type 17 (recessive torsion dystonia)
    1. Three sisters from Lebanese family suffering from recessively inherited primary focal torsion dystonia with onset in adolescence
    2. Site of onset: cervical with progression to segmental in two sisters and generalized dystonia in one
    3. Prominent features
        1. Dystonia: not levodopa responsive in this family
        2. Dysarthria
17. Dystonia type 18 (paroxysmal exertion-induced dyskinesia 2)
    1. The attacks: combination of chorea, athetosis, and dystonia in excessively exercised body regions
    2. Legs: most frequently affected
    3. Other features
        1. Epilepsy
        2. Hemolytic anemia
        3. Migraine
    4. A ketogenic diet: an effective therapeutic regimen
    5. Closely resembles DYT type 9 (paroxysmal choreoathetosis with episodic ataxia and spasticity): remains to be seen whether DYT type 18 and DYT type 9 are the same condition
18. Dystonia type 19 (episodic kinesigenic dyskinesia 2): A second form of paroxysmal kinesigenic dyskinesia was designated DYT type 19
19. Dystonia type 20 (paroxysmal nonkinesigenic dyskinesia 2)
    1. A second form of paroxysmal nonkinesigenic dyskinesia was described in a single Canadian family
    2. Clinical features similar to those of DYT8 dystonia/dyskinesia

6. Important clinical "red flags" leading to correct diagnosis of a specific genetic form before molecular testing (Brűggermann and Klein 2010)
    1. Diurnal variation of symptoms and response to levodopa in DRD (DYT5)
    2. Prominent orobulbar and speech involvement (DYT6)
    3. A combination of dystonia with myoclonus, ameliorated by alcohol intake in myoclonus-dystonia (DYT11), and abrupt

onset of severe dystonia and parkinsonism in RDP (DYT12)
4. An inherited dystonia also should be considered in the case of an early onset and when a certain ethnic background and positive family history are present (e.g., a high prevalence of DYT1 dystonia in Ashkenazi Jews and of DYT3 X-linked dystonia parkinsonism [XDP, "lubag"] in Filipinos)
5. Notably, the presence of a heritable condition may be masked by a small number of family members, nonpaternity, or adoption
6. Similarly, reduced penetrance, variable expressivity, and de novo mutations are potential reasons for a "pseudo"-negative family history
7. With the exception of five rare forms (DYT2, DYT3, DYT5b, DYT16, and DYT17), all monogenic dystonias follow an autosomal dominant pattern of transmission with reduced penetrance

Diagnostic Investigations

1. Electromyography shows a simultaneous contraction of both agonist and antagonist muscles
2. MRI of the brain (Cloud and Jinnah 2010)
    1. Warranted for all ages
    2. Can identify a causal structural defect
    3. Can provide clues to some degenerative disorders in adults and specific treatable developmental or metabolic disorders in younger individuals, such as Wilson disease, glutaric aciduria, and biotin-responsive basal ganglia disease
3. Dopa-responsive dystonia
    1. GTPCH1-deficient dopa-responsive dystonia
        1. Decreased concentration of both total biopterin (BP) and neopterin (NP) in cerebrospinal fluid in patients with GTPCH1 deficiencies
        2. Phenylalanine loading test to detect a subclinical defect in phenylalanine metabolism
        3. DNA mutation analysis to detect *GCH1* mutation
    2. TH-deficient dopa-responsive dystonia
        1. Normal BP and NP and reduced-3-methoxy-4-hydroxy-phenylethyle-neglycol in CSF
        2. DNA mutation analysis to detect *TH* mutation
4. Mutational screening has become available on a commercial basis for most of the known dystonia-causing genes
    1. For 10 of the 20 DYT loci (DYT1, DYT3, DYT5a, DYT5b, DYT6, DYT8, DYT11, DYT12, DYT16, and DYT18), genes have been identified (Brűggermann and Klein 2010)
    2. Current guidelines for genetic testing and counseling are based on criteria established by the European Federation of Neurological Societies that were revised in 2009
        1. Molecular testing for the GAG deletion in the *DYT1* gene is recommended in patients with limb-onset generalized dystonia and symptom onset before the age of 26 years, regardless of family history
        2. Comprehensive mutational analysis for GCH1 mutations, including gene dosage studies, is recommended in patients with early-onset generalized dystonia and clear symptom relief following levodopa therapy, irrespective of family history
        3. Mutational screening for *SGCE* mutations is recommended only in cases with the typical combination of dystonia and myoclonus and a suggestive family history
        4. RDP and tyrosine hydroxylase (TH)-associated DRD (DYT5b) are exceedingly rare. XDP (DYT3) is restricted to a specific population. Therefore, no general recommendations have been proposed for these forms (Harbo et al. 2009)
        5. Diagnostic DYT1 testing in conjunction with genetic counseling is recommended for patients with primary torsion dystonia with onset before age 26 years, as this single criterion detected 100% of clinically ascertained carriers (Bressman et al. 2000)

3. Molecular studies of dystonia (Fuchs and Ozelius 2013): A combination of next-generation and traditional Sanger sequencing has expanded the phenotypic spectrum associated with some of the dystonia plus (*ATP1A3*) and paroxysmal (*PRRT2*) loci

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive inheritance: 25%
        2. Autosomal dominant inheritance: not increased unless one of the parent carries a mutant allele in which case, there is a 50% risk of having an affected sib
        3. X-linked recessive inheritance; 50% of male sib will be affected given the mother is a carrier
        4. Secondary dystonias: risk depending on the etiology
        5. If one of the parents has a GCH1 pathogenic variant, each sib has a 50% chance of inheriting the mutant allele at conception. Because of gender-related incomplete penetrance, a sib who inherits a GCH1 pathogenic variant may be asymptomatic (Furukawa 2015)
        6. If neither parent has a GCH1 pathogenic variant, the risk to the sibs of the proband is usually very low (Furukawa 2015)
    2. Patient's offspring
        1. Autosomal recessive inheritance: not increased (all offspring are carriers) unless the spouse is also a carrier in which case, there is a 50% risk of having an affected offspring
        2. Autosomal dominant inheritance: 50%
        3. X-linked recessive inheritance: None of the sons will be affected; all of the daughters will be carriers
        4. Secondary dystonias: risk depending on the etiology
2. Prenatal diagnosis is possible for some forms of dystonia by DNA analysis of the fetal blood obtained from amniocentesis of CVS provided the disease-causing allele(s) of an affected family member have been identified
3. Management (Goetz and Horn 2001; Klein and Ozelius 2002; Cloud and Jinnah 2010)
    1. Treatment of childhood dystonia (Delnooz and van de Warrenburg 2012; Bertucco and Sanger 2014)
        1. Begins with proper diagnosis and classification
        2. An appropriate search for underlying etiology
        3. An assessment of the associated functional impairment
        4. Must be tailored to the individual needs of the patient
        5. Physical therapy and occupational therapy can be useful in many patients.
        6. Augmented feedback enhances motor learning and is effectively used in rehabilitation
        7. Noninvasive neurostimulation techniques: transcranial direct current stimulation and transcranial magnetic stimulation
        8. Deep brain stimulation
        9. Botulinum neurotoxin: currently the mainstay of treatment for focal and segmental dystonia (cervical dystonia, blepharospasm, oromandibular dystonia, focal hand dystonia, spasmodic dystonia)
        10. Oral drug therapy
            1. Anticholinergic agents: trihexyphenidyl
            2. GABA-mimetic agents: baclofen and clonazepam
            3. Dopamine-altering agents: levodopa
        11. Oral medications and deep brain stimulation: the mainstays of therapy for generalized dystonia
    2. Generalized idiopathic dystonia
        1. Medical therapy
            1. Anticholinergic agents (trihexyphenidyl): first choice (a moderate response in about 40-50% of dystonia patients)
            2. Benzodiazepines (diazepam, clonazepam)

    3. Dopamine depletors (tetrabenazine)
    4. γ-Aminobutyric acidergics (baclofen)
    5. Atypical neuroleptics (clozapine, olanzapine)
  2. Intrathecal baclofen infusion
  3. Ablative therapies, reserved for patients in whom medical therapies fail
    1. Pallidotomy
    2. Thalamotomy
3. Dopa-responsive dystonia
  1. A dramatic response to small dosages of levodopa (100 mg a day) (confirms the diagnosis)
  2. Maintenance with low-dose levodopa for life may improve from severe inability to completely normal function
4. Focal dystonias
  1. Unresponsive to systemic drug treatment in most case
  2. Frequently well controlled by periodic botulinum toxin (BTX) injections into the muscles directly involved in the dystonia (Bhidayasiri 2006)
  3. Try with intrathecal baclofen and surgery if oral medications fail
5. Cervical dystonias resistant to BTX: selective peripheral denervation
6. Disorders with dystonia that have specific disease-modifying therapies (Jinnah and Factor 2015)
  1. Abetalipoproteinemia (Bassen-Kornzweig): vitamin E, reduced-fat diet
  2. Aromatic amino acid decarboxylase deficiency: dopamine agonists and monoamine oxidase inhibitors
  3. Ataxia with vitamin E deficiency: vitamin E
  4. Autoimmune movement disorders: address autoimmune process
  5. Biotinidase deficiency: biotin
  6. Cerebral folate deficiency: folic acid
  7. Cerebrotendinous xanthomatosis: chenodeoxycholic acid
  8. Cobalamin deficiencies (inherited subtypes A–G): cobalamin derivatives and/or protein restriction
  9. Coenzyme Q10 deficiency: coenzyme Q10
  10. Cerebral creatine deficiency type 3: creatine
  11. Dopa-responsive dystonia, classic: levodopa
  12. Dopa-responsive dystonia, complicated: levodopa, 5-hydroxytryptophan, and/or tetrahydrobiopterin
  13. Dystonia with brain manganese accumulation: chelation therapy
  14. Galactosemia: lactose restriction
  15. Glucose transporter 1 deficiency: ketogenic diet
  16. Glutaric aciduria type 1: avoid or treat aggressively any intercurrent illness, lysine restriction
  17. Homocystinuria: methionine restriction
  18. Guanidinoacetate methyltransferase deficiency: arginine restriction, creatine, and ornithine
  19. Maple syrup urine disease: leucine restriction +/− thiamine
  20. Methylmalonic aciduria: avoid or treat aggressively any intercurrent illness, protein restriction
  21. Molybdenum cofactor deficiency (sulfite oxidase): cyclic pyranopterin monophosphate
  22. Niemann-Pick type C: n-butyldeoxynojirimycin (Miglustat)
  23. Paraneoplastic movement disorders: address underlying malignancy
  24. Propionic aciduria: avoid or treat aggressively any intercurrent illness, protein restriction
  25. Pyruvate dehydrogenase deficiency: thiamine, ketogenic diet, and dichloroacetate
  26. Rapid-onset dystonia parkinsonism: avoid or treat aggressively any

intercurrent illness, protein restriction

27. Wilson disease: zinc and tetrathiomolybdate

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Fig. 1 A 7-year-old girl with progressive dystonia showing dystonic posturing with gait locking of the knees and swiveling of the hips to propel the legs forward. She developed normally until age 6 when she started to have loss of balance, falling, unable to get the foot off the ground, stiffing of lower and upper extremities, and slurring of speech. Plasma amino acids, urine organic acids, blood chemistry, lactate/pyruvate, ceruloplasmin, copper, arsenic, lead, 5-methyltetrahydrofolate, neurotransmitter metabolites/amines, tetrahydrobiopterin/neopterin, and various lysosomal enzymes were all normal. No mutations were detected on mitochondrial myopathy mtDNA, *DYT1*, and *PANK2*. MRI of the brain showed bilateral hyperdense basal ganglia lesions. The use of levodopa/dopamine agonists has at best been minimally beneficial

Dystrophinopathies

Contents

The dystrophinopathies include a spectrum of muscle disease caused by mutations in the *DMD* gene that encodes the protein dystrophin. They are characterized by a spectrum of muscle disease that ranges from mild to severe. The mild end of the spectrum includes the phenotypes of asymptomatic increase in serum concentration of creatine phosphokinase (CPK) and muscle cramps with myoglobinuria and isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that are classified as Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) when skeletal muscle is primarily affected and as X-linked dilated cardiomyopathy (XLDCM) when the heart is primarily affected. In this chapter, I will limit my discussion on DMD and BMD.

DMD is one of the most common types of muscular dystrophy in childhood, primarily affecting skeletal and cardiac muscle. It is one of the most common of all clinical genetic disorders. Its incidence is estimated to be approximately 1 in 3,500 live male births. BMD is a milder allelic form of dystrophin deficiency, affecting 1 in 30,000 male births.

Synonyms and Related Disorders

Becker and Duchenne muscular dystrophy

Genetics/Basic Defects

1. DMD (Worton and Thompson 1988):
    1. Inheritance:
        1. X-linked recessive.
        2. Exceptionally high mutation rate of 10^{-4} in both sperm and eggs.
        3. Approximately 1/3 of cases are due to new genetic mutations.
        4. Approximately 2/3 of cases occurring by inheritance of the disease-causing gene from the carrier mother.
        5. Only males affected (as a rule).
    2. *DMD* gene:
        1. Observation of a series of young females affected clinically as Duchenne muscular dystrophy with an X-autosome translocation (Jacobs et al. 1981):

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1. Breakpoint in the X chromosome in the same place (Xp21.1)
2. Different autosomes involved for each affected female
3. Mapping of dystrophin gene to chromosome Xp21

2. The largest human gene, covering 2.5 megabases and including 79 exons.
3. The enormity of the DMD gene along with the spontaneous mutation rate of each base pair allows a high frequency of novel mutations.
4. The most common molecular defect in the DMD gene (Falzarano et al. 2015):
   1. Deletion of one or more exons, occurring in 65% of DMD cases, while the duplication accounts for 6–10% of cases.
   2. The remaining cases (approximately 25%) are due to small mutations (missense, nonsense, and splice site variations) and small rearrangements (insertions/deletions, small inversion).
   3. However, a lower rate of cases (approximately less than 2%) is caused by complex rearrangements and deep intronic changes.

3. Dystrophin, the product (protein) of the human dystrophin gene (*dys*) (Hoffman et al. 1987):
   1. Loss of dystrophin at the muscle membrane clearly related to mutations in the gene encoding dystrophin at band Xp21.
   2. Cloning of the dystrophin gene by positional cloning in the late 1980s constituted the initial proof that deletions in the Xp21 region were associated with the disease.
   3. The dystrophin gene (Muntoni et al. 2003):
      1. The largest gene of the 30,000 genes that encode proteins in the human genome
      2. Consisting of 79 exons spanning more than 2.6 million bp of genomic sequence
      3. Correspond to about 0.1% of the total human genome
      4. Correspond to about 1.5% of the entire X chromosome
   4. Southern blot analysis of affected boys with a complete set of cDNA probes:
      1. Over 60% with detectable deletions
      2. Six percent with duplications (Hu et al. 1990)
      3. A number of point mutations described recently
   5. Consequences of absent dystrophin in skeletal and cardiac muscles in affected patients:
      1. Muscle contraction leading to membrane damage and activation of the inflammatory cascade
      2. Progressing to muscle necrosis, fibrosis, and loss of function
   4. The DMD phenotype most frequently due to mutations that cause a disruption in the reading frame (Wagner 2002)
2. BMD:
   1. Inheritance: X-linked recessive (same as DMD).
   2. Also caused by mutations in the gene for dystrophin at Xp21.1.
   3. The BMD phenotype most often due to mutations that preserve the open reading frame but in which portions of the protein are deleted. Frame deletions of the long rod segment of the gene are particularly forgiving and produce a mild phenotype (Wagner 2002).
3. Molecular basis for Duchenne versus Becker muscular dystrophy: correlation of severity with the type of deletion (Koenig et al. 1989)
4. Mechanism for female DMD and BMD:
   1. Turner syndrome with a *dystrophin* mutation on the remaining X chromosome (Chelly et al. 1986)
   2. Skewed X inactivation either in the female DMD mutation carriers (Yoshioka et al. 1998)
   3. Balanced X-autosome translocation patients (Verellen-Dumoulin et al. 1984)
   4. Uniparental disomy of the entire X chromosome with mutations (Quan et al. 1997)

5. Co-occurrence of mutations in both dystrophin and androgen receptor genes (Katayama et al. 2006)
6. Double dystrophin mutations on both X chromosomes (Fujii et al. 2009)

Clinical Features

1. DMD (Roland 2000):
    1. During early infancy:
        1. Asymptomatic
        2. Normal motor milestones
        3. Rare global developmental delay or delayed achievement of early motor milestones
    2. Four to five years of age: onset of symptoms:
        1. A waddling gait
        2. Difficulty in climbing stairs due to pelvic weakness
        3. Difficulty in running
        4. Toe walking resulting from tight Achilles tendon
        5. Inability to jump
        6. Frequent falling
        7. Neck flexor weakness with marked head lag when pulling to sit from the supine position
    3. Progressive difficulty in rising from the floor secondary to weakness of proximal pelvic girdle and proximal leg muscle, resulting in the Gower's maneuver requiring the use of the hands to "climb up the legs."
    4. Pseudohypertrophy of muscles, especially calf muscles: unusually firm and rubbery consistency on palpation.
    5. Compensatory lumbar lordosis to maintain an upright posture secondary to weakness of hip extensors.
    6. Weakness of the arms (proximal more severely affected than distal) apparent as the disease progresses.
    7. Marked laxity of the shoulder girdle musculature with prominent spontaneous winging of the scapulae.
    8. Inability to walk usually before 13 years of age.
    9. Rapid development of fixed skeletal deformities following loss of ambulation:
        1. Equinovarus deformities of the feet
        2. Scoliosis
        3. Wheelchair confinement by adolescence
    10. Unexplained cardiac arrest and/or myoglobinuria: features of malignant hyperthermia during general anesthesia in rare instances.
    11. Progressive and restrictive respiratory deficit with nocturnal hypoventilation in the latter teens to early 20s secondary to weak intercostal muscles.
    12. Eventual respiratory failure requiring assisted ventilation.
    13. Myocardial disease manifesting predominantly as cardiomyopathy and congestive heart failure: characteristic of Duchenne (and Becker) muscular dystrophies (Cox and Kunkel 1997).
    14. Some degree of mental impairment is usually present. Approximately 25% of patients have IQ below 75, presumably due to the lack of dystrophin in the brain.
    15. Natural history:
        1. Progressive and predictable deterioration of muscle function
        2. Cause of death: cardiopulmonary insufficiency in the late second or third decade
    16. Female carriers:
        1. Usually asymptomatic.
        2. Manifesting female carriers (rare): occasional, slow progressive myopathy of moderate severity with elevated CPK (>1,000) and associated symptoms in about 8% of carriers. The following conditions induce expression of the disease phenotype:
            1. Random X inactivation: the extent of clinical involvement is dependent in part upon the degree of skewed X-chromosome inactivation in somatic cells.

2. Turner syndrome having a single X chromosome.
3. X-autosome translocation that disrupts the dystrophin gene and causes nonrandom inactivation of the normal allele on the other X chromosome.

2. BMD
   1. A more benign and variable presentation with later onset and slower progression.
   2. Onset of symptoms after age 6–12.
   3. Progressive symmetrical muscle weakness and atrophy:
      1. Proximal greater than distal.
      2. Often with calf hypertrophy.
      3. Weakness of quadriceps femoris may be the only sign.
   4. Activity-induced cramping in some patients.
   5. Flexion contractures of the elbows may occur late in the course.
   6. Wheelchair dependency, if present, after 16 years of age.
   7. Preservation of the neck flexor muscle strength in BMD, differentiating it from DMD.
   8. Rare BMD patients not diagnosed until adulthood and never lose ambulation.
   9. A proportion of cases have some degree of mental impairment.
   10. Congestive heart failure from dilated cardiomyopathy (Cox and Kunkel 1997), a common cause of morbidity and the most common cause of death, despite the milder skeletal muscle involvement.
   11. Death usually in the fourth or fifth decade.
   12. Female carriers:
      1. Clinical features similar to DMD female carriers.
      2. About 5–10% of female carriers show some degree of muscle weakness.
      3. Often with calf hypertrophy.
      4. May develop dilated cardiomyopathy.
3. Differential diagnosis with other clinically defined types of muscular dystrophy (Emery 2002; Nair 2014):
   1. Congenital muscular dystrophy
   2. Emery–Dreifuss muscular dystrophy
   3. Distal muscular dystrophy
   4. Facioscapulohumeral muscular dystrophy
   5. Oculopharyngeal muscular dystrophy
   6. Limb–girdle muscular dystrophy
   7. Congenital myopathies (Gilbreath et al. 2014):
      1. Nemaline myopathy
      2. Core myopathy (including minicore)
      3. Fiber-type disproportion
      4. Centronuclear myopathy (including myotubular myopathy)
   8. Disorders of carbohydrate metabolism
   9. Endocrine myopathies
   10. Kennedy disease
   11. Lambert–Eaton myasthenic syndrome
   12. Metabolic myopathies
   13. Neuromuscular and myopathic complications of HIV
   14. Polymyositis
   15. Spinal muscular atrophy

Diagnostic Investigations

1. Determination of serum creatine phosphokinase (CPK):
   1. Fifty-fold elevation (BMD) to 100-fold elevation (DMD) in affected boys, resulting from leakage of the muscle isoform
   2. Serum creatine kinase levels: range of values overlapping with the normal range in carrier females, making the test less than definitive
2. Determination of other enzymes: grossly elevated aldolase, SGOT, lactic dehydrogenase, and pyruvate kinase
3. Electrocardiography and echocardiography to detect cardiac involvement:
   1. Electrocardiography (Perloff et al. 1967):
      1. Abnormalities in the early stage of the disease:
         1. Tall R-wave
         2. Deep Q-wave
      2. Arrhythmias
      3. Progressive cardiomyopathy in the mid-teens:
         1. Myocardial dilatation

    2. Myocardial thickening
  2. Echocardiography:
    1. Left ventricular dilatation and dysfunction
    2. Mitral regurgitation secondary to dilated cardiomyopathy or associated mitral valve prolapse
4. Radiography for scoliosis
5. Muscle MRI (Zheng et al. 2015):
  1. The trefoil with single fruit sign in muscle MRI: highly specific for dystrophinopathies
  2. The three leaflets (trefoil): formed by relative sparing of the sartorius, gracilis, and adductor longus muscles
  3. The single fruit: formed by semitendinosus muscle with relative sparing
6. Pulmonary function testing with negative inspiratory force and forced vital capacity as disease progresses
7. Cytogenetic analysis:
  1. Males affected with DMD and other X-linked disorders such as retinitis pigmentosa, chronic granulomatous disease, McLeod red cell phenotype, glycerol kinase deficiency, and adrenal hypoplasia as part of contiguous gene deletion syndrome:
    1. High-resolution chromosome studies:
      1. To detect visible deletions
      2. To detect chromosome rearrangements involving Xp21.1
    2. FISH analysis with probes covering the *GK* and *NRDB1* genes in addition to exons in the *DMD* gene
  2. Females with classic DMD:
    1. May have X-chromosome rearrangement
    2. May have deletion involving Xp21.1
    3. May have complete absence of an X chromosome (45,X)
    4. May have complete uniparental disomy of the X chromosome
    5. Warrant high-resolution chromosome studies
8. Electromyography (EMG) to distinguish a myopathic process from a neurogenic disorder:
  1. Not diagnostic
  2. Demonstrating characteristic myopathy
  3. Reduction in the duration and amplitude of motor unit action potentials
  4. An enhanced frequency of polyphasic potentials
9. DNA analyses for diagnostic confirmation:
  1. Deletion of the dystrophin gene in 60% of patients: 98% of all deletions which occur in hotspots within the dystrophin gene can be recognized by multiplex PCR (Beggs et al. 1990) which amplifies 18–25 of the gene's 79 exons from genomic DNA obtained from blood samples.
  2. Duplications (6% of cases): the next most common mutation of the dystrophin gene, also detectable by multiplex PCR amplification.
  3. Point mutations (1/3 of patients) difficult to identify due to the large size of the gene.
  4. Enhanced single-strand conformation polymorphism (SSCP) (Mendell et al. 2001) and heteroduplex analysis: highly sensitive and possible to detect approximately 90% of patients with DMD.
  5. RNA-based methods, such as reverse transcriptase PCR (RT-PCR).
  6. Protein truncation test: to rapidly screen the DMD gene for translation-terminating mutations (Roest et al. 1993).
  7. Routinely, the molecular diagnosis is done by a multiplex ligation-dependent probe amplification (MLPA) or array comparative genome hybridization (aCGH), followed, if negative, by Sanger sequencing of all exons (Boulez et al. 2015).
10. Muscle biopsy (needle biopsy (Heckmatt et al. 1984) vs. open biopsy under general anesthesia), frequently performed when a clinically suspected DMD patient does not have a large deletion or duplication by genomic DNA testing:
  1. Histology:
    1. Rounding of muscle fibers
    2. Marked variability in muscle fiber size
    3. Increased central nucleation
    4. Fiber splitting

5. The presence of necrotic and regenerating fibers along with large, round hyaline fibers
6. Virtual replacement of muscle fibers by fatty and fibrous tissue in late stage

2. Dystrophin determination by Western blot analysis or immunostaining (Hoffman et al. 1988; Beggs and Kunkel 1990):
   1. Usually little or no detectable dystrophin in patients with DMD
   2. Dystrophin reduced in amount or abnormal in size (larger or smaller sized) in patients with BMD

11. Carrier testing (Mathews 2003):
    1. Carrier testing of young girls or genetic testing of siblings of patients with DMD should be delayed until they are old enough to participate in the decision-making process.
    2. Appropriate to test the mother who has an affected boy with deletion or duplication identified by standard DNA screening, especially if there are other female relatives of childbearing age who are at risk for being carriers.
    3. Possibility of gonadal mosaicism (up to 15%) exists when the mother does not carry the boy's mutation:
       1. Her sisters could not have inherited the mutation.
       2. Her daughter may have inherited the mutations.
    4. Offer linkage analysis to modify risk of carrier status if no mutation is known or if tissue for DNA analysis is not available:
       1. Knowledge of a childhood CPK level in the at-risk girl is helpful.
       2. Elevated CPK in an at-risk female is presumptive evidence of her being a carrier.
    5. Muscle biopsy:
       1. Not a helpful test in determining carrier status.
       2. Skeletal muscle biopsy for Western blot and immunohistochemistry studies of dystrophin can also be considered in symptomatic at-risk females with a high CPK level and normal molecular genetic testing for DMD (Darras et al. 2014).

Genetic Counseling

1. Recurrence risk (Darras et al. 2014):
   1. Patient's sib given that the mother is a carrier (has a disease-causing mutation) (the carrier mother with one defective gene and one normal gene is usually not affected):
      1. Fifty percent risk to her son to receive the disease gene and express the disease.
      2. Fifty percent risk to her daughter to receive the disease gene and become a carrier.
      3. The mother, regardless of proven carrier status or who does not have a *DMD* mutation detectable in her DNA, has an empiric risk of 15–20% of having an affected male fetus due to the presence of maternal germinal mosaicism.
      4. The mother with concomitant somatic and germline mosaicism: the risk to sibs of inheriting a DMD mutation may be higher than if the mother has germline mosaicism only (van Essen et al. 2003).
   2. Patient's offspring:
      1. Males with DMD: patients usually succumb or are too debilitated to reproduce.
      2. Males with BMD- and *DMD*-associated dilated cardiomyopathy:
         1. May reproduce.
         2. None of the sons will inherit the mutation.
         3. All the daughters are carriers.
   3. Germline mosaicism (van Essen et al. 2003; den Helderman-van Enden et al. 2009):
      1. Causes the presence of multiple affected offspring from apparently noncarrier parents.
      2. In X-linked DMD/BMD, the recurrence risk for noncarrier females due to germline mosaicism has been estimated to be between 14% and 20% (95% confidence interval) (Darras and Francke 1987; Bakker et al. 1987, 1989; van

Essen et al. 1992) if the risk haplotype is transmitted.
3. A recurrence risk of 8.6% (4.8–12.2) if the risk haplotype is transmitted with a remarkable difference between proximal (15.6%) (4.1–27.0) and distal (6.4%) (2.1–10.6) deletions (den Heldermanvan Enden et al. 2009). Overall, most mutations originated in the female. Deletions occur more often on the X chromosome of the maternal grandmother, whereas point mutations occur on the X chromosome of the maternal grandfather. In unhaplotyped de novo DMD/BMD families, the risk of recurrence of the mutation is 4.3%.

2. Prenatal diagnosis (Darras et al. 2014):
   1. In the case of a known and readily detectable gene defect:
      1. Amniocentesis and mutation analysis of amniocytes, usually by multiplex PCR.
      2. Preimplantation diagnosis by single-cell PCR of blastomere or polar body may be an option for some families in which the pathogenic variant has been identified.
      3. Fetal nucleated erythrocytes from maternal blood analyzed by multiplex PCR.
   2. In the case of unknown gene defect:
      1. Fetal sexing, allowing females to proceed to the term.
      2. Linkage analysis.
      3. Fetal muscle biopsy for quantitative dystrophin analysis may serve as a diagnostic option (Nevo et al. 1999).
   3. Comparative genomic hybridization (CGH) (Bovolenta et al. 2010):
      1. Molecular diagnosis of DMD requires a great deal of effort due to enormous size of the gene and to allele heterogeneity.
      2. While multiplex ligation-dependent probe amplification (MLPA) represents the standard molecular technique for detecting exonic DMD gene rearrangements (Kesari et al. 2008), several comparative genomic hybridization (CGH) platforms have recently been reported to rapidly screen the entire DMD gene, as well as neighboring sequences, for deletions and duplications (Hegde et al. 2008; del Gaudio et al. 2008; Bovolenta et al. 2008).

3. Management (Kapsa et al. 2003; Mathews 2003):
   1. Largely supportive:
      1. Physical therapy to eliminate the need for surgical release of contractures:
         1. Night splints with ankle–foot orthoses (AFOs)
         2. Daily stretching
         3. Crucial to maintain ambulation as long as possible because its loss is associated with contractures and scoliosis and, in turn, associated with restrictive lung disease
      2. Regular use of an incentive spirometer at home to prolong pulmonary function
      3. Continuous positive airway pressure (CPAP)
      4. Bilevel positive airway pressure (BiPAP): more physiologic
      5. Careful monitoring of pulmonary function
      6. Psychological support
   2. American College of Chest Physicians statement on the respiratory and management of patients with Duchenne dystrophy undergoing anesthesia (Birnkrant 2009).
   3. Adiponectin proves to be an extremely powerful hormone capable of protecting the skeletal muscle against inflammation and injury, thereby offering novel therapeutic perspectives for dystrophinopathies (Abou-Samra et al. 2015).
   4. Treatment of dystrophic cardiomyopathies (Finsterer and Cripe 2014):
      1. Presymptomatic treatment: steroids, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and mineralocorticoid receptor antagonists.
      2. Pharmaceutical agents (steroids) have shown great promise in delaying the progression of DMD:
         1. ACE inhibitors, ARBs, or β-blockers, in monotherapy or in combination, in increasing dosages (until a beneficial effect becomes evident or adverse effects occur), and the use of diuretics

2. Glucocorticoid corticosteroids, prednisone (Biggar et al. 2002), and deflazacort (Flanigan 2014)
3. Nonpharmacological cardiac treatments with a direct effect include:
    1. Implantation of a pacemaker
    2. Implantable cardioverter–defibrillator (ICD)
    3. Cardiac resynchronization therapy (CRT) system
    4. Intra-aortic balloon pump
    5. The use of a ventricular assist device (VAD)
    6. Heart transplantation
4. Indirect cardiac therapy includes:
    1. Pharmacotherapy, such as pain relief
    2. Nonpharmacological measures, such as orthopedic surgery (release of joint contractures, spine fusion to minimize painful spinal deformity and secondary pulmonary complications) or nocturnal or whole-day ventilation by noninvasive positive pressure ventilation

5. Multidisciplinary care of Duchenne muscular dystrophy (Bushby et al. 2010):
    1. Physical therapy interventions:
        1. Stretching and positioning
        2. Assistive devices for musculoskeletal management: orthoses
    2. Surgical intervention for lower-limb contractures:
        1. Early ambulatory phase: heel-cord (tendo-Achilles) lengthenings for equinus contractures, hamstring tendon lengthenings for knee-flexion contractures, anterior hip-muscle releases for hip-flexion contractures, and even excision of the iliotibial band for hip-abduction contractures.
        2. Middle ambulatory phase: bilateral multilevel (hip–knee–ankle or knee–ankle) procedures, bilateral single-level (ankle) procedures, and, rarely, unilateral single-level (ankle) procedures for asymmetric involvement.
        3. Late ambulatory phase: generally been ineffectively served to obscure the benefits gained by more timely and earlier interventions.
        4. Early non-ambulatory phase: generally ineffective.
        5. Late non-ambulatory phase: severe equinus foot deformities of more than 30° can be corrected with heel-cord lengthening or tenotomy and varus deformities (if present) with tibialis posterior tendon transfer, lengthening, or tenotomy.
    3. Assistive/adaptive devices for function:
        1. AFOs (ankle–foot orthoses): not indicated for use during ambulation because they typically limit compensatory movements needed for efficient ambulation, add weight that can compromise ambulation, and make it difficult to rise from the floor.
        2. Prescribe a powered wheelchair when dependency becomes inevitable.
    4. Recommendation for exercise
6. Genetic therapies in DMD: the use of viral and plasmid vectors to deliver dystrophin to dystrophin-deficient muscle in vivo (Kapsa et al. 2003; Van Deutekom and Van Ommen 2003):
    1. Truncated dystrophin genes (minidystrophin and microdystrophin transgenes) improve force output and other features of the dystrophic *mdx* phenotype.
    2. Tissue-specific promoters: targeted transgene expression via muscle-specific promoters, a good platform for vector-mediated therapeutic delivery of *dys* to dystrophic muscle.
    3. Plasmid vectors.
    4. Viral vectors:
        1. Adenoviral vectors
        2. Adeno-associated vectors
        3. Retroviral vectors
        4. Lentiviral vectors
        5. Other viral vectors including herpes simplex virus, Epstein–Barr virus, and chimeric adeno-retrovirus
7. Corrective gene therapy (Kapsa et al. 2003; Nelson et al. 2009):

1. Targeted corrective gene conversion therapies:
    1. Introduction of construct of homologous DNA containing a nonhomologous sequence into mammalian cells in vitro induces specific genetic transformations in the host chromosomal DNA.
    2. An attractive therapeutic strategy for DMD if the DNA can be delivered to the muscles efficiently.
2. Small fragment homologous replacement (SFHR) involves the application of PCR amplicons to correct mutant loci in vitro or in vivo.
3. Chimeraplasty with hybrid RNA–DNA molecules (chimeraplasts) that promote gene conversion via intranuclear DNA mismatch repair mechanisms.
4. Gentamicin:
    1. An aminoglycoside antibiotics targeting functional complexes (typically ribosomes)
    2. Causes a relaxation in codon recognition
    3. Enables stop codon readthrough of the *mdx* nonsense mutation (a mutation that produces a stop codon in the transcribed mRNA) in exon 23 of the dystrophin gene in the *mdx* mouse
5. Cell-mediated delivery of *dys*:
    1. Use cell transplantation to deliver normal (non-dystrophic) *dys* to dystrophic muscle.
    2. Use donor myogenic precursor cells to remodel the dystrophic muscle of the recipient.
    3. Systemic applications of stem-cell subpopulations.
    4. Use autologous cells (as an alternative to donor cells) which can be isolated, genetically engineered, and used to deliver functional dystrophin to the dystrophic muscle.
6. Muscle-derived precursor cells:
    1. Delivery of normal dystrophin by the transplantation of non-dystrophic muscle-derived precursor cells
    2. Resulting in some recovery of normal function in dystrophic muscle
    3. Greatly compromised by host immune response
7. Non-muscle stem cells:
    1. Induction of a few systemically injected bone marrow cells to enter muscle after regeneration induced by injury.
    2. These cells with neuronal, osteogenic, myogenic, and hemopoietic expression profiles may provide alternatives for cell-based delivery of non-dystrophic loci to dystrophic muscle.
8. Utrophin:
    1. A 395 kDa ubiquitous protein homologue of dystrophin.
    2. Utrophin expression has a widespread sarcolemmal distribution in human dystrophic muscle.
9. Other alternative approaches that may be useful in the support of functional improvement in dystrophic muscle include:
    1. α7β1 integrin
    2. Myoprotective or myeloproliferative cytokine factors such as leukemia inhibitory factor and insulin-like growth factor-1
    3. Inhibition of myostatin
10. Experimental molecular therapies (replace or correct missing or dysfunctional dystrophin) (Rodino-Klapac et al. 2013; Finsterer and Cripe 2014):
    1. Exon skipping with antisense oligonucleotides.
    2. Gene replacement or gene transfer with adeno-associated viruses.
    3. Mutation suppression with molecules such as aminoglycosides that read through nonsense mutations (premature stop codons).
    4. Other strategies include stem-cell therapy or the introduction of surrogate gene products (such as utrophin)

to compensate for the loss of dystrophin.

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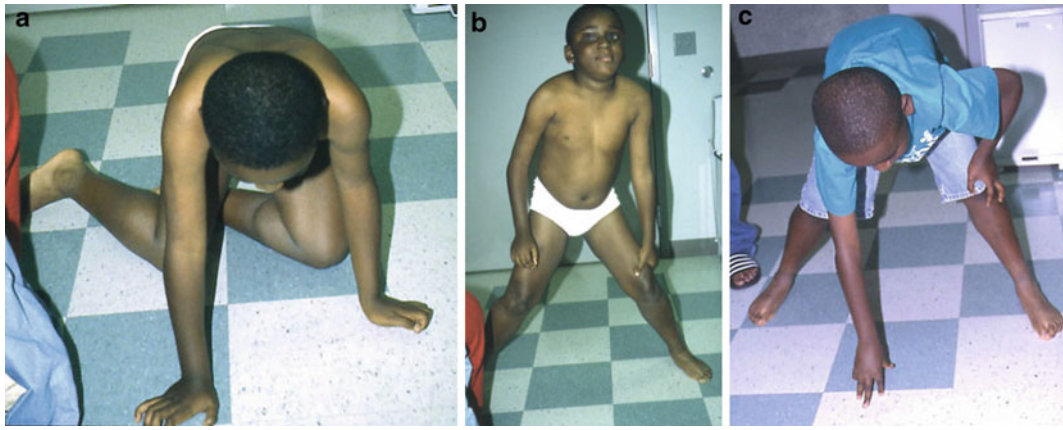

Fig. 1 (**a**–**c**) A 10-year-old boy with DMD showing Gower sign maneuver. He walked before 16 months of age and had trouble getting up. Radiography showed mild cardiomegaly. Muscle biopsy showed the absence of dystrophin. Molecular genetic analysis revealed exons 45–50 deletion of the dystrophin gene

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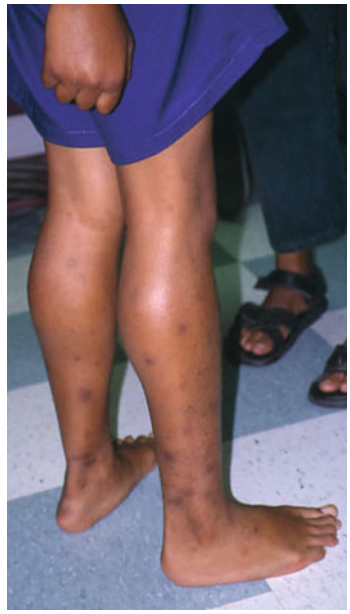

Fig. 2 A 12-year-old boy with DMD showing moderate calf hypertrophy. He began to fall frequently at school, could not get up from sitting position, and had waddling gait, proximal muscle weakness, prominent lordosis, decreased deep tendon reflexes, and mild mental retardation. Muscle biopsy revealed the absence of dystrophin

Fig. 3 A 10-year-old boy with DMD starting to use wheelchair for ambulation. He had tiptoe walking at the age of 6 and markedly elevated CPK at 24,000–26,000. Muscle biopsy of the quadriceps femoris muscle showed marked variation in fiber size, moderate number of necrotic fibers, occasional regeneration fibers and hyalinized fibers, mild increase in internal nuclei, a few split fibers, and moderate increase in perimysial and endomysial connective tissue. Molecular genetic analysis revealed deletion of exon 45 of the dystrophin gene

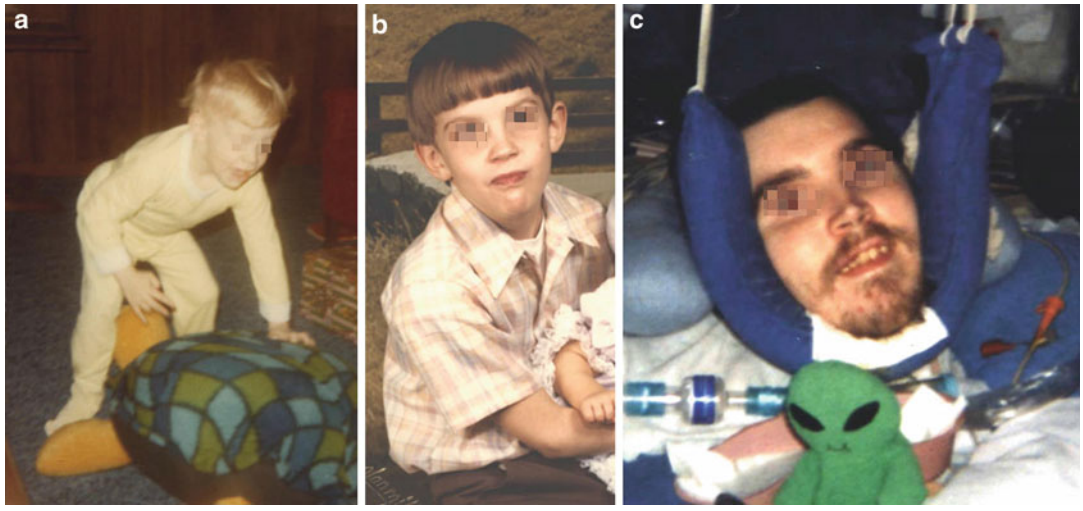

Fig. 4 (**a**–**c**) A male with DMD at 4 (**a**), 10 (**b**), and 29 (**c**) years old showing the progression of the disease. He has deletion of exons 49–54 of the dystrophin gene

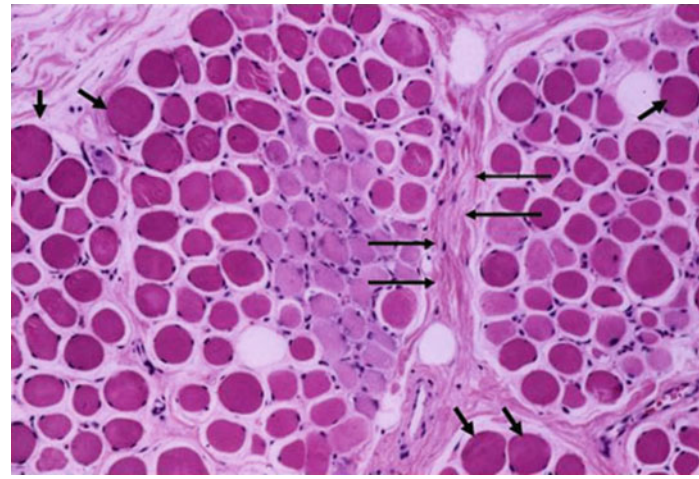

Fig. 5 Biopsy of the left calf muscle of another patient at age 4 showed widening of the perimysium (*large arrows*) and endomysium with fibrosis and variation of fiber size with the presence of large rounded fibers (*small arrows*). Degenerative fibers were often seen (H & E, x400)

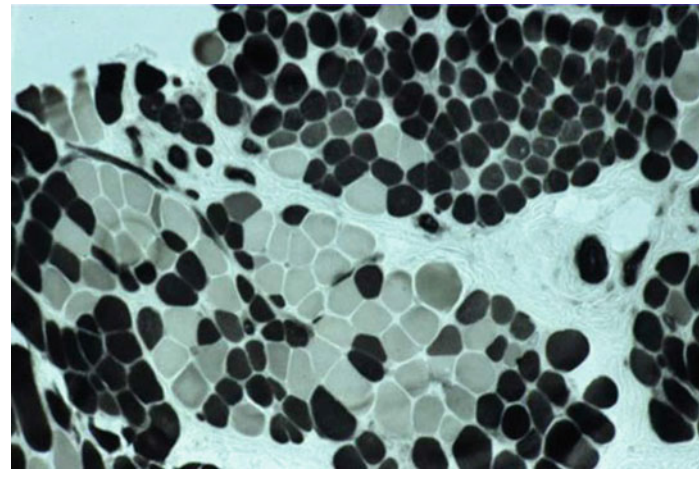

Fig. 6 Enzyme histochemical stain showed both type I (*dark stained*) and type II (*light stained*) fibers are randomly affected and there is a remarkable variation of fiber size even at the early stage (myosin ATPase at 4.6, ×400)

Ectrodactyly-Ectodermal Dysplasia-Clefting (EEC) Syndrome

Contents

EEC syndrome is an ectodermal dysplasia syndrome associated with ectrodactyly and cleft lip/palate.

Genetics/Basic Defects

1. Inheritance (Akahoshi et al. 2003; Barrow et al. 2002; Clements et al. 2010)
   1. Familial cases (50%)
      1. Autosomal dominant inheritance.
      2. Variable clinical expression (Penchaszadeh and de Negrotti 1976; Annerén et al. 1991) and incomplete penetrance (93–98%) (Tse et al. 1990; Roelfsema and Cobben 1996).
      3. A report of a three-generation Brazilian family with three individuals (mother, son and grandfather) affected by EEC syndrome, determined by a novel mutation c.1037C > G (p.Ala346Gly). The disorder in this family exhibits a broad spectrum of phenotypes (Alves et al. 2015).
   2. Sporadic cases (50%): more severe phenotype than the familial cases
2. At least three distinctive EEC loci identified
   1. EEC1 (7q11.2-q21.3) (Qumsiyeh 1992; Scherer et al. 1994)
   2. EEC2 (chromosome 19 pericentromeric region)
   3. EEC3 (3q27)
3. Characterization of the split hand/split foot malformation locus SHFM1 at 7q21.3-q22.1 (Crackower et al. 1996)
4. Molecular basis of EEC
   1. Causative mutations for EEC syndrome have only been identified in *p63* with identification of heterozygous mutations in the DNA-binding domain of the *p63* gene at 3q27.
   2. Heterozygous germline mutations in the p63 gene underlie EEC syndrome (Celli et al. 1999; Wessagowit et al. 2000).
   3. The *p*63 protein:
      1. A member of the *p53* family.
      2. Implicated in apoptosis rather than tumor suppression. Increased susceptibility for cancer development has not been shown in patients with EEC syndrome.
   4. Pathogenic mutations in the *TP63* transcription factor have been identified as the

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molecular basis of EEC syndrome, and to date 34 mutations have been reported (Clements et al. 2010). The majority of mutations involve heterozygous missense mutations in the DNA-binding domain of TP63, a region critical for direct interactions with DNA target sequences.

5. Genotype-phenotype correlation
    1. A genotype-phenotype correlation described for *p63* mutations in EEC syndrome, limb-mammary syndrome, and isolated split hand/split foot malformation: a specific pattern of missense mutations exists in EEC syndrome that are not generally found in split hand/foot malformation or limb-mammary syndrome (Van Bokhoven et al. 2001).
    2. Emerging paradigm for genotype-phenotype correlation (Clements et al. 2010).
    3. EEC syndrome, the prototype of all TP63 ectodermal dysplasia disorders, is the most prevalent syndrome resulting from mutations in the *TP63* gene (Brunner et al. 2002; Bougeard et al. 2003) with more than 200 cases reported in the literature.
6. EEC syndrome as a model of apoptosis disturbance
    1. Split hands and feet are caused by a failure of cell death between fingers and between toes.
    2. Urogenital anomalies are due to abnormal regression of Wolffian or Mullerian duct.
    3. Facial clefts are attributed to the abnormal elimination of excess cells during fusion of the archetypal plate.

Clinical Features

1. Significant phenotypic variation and intra-/interfamilial variability (Rodini and Richieri-costa 1990; Buss et al. 1995; Bigatà et al. 2003)
2. Cardinal signs (triad)
    1. *E*ctrodactyly
    2. *E*ctodermal dysplasia
    3. Orofacial *c*lefts
3. Distal limb malformations: highly variable
    1. Ectrodactyly (84%)
        1. Also called split hand/foot malformation
        2. A central reduction of the hands and feet that is often associated with syndactyly.
    2. Present in all four or any combination of extremities involved or not present at all
4. Ectodermal dysplasia (77%): may exhibit the following signs:
    1. Sparse scalp hair
    2. Sparse eyebrows and eyelashes
    3. Thin and brittle nails
    4. Hypohidrosis
    5. Thin and dry skin with an increased susceptibility to eczema
    6. Dental anomalies
        1. Hypodontia
        2. Coniform-shaped teeth
        3. Enamel dysplasia
5. Characteristic face
    1. Bilateral cleft lip and/or palate (68%)
    2. Maxillary hypoplasia
    3. Short philtrum
    4. Broad nasal tip
    5. Choanal atresia
    6. Anomalies of the lacrimal ducts resulting in blepharitis, keratitis, and dacryocystitis (59%)
6. Common ocular signs and symptoms (Kennedy et al. 2015)
    1. Photophobia
    2. Blepharospasm
    3. Epiphoria
    4. Corneal neovascularization and scarring
7. Urogenital defects (23%) (Rollnick and Hoo 1988)
    1. Hydronephrosis
    2. Hydroureter
    3. Renal agenesis
8. Conductive hearing loss (14%)
9. Developmental delay
10. Occasional CNS malformations
    1. Rare growth hormone deficiency secondary to hypothalamic-pituitary insufficiency

2. Holoprosencephaly associated with hypogonadotropic hypogonadism and central diabetes insipidus (Van Maldergem et al. 1992)
3. Isolated absent septum pellucidum

11. Phenotype overlapping with split hand/foot malformations
12. Diagnostic criteria (Buss et al. 1995)
    1. Major
        1. Ectodermal dysplasia
        2. Ectrodactyly
        3. Cleft lip/palate
        4. Lacrimal duct anomalies
    2. Minor
        1. Renal anomalies
        2. Deafness
        3. Mental retardation
        4. Choanal atresia
13. TP63 (P63) mutation associated disorders (Clements et al. 2010; Sharma et al. 2015): Clinical features overlap with EEC syndrome, although several distinct characteristics may help distinguish them.
    1. Ankyloblepharon-ectodermal dysplasia-clefting (AEC) (Hay-Wells) syndrome (McGrath et al. 2001; Sawardekar and Zaenglein 2011): Typical features include:
        1. Ankyloblepharon filiforme (partial eyelid fusion)
        2. Skin erosions
        3. Ectodermal dysplasia
        4. Orofacial clefts
        5. Sparse eyebrows and eyelashes
    2. Acrodermato-ungual-lacrimal-tooth (ADULT) syndrome (Chan et al. 2004; Avitan-Hersh et al. 2010; Berk et al. 2012): Common features include:
        1. Ectrodactyly
        2. Syndactyly
        3. Mammary gland/nipple hypoplasia
        4. An absence of clefting
        5. Increased skin freckling (excessive skin)
        6. Dry skin
        7. Dysplastic nails
        8. Lacrimal duct atresia
        9. Primary hypodontia
        10. Early loss of permanent teeth
    3. Rapp-Hodgkin syndrome (Bougeard et al. 2003; Chan et al. 2005; Clements et al. 2010): Typical features include:
        1. Cleft lip and palate
        2. Small mouth
        3. Narrow nose
        4. Coarse and wiry hairs progressing to alopecia in adults
        5. Oligodontia or anodontia
        6. Hypoplasia of the nails
        7. Abnormalities of the lacrimal ducts
        8. Deformed ears and ear canals
        9. Hyperplastic mucosa
        10. Cheilitis angularis
        11. Renal dysplasia
        12. Inguinal hernia
        13. Hypospadias in males
        14. Urethral reflux
        15. Perioral ulcer
    4. Limb-mammary syndrome (Van Bokhoven et al. 1999, 2001)
        1. Similar limb defects to those seen in EEC syndrome, including absence or severe hypoplasia of digits and fusion/separation defects such as syndactyly
        2. Additional clinical features
            1. Mammary gland/nipple hypoplasia
            2. Lacrimal duct obstruction
            3. Cleft palate with or without bifid uvula
            4. Dystrophic nails
            5. Hypohydrosis
            6. Teeth defects

Diagnostic Investigations

1. Ophthalmologic evaluation for tear duct obstruction
2. Early audiological assessment
3. Renal ultrasound for associate renal anomalies
4. Radiographic evaluation for ectrodactyly
5. Starch-iodine test (the skin is painted with tincture of iodine, air-dried, and sprayed with starch) after sweat stimulation with intradermal injections of pilocarpine to demonstrate hypohidrosis (Bigatà et al. 2003)

6. Direct molecular analysis is possible for EEC (TP63-related disorders) (www.genetests.org)

Genetic Counseling

1. Counseling according to autosomal dominant inheritance
    1. Patient's sib:
        1. Recurrence risk of 50% if a parent is affected
        2. Recurrence risk not increased if both parents are normal
    2. Patient's offspring: recurrence risk of 50%
    3. Dilemmas in counseling due to highly variable clinical expression (Tse et al. 1990)
    4. Consider the possibility of nonpenetrance due to gonadal mosaicism
2. Prenatal diagnosis
    1. Prenatal ultrasonography (Bronshtein and Gershoni-Baruch 1993; Rios et al. 2012)
        1. The prenatal diagnosis of EEC syndrome can be done early by the 2D US, when the hands and feet malformations (lobster-claw deformity) are associated with a cleft lip and/or palate deformities (Leung et al. 1995).
        2. The 3D US in the rendering mode has been used to better define the malformations; this mode is better to explain the malformations to the parents.
    2. Molecular genetic analysis of p63 gene mutation (South et al. 2002)
        1. On fetal DNA extracted from CVS and amniocytes by direct sequencing and restriction endonucleases digestion (loss of *AciI* site on mutant allele)
        2. Using a preimplantation genetic diagnostic approach
3. Management (Bigatà et al. 2003)
    1. Supportive (multidisciplinary team approach) (Kennedy et al. 2015)
        1. Artificial tear for tear duct blockage.
        2. Anticipate recurrent ophthalmologic infections.
        3. If a non-healing epithelial defect is present with concern for perforation, amniotic membrane transplant by way of surgery or in-office placement of a commercially available ring should be considered.
        4. Corneal perforation can be managed with cyanoacrylate glue and bandage contact lens (Felipe et al. 2012).
        5. Rigid gas-permeable scleral contact lenses (GP-ScCL) have been reported useful in cases of severe ocular surface disease, particularly non-healing epithelial defects (Romero-Rangel et al. 2000; Schornack 2011).
        6. In cases of ocular surface disease related to limbal stem cell deficiency, the benefit is limited to symptomatic improvement of photophobia and pain rather than restoration of a normal ocular surface with corneal epithelium (Van Bokhoven et al. 2001). However, one report does claim that GP-ScCL may provide an environment for damaged but viable epithelial limbal stem cells to recover, restoring a physiologic corneal epithelium (Romero-Rangel et al. 2000).
        7. Periodic odontologic management to prevent dental malocclusion and caries.
        8. Simple emollients for dry skin.
    2. Surgery
        1. Early surgery for tear duct blockage
        2. Surgery for all defects causing functional impairment
            1. Cleft lip/palate
            2. Ectrodactyly
            3. Associated anomalies

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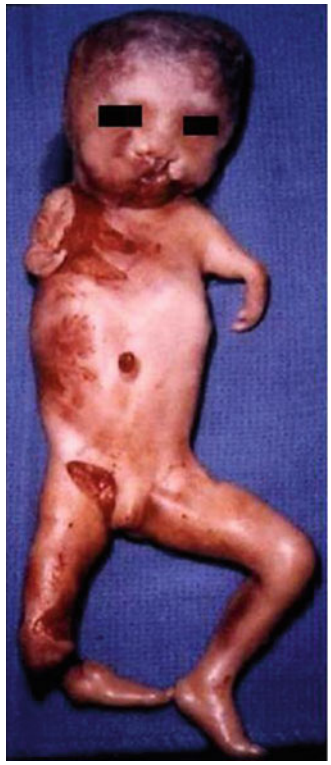

Fig. 1 A stillborn with severe EEC syndrome

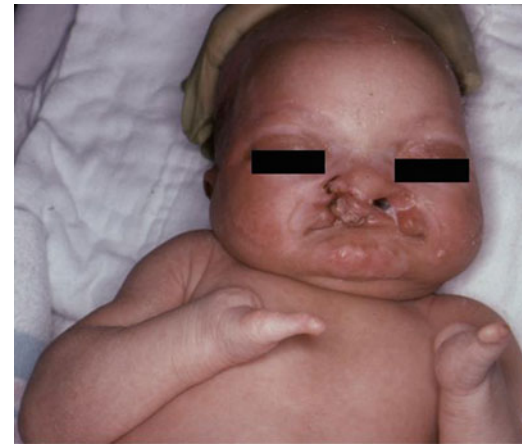

Fig. 2 An infant with EEC syndrome

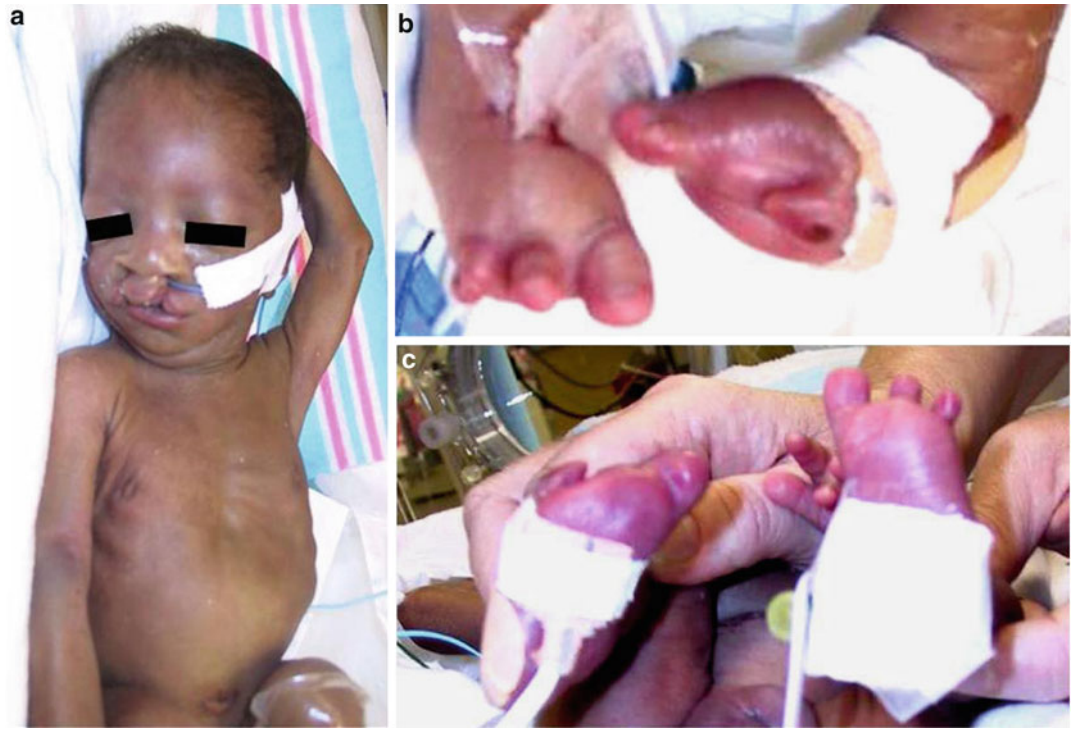

Fig. 3 (**a**–**c**) An infant with EEC syndrome

Ehlers-Danlos Syndrome

Contents

Ehlers-Danlos syndrome (EDS) is a group of clinically and genetically heterogeneous heritable connective tissue disorders (Yeowell and Pinnell 1993) affecting the skin, ligaments, joints, blood vessels, and internal organs. EDS is characterized by skin extensibility, joint hypermobility (JHM), and tissue fragility. EDS results from mutations in genes involved in extracellular matrix formation and organization, leading to a predisposition for loss of structural integrity in tissues within multiple organ systems (Barabas 1967). The prevalence of EDS is estimated to be about 1 in 5,000 births (Steinmann et al. 1993).

Synonyms and Related Disorders

EDS I (Gravis type); EDS II (mitis type); EDS III (hypermobile type); EDS IV (arterial-ecchymotic type); EDS IX (occipital horn syndrome/X-linked cutis laxa); EDS VI (kyphoscoliotic type); EDS VIIA, VIIB (arthrochalasis type); EDS VIIC (dermatosparaxis type); EDS VIII; EDS X; EDS XI.

Genetics/Basic Defects

1. The Villefranche classification of EDS (Pope and Burrows 1997; Beighton et al. 1998; Mao and Bristow 2001; Byers and Murray 2014)
    1. Classic type (includes EDS type I, gravis type and EDS type II, mitis type)
        1. Autosomal dominant inheritance.
        2. Mutations in the *COL5A1* gene (mapped at 9q34.2-q34.3), *COL5A2* (Michalickova et al. 1998) (mapped at 2q31), and *COL1A1* (mapped at 17q21.31-q22) genes result in EDS I (Nuytinck et al. 2000). Mutations in the *COL1A1* are not a major cause of classic EDS.
        3. Mutations in the *COL5A1* can result in EDS I (Wenstrup et al. 2000) and II (De Paepe et al. 1997), and *COL5A2* genes result in EDS II.
    2. Hypermobile type (EDS type III)
        1. Autosomal dominant inheritance in the classic form of type III EDS.
        2. Mutations in *COL3A1*, typically cause EDS IV, also cause EDS III.
        3. Mutations in the *TNXB* gene that encodes tenascin-X (neither a collagen nor a collagen-modifying protein) result in a variation of the classic form of the Ehlers-Danlos syndrome (Byers 2001;

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_78

Schalkwijk et al. 2001): an autosomal recessive disorder with clinical findings (joint hypermobility, soft hyperextensible skin, and easy bruising without skin scars) compatible with Beighton's description of Ehlers-Danlos syndrome type III or "benign familial hypermobility."

3. Vascular type (EDS type IV, arterial-ecchymotic type) (Byers 1995)
   1. Autosomal dominant inheritance.
   2. *COL3A1 l*ocus: 2q31.
   3. Caused by mutations in the gene that encodes type III procollagen (*COL3A1*), which is the major component of blood vessels, viscera, and the uterus. Consequently, individuals with this type often experience life-threatening vascular and gastrointestinal complications.
   4. Constitutes less than 4% of all EDS cases, usually associated with life-threatening arterial dissections and ruptures in adults (Abayazeed et al. 2014)
4. Kyphoscoliosis type (EDS type VI, ocular-scoliotic type) (Yeowell and Walker 2000)
   1. Autosomal recessive inheritance
   2. *PLOD* gene mapped to 1p36.3-p36.2
   3. Caused by mutations in the *PLOD* gene encoding lysyl hydroxylase
   4. Caused by deficient activity of the enzyme procollagen lysyl hydroxylase
   5. EDS VIA (kyphoscoliosis): reduced activity of lysyl hydroxylase
   6. EDS VIB: normal enzyme level
5. Arthrochalasis type (EDS types VIIA and VIIB, arthrochalasis multiplex congenita) (Byers et al. 1997; Giunta et al. 1999)
   1. Autosomal dominant inheritance
   2. EDS VIIA caused by mutations in the genes for type I collagen (*COL1A1*)
   3. EDS VIIB caused by mutations in the genes for type I collagen (*COL1A2*), mapped at 7q22.1
6. Dermatosparaxis type (EDS type VIIC)
   1. Autosomal recessive inheritance
   2. Caused by homozygous mutations in the *ADAMTS2* gene (5q23) encoding procollagen I N-terminal peptidase resulting in procollagen peptidase deficiency

2. Other types not in the Villefranche Nosology (Pope and Burrows 1997; Byers and Murray 2014; Colombi et al. 2015)
   1. EDS type V
      1. X-linked recessive inheritance (Beighton and Curtis 1985)
      2. Described in only two families with clinical features similar to EDS II
      3. Molecular basis unknown
   2. EDS type VIII (periodontitis)
      1. Autosomal dominant inheritance
      2. Similar to classic type except the presence of periodontal friability
      3. Gingival recessions
      4. Periodontitis
      5. Premature loss of permanent teeth
      6. Alveolar bone resorption by the third decade
      7. Atrophic scars
      8. Joint hypermobility
      9. Umbilical hernia
      10. Arachnodactyly
   3. EDS type IX (occipital horn syndrome (X-linked cutis laxa))
      1. An X-linked recessive condition allelic to Menkes syndrome
      2. Abnormal copper utilization secondary to defective copper transport resulting in decreased activity of lysyl oxidase, an important copper-dependent enzyme required for cross-linking in collagen biosynthesis and elastin fibers
   4. EDS type X (fibronectin-deficient)
      1. Autosomal recessive inheritance
      2. Described only in a single family
      3. Associated platelet aggregation due to a defect in fibronectin
   5. EDS type XI (familial joint hypermobility syndrome)
      1. Autosomal dominant inheritance
      2. Previously removed from the EDS classification

6. Classic vascular-like (*COL1A1*)
    1. Autosomal dominant inheritance
    2. Hyperextensible skin
    3. Atrophic scarring
    4. Easy bruising
    5. Joint hypermobility
    6. Propensity for arterial rupture at adult age
7. Cardiac valvular (*COL1A2*)
    1. Autosomal recessive inheritance
    2. Severe mitral valve regurgitation/insufficiency
    3. Arrhythmia, atrial fibrillation and septal defect, left ventricular enlargement
    4. Joint hypermobility
    5. Skin hyperextensibility
8. EDS due to tenascin-X deficiency (*TNXB*)
    1. Autosomal recessive inheritance
    2. Marked skin hyperextensibility
    3. Normal scarring
    4. Generalized joint hypermobility
    5. Severe easy bruising
9. EDS/OI overlap (*COL1A1*, *COL1A2*) (Malfait and De Paepe 2014) (please see the chapter of "▶ Osteogenesis Imperfecta/Ehlers-Danlos Syndrome Overlap Syndrome")
    1. Autosomal dominant inheritance
    2. Short stature
    3. Blue sclerae
    4. Mild signs of bone fragility
    5. Osteopenia
    6. Infrequent fractures
    7. Generalized JHM
    8. Skin hyperextensibility
    9. Atrophic/hypertrophic scars
    10. Easy bruising
    11. Signs of vascular fragility
    12. Valvular regurgitation
10. Musculocontractural type 1/D4ST1 deficiency (*CHST14*)
    1. Autosomal recessive inheritance
    2. Congenital contractures of thumbs and fingers
    3. Craniofacial dysmorphisms
    4. Blue sclerae
    5. Microcornea
    6. Clubfoot
    7. Arachnodactyly
    8. Severe kyphoscoliosis
    9. Muscle hypotonia
    10. JHM
    11. Hyperextensible skin
    12. Atrophic scars
    13. Easy bruising
    14. Wrinkled palms
11. Musculocontractural type 2 (*DSE*)
    1. Autosomal recessive inheritance
    2. Hyperextensible fragile skin
    3. Atrophic scarring
    4. Easy bruising
    5. Muscle hypoplasia
    6. Gross motor development delay
    7. Facial dysmorphisms
    8. Arachnodactyly
    9. Adducted thumbs
    10. Clubfoot
    11. Inguinal hernia
    12. Generalized mild cerebral atrophy
12. With progressive kyphoscoliosis, myopathy, and hearing loss (*FKBP14*)
    1. Autosomal recessive inheritance
    2. Severe hypotonia and weakness at birth
    3. Hyperextensible skin
    4. Joint hypermobility
    5. Severe progressive scoliosis
    6. Sensorineural hearing impairment
    7. Myopathy
    8. Vascular dissection
13. Brittle cornea syndrome type 1 (*ZNF469*)
    1. Autosomal recessive inheritance
    2. Blue sclerae
    3. Corneal rupture
    4. Keratoconus/keratoglobus
    5. Skin hyperextensibility
    6. Joint hypermobility
14. Brittle cornea syndrome type 2 (*PRDM5*)
    1. Autosomal recessive inheritance
    2. Corneal rupture
    3. Microcornea
    4. Cornea plana
    5. Keratoconus/keratoglobus
    6. Myopia

7. Hyperextensible skin
8. Easy bruising
9. JHM (localized)
10. Pectus excavatum
11. Scoliosis
12. Mitral valve prolapse
13. Hearing loss (conductive and sensorineural deafness)

15. Spondylocheirodysplasia, EDS-like (*SLC39A13*)
    1. Autosomal recessive inheritance
    2. Protuberant eyes
    3. Blue sclerae
    4. Hyperextensible skin
    5. Easy bruising
    6. JHM
    7. Hands with wrinkled palms
    8. Tenar muscle atrophy
    9. Tapering fingers
    10. Spondyloepiphyseal dysplasia
16. Progeroid type 1 (*B4GALT7*)
    1. Autosomal recessive inheritance
    2. Aged appearance
    3. Short stature
    4. Forearm bones and elbow anomalies, radioulnar
    5. Synostoses
    6. Bowing of the extremities
    7. Facial dysmorphisms
    8. Hyperextensible skin
    9. Atrophic/papyraceous scars
    10. Joint hypermobility
    11. Pes planus
    12. Developmental delay
    13. Muscle hypotonia
17. Progeroid type 2/spondyloepimetaphyseal dysplasia with joint laxity type 1 (*B3GALT6*)
    1. Autosomal recessive inheritance
    2. Aged appearance
    3. Developmental delay
    4. Disproportionate short stature
    5. Craniofacial disproportion
    6. Generalized severe osteopenia
    7. Defective wound healing
    8. Hyperextensible skin
    9. Joint hypermobility
    10. Muscle hypotonia
    11. Spondyloepimetaphyseal dysplasia

Clinical Features

1. Classic type (EDS I and II) (McKusick 1972; Beighton 1992; Beighton et al. 1998; Malfait et al. 2011)
    1. Major diagnostic criteria: The presence of scars with joint hypermobility suggests the classical type.
        1. Skin hyperextensibility
        2. Widened atrophic scars (the hallmark "cigarette-paper" scars, a manifestation of tissue fragility)
        3. Joint hypermobility
        4. Positive family history
    2. Minor diagnostic criteria
        1. Smooth, velvety skin
        2. Molluscoid pseudotumors
            1. Fresh lesions associated with scars
            2. Frequently found over pressure points such as elbow and knees
        3. Subcutaneous spheroids
            1. Small subcutaneous spherical hard bodies
            2. Frequently mobile and palpable on the forearms and shins
            3. May be calcified and detectable radiologically
        4. Complications of joint hypermobility
            1. Sprains
            2. Dislocations
            3. Recurrent joint subluxations in the shoulder, patella, and temporomandibular joints (TMJ)
            4. Pes planus
        5. Muscle hypotonia
        6. Delayed gross motor development
        7. Easy bruising
        8. Manifestations of tissue extensibility and fragility
            1. Hiatal hernia
            2. Anal prolapse in childhood
            3. Cervical insufficiency

9. Surgical complications (postoperative hernias)
10. Positive family history

3. Other features
   1. Families with variable severity (mild, moderate, and severe) of the skin manifestations
   2. Dyspareunia and sexual dysfunction: occasional complaints
   3. Fatigue: a frequent complaint

2. Hypermobile type (EDS III) (Levy 2016)
   1. Major diagnostic criteria
      1. Skin involvement (variable hyperextensibility and/or smooth, velvety skin)
      2. Generalized joint hypermobility (dominant clinical feature)
      3. Absence of fragility or other significant skin or soft tissue abnormalities
   2. Minor diagnostic criteria: supportive
      1. Positive family history of EDS, hypermobility type (or family history of joint laxity), without significant skin or soft tissue fragility, in a pattern consistent with autosomal dominant inheritance
      2. Recurrent joint dislocations (particularly shoulder, patella, and temporomandibular joints)
      3. Chronic joint/limb and back pain (early onset, chronic, and possibly debilitating)
      4. Easy bruising
      5. Functional bowel disorders (functional gastritis, irritable bowel syndrome)
      6. Neurally mediated hypotension or postural orthostatic tachycardia
      7. High narrow palate
      8. Dental crowding
   3. Other features
      1. Early-onset, chronic, and possibly debilitating musculoskeletal pain
      2. Aggravation of joint symptoms during pregnancy, but a complete return to the former status is possible
   4. Natural history and manifestations (Castori et al. 2010)
      1. The most difficult form to diagnose
      2. A diagnosis of exclusion for the following disorders:
         1. Underlying bone dysplasia
         2. Neuromuscular disorder (such as Bethlem myopathy)
         3. Various similar connective tissue disorders, including other types of EDS and the fibrillinopathies
      3. Lack of a major clinical trait except for joint hypermobility
      4. Lack of specific diagnostic laboratory tests, although tenascin-X monoallelic or biallelic inactivation can be documented in no more than 10% of the patients (Schalkwijk et al. 2001; Zweers et al. 2003).
      5. Clinical presentations
         1. Recurrent articular dislocations (also after surgical repair)
         2. Chronic/recurrent articular pain in adults or young adults with joint hypermobility and/or a history of infancy/childhood joint hypermobility
         3. Soft/velvety skin and/or easy bruising with joint hypermobility or a history of infancy/childhood joint hypermobility
         4. Chronic asthenia with recurrent articular pain and negative screening for inflammatory arthritis
         5. Acute thoracic pain due to spontaneous rib luxation/subluxation (rare)
         6. Early-onset uterine/vesical/rectal prolapse (19%)
         7. Chronic gastrointestinal discomfort including chronic recurrent dyspepsia/gastritis, gastro-esophageal reflux, irritable bowel disease, recurrent unexplained abdominal pain, and constipation/diarrhea

3. Vascular type (EDS IV) (Beridze and Frishman 2012; Pepin et al. 2015)
   1. Major diagnostic criteria: The presence of any two or more major criteria is highly indicative of the diagnosis of EDS IV;

biochemical testing is strongly recommended to confirm the diagnosis. Arterial/intestinal/uterine fragility or rupture (presenting signs in 70% of adults with vascular type of EDS).

1. Arterial aneurysms, dissection, or rupture: Spontaneous arterial rupture peaks in the third or fourth decade but may occur earlier, most commonly involves midsized arteries, and is the most common cause of sudden death. The sites of arterial rupture are the thorax and abdomen (50%), head and neck (25%), and extremities (25%).
2. Intrapartum uterine rupture and pre-/postpartum arterial rupture result in 15% mortality. Vaginal and perineal tears may complicate pregnancies during delivery.
3. Gastrointestinal ruptures occur in about 25% of patients, most common in the sigmoid colon. Ruptures of the small bowel and stomach are rare. The rupture may present as an acute abdomen.
4. Family history of the vascular type of EDS.

2. Minor diagnostic criteria: The presence of one or more minor criteria contributes to the diagnosis of the vascular type of EDS, but is not sufficient to establish the diagnosis.
    1. Thin translucent skin (especially noticeable on the chest or abdomen)
    2. Characteristic facial appearance in some affected patients due to a decrease in the subcutaneous adipose tissue
        1. Thin vermillion of the lips and philtrum
        2. Micrognathia
        3. Narrow nose
        4. Prominent eyes
    3. Acrogeria (an aged appearance of the extremities, particularly the hands)
    4. Hypermobility of small joints (usually limited to the digits)
    5. Tendon and muscle rupture (knee)
    6. Talipes equinovarus (clubfoot) (12%)
    7. Early-onset varicose veins
    8. Arteriovenous, carotid-cavernous sinus fistula
    9. Pneumothorax/pneumohemothorax (common in childhood)
    10. Mitral valve prolapse
    11. Easy bruising
        1. Lifelong history
        2. Spontaneous or with minimal trauma
    12. Extensive scars and hyperpigmentation over bony prominences and skin
    13. Chronic joint subluxations/dislocations
        1. TMJ
        2. Patella
        3. Ankles
    14. Congenital dislocation of the hips
    15. Talipes equinovarus (clubfoot)
    16. Gingival recession
    17. A positive family history consistent with autosomal dominant inheritance with sudden death in close relatives
3. Other features
    1. An uncommon subtype: Diagnosis often made only after a catastrophic complication or at postmortem examination
    2. Acute abdominal and flank pain (diffuse or localized): a common manifestation of arterial or intestinal rupture
    3. The single vessel most commonly affected: the iliac artery (Abayazeed et al. 2014)
    4. Subcutaneous venous pattern particularly apparent over the chest and abdomen
    5. Hypermobility of large joints and hyperextensibility of the skin: unusual in the vascular type
    6. The teenage boys: at higher risk for arterial rupture possibly due to further weakening of the defective collagen during the prepubertal growth spurt
    7. Patients undergoing surgery: Prone to have arterial rupture in the postoperative period, possibly due to increased

collagenase activity after surgical trauma
8. Aneurysms (if present) resulting from arterial tears with walled-in hematomas or pseudoaneurysms
9. Danger of varicose vein surgery in unrecognized cases since the extreme fragility of all blood vessels can lead to a loss of a limb or even loss of life

4. EDS V
   1. An extremely rare X-linked, recessively inherited disorder
   2. Clinically similar to EDS II
      1. Joint hyperextensibility
      2. Slightly hyperelastic skin
      3. Skin subject to mildly abnormal scarring
   3. Normal life span
   4. Asymptomatic female carriers
5. Kyphoscoliosis type (EDS VI) (Yeowell and Steinmann 2013)
   1. Major diagnostic criteria: Presence of three major criteria is suggestive of diagnosis of EDS, kyphoscoliosis type.
      1. Generalized joint laxity (recurrent joint dislocations common in adults)
      2. Severe muscle hypotonia at birth
      3. Kyphoscoliosis, present at birth or within the first year of life, progressive (adults with severe kyphoscoliosis are at risk for restrictive lung disease and pneumonia)
      4. Scleral fragility and rupture of the ocular globe
   2. Minor diagnostic criteria
      1. Tissue fragility, including atrophic scars
      2. Easy bruising
      3. Marfanoid habitus
      4. Microcornea (most patients)
      5. Radiologically considerable osteopenia (osteoporosis)
      6. Family history (e.g., affected sibs)
   3. Other features
      1. Pronounced muscular hypotonia leading to delayed gross motor development.
      2. Severe phenotype often results in loss of ambulation in the second or third decade.
      3. Scleral fragility leading to rupture of the ocular globe after minor trauma.
      4. Cardiovascular complications.
         1. Vascular rupture: the major life-threatening complication.
         2. Both aortic dilatation/dissection and rupture of medium-sized arteries may occur.
         3. Mitral valve prolapse common.
      5. Differential diagnosis: severe neonatal form of Marfan syndrome.
6. Arthrochalasia type (EDS VIIA and VIIB)
   1. Major diagnostic criteria
      1. Severe generalized joint hypermobility, with recurrent subluxations
      2. Congenital bilateral hip dislocation (present in all biochemically proven individuals, may lead to short stature)
   2. Minor diagnostic criteria
      1. Skin hyperextensibility
      2. Tissue fragility, including atrophic scars
      3. Easy bruising
      4. Muscle hypotonia
      5. Kyphoscoliosis (may lead to short stature)
      6. Radiologically mild osteopenia
   3. Other features
      1. Short stature resulting from complication of severe kyphoscoliosis and/or hip dislocation
      2. Differential diagnosis: Larsen syndrome
7. Dermatosparaxis type (EDS VIIC)
   1. Major diagnostic criteria
      1. Severe skin fragility (wound healing not impaired, scars not atrophic)
      2. Sagging, redundant skin (redundancy of the facial skin resulting in an appearance resembling cutis laxa) analogous to the animal disease dermatosparaxia
   2. Minor diagnostic criteria
      1. Soft, doughy skin texture
      2. Easy bruising (substantial)
      3. Premature rupture of fetal membranes
      4. Large hernias (umbilical, inguinal)

3. Other features
    1. Blue sclerae
    2. Palmar creases
    3. Micrognathia
    4. Joint laxity without subluxations
8. EDS VIII
    1. Chronically inflamed, heavily pigmented, discrete, and pretibial plaques (granulomatous collagen degeneration)
    2. Premature periodontal disease
    3. Premature loss of teeth
    4. Hypermobile joints
    5. Thin, soft, and hyperextensible skin
    6. Easy bruising skin
    7. Skin prone to abnormal scarring
    8. No consistent biochemical or structural changes detectable
9. Occipital horn syndrome (EDS IX)
    1. Also called X-linked cutis laxa
    2. Skeletal dysplasia
        1. Occipital horns
        2. Broad clavicles
        3. Deformed radii, ulnae, and humeri
        4. Narrow rib cage
        5. Undercalcified long bones
        6. Coxa valga
    3. Unusual facial appearance
    4. Hypermobility of finger joints
    5. Limitation of extension of elbows
    6. Chronic diarrhea
    7. Genitourinary abnormalities
        1. Bladder diverticulae
        2. Susceptible to rupture of the bladder
    8. Vascular complications (Mentzel et al. 1999)
        1. Splenic artery aneurysm
        2. Hepatic artery aneurysm
    9. Neuropathologic findings
        1. Neovascularization and extreme reduplication of the cerebral arteries with cystic medial degeneration
        2. Cerebellar hypoplasia
        3. Focal cortical dysplasia
        4. Cerebellar heterotopias
    10. Abnormal copper utilization
        1. Depleted serum copper level
        2. Depleted serum ceruloplasmin level
10. Ehlers-Danlos syndrome with fibronectin deficiency (EDS X)
    1. A mild, recessively inherited variant of Ehlers-Danlos syndrome
    2. Resembling EDS types II and III
    3. Thin, fragile, and easily scarred skin
    4. Joint hypermobility
    5. Excessive bruising
    6. Abnormal platelet aggregation but correctable with normal fibronectin

Diagnostic Investigations

1. Classic type
    1. Ultrastructural studies
        1. Disturbed collagen fibrillogenesis
        2. A characteristic “cauliflower” deformity of collagen fibrils
    2. Abnormal electrophoretic mobility of the proα1(V) and proα2(V) chains of collagen type V in some patients
    3. Demonstration of a mutation in *COL5A1* and/or *COL5A2* genes
    4. Echocardiogram to measure aortic root size (Tiller et al. 1998)
2. Hypermobile type: *TNXB* sequencing or *COL3A1* mutation study
3. Vascular type (Pepin et al. 2015)
    1. Diagnosis of vascular type is established in a proband with any one of the following:
        1. Identification of a heterozygous *COL3A1* pathogenic variant on molecular genetic testing (sequence analysis, gene-targeted deletion/duplication analysis)
        2. Abnormalities in synthesis and mobility of type III collagen chains on biochemical analysis of type III procollagen from cultured fibroblasts when vascular EDS is suspected but molecular genetic testing does not identify a *COL3A1* pathogenic variant or a variant of uncertain significance is identified
    2. Surveillance of aneurysm by MRI or CT scan without contrast material or venous subtraction angiography

4. Kyphoscoliosis type
    1. Demonstration of deficient activity of the enzyme procollagen lysine hydroxylase in affected individuals, diagnosed by biochemical testing of the urine and enzyme assay of cultured fibroblasts
    2. Demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in the urine measured by HPLC, a highly sensitive and specific test (Malfait et al. 2011)
    3. Demonstration of mutations of the *PLOD* gene that encodes the enzyme procollagen lysyl hydroxylase (Malfait et al. 2011)
    4. Echocardiogram to measure aortic root size (dilatation) (Tiller et al. 1998)
5. Arthrochalasis type
    1. Electrophoretic demonstration of pNα1 (I) or pNα2(I) chains extracted from dermal collagen or harvested from cultured skin fibroblasts
    2. Mutation analysis (complete or partial exon 6 skipping in cDNAs of *COL1A1* or *COL1A2*, respectively)
6. Dermatosparaxis type (Smith et al. 1992): electrophoretic demonstration of pNα1(I) or pNα2 (I) chains from collagen type I extracted from dermis in the presence of protease inhibitors, or obtained from cultured skin fibroblasts

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive: 25% risk of having an affected sib
        2. Autosomal dominant: risk low (1–5%) unless the parent is affected or having somatic mosaicism or germline mosaicism
        3. X-linked recessive: 50% risk of having an affected brother if the mother is a carrier
    2. Patient's offspring
        1. Autosomal recessive: risk not increased unless the spouse is a carrier.
        2. Autosomal dominant: 50% risk of having an affected offspring.
        3. X-linked recessive: None of the sons will be affected; all daughters will be carriers.
2. Prenatal diagnosis (Yeowell and Steinmann 2013)
    1. Possible by demonstrating the disease-causing mutation in the fetal cells from CVS or amniocentesis or by linkage analysis for families in which linkage has been established
    2. Possible by biochemical assay on cultured fetal cells for demonstrating biochemical defect in the specific type of collagen
3. Preimplantation genetic diagnosis may be an option for some families in which the disease-causing mutations have been identified.
4. Management
    1. General approach: conservative and preventive management of most skin and joint problems
        1. Avoid tension when sutures are applied.
        2. Leave removable sutures in place for twice the usual time.
        3. Physical therapy to strengthen the muscles that need to provide support for the loose ligaments.
    2. Classic type (Malfait et al. 2011)
        1. Medical intervention limited to symptomatic therapy and prophylactic measures.
        2. Wear protection pads or stocking.
        3. Avoid contact sports.
        4. Physiotherapy for children with hypotonia and delayed motor development.
        5. Antimicrobial prophylaxis for patients with mitral valve prolapse.
        6. Ascorbic acid helps avoid easy bruising but does not change the basic clinical picture.
    3. Hypermobile type (Levy 2016)
        1. Physical therapy tailored to the individual.
        2. Assisted devices
            1. Braces to improve joint stability
            2. Wheelchair or scooter to offload stress on lower-extremity joints
            3. Suitable mattress to improve sleep quality
        3. Pain medication tailored to symptoms: Severe pain may need pain specialist's help.

4. Appropriate therapy for gastritis/reflux/delayed gastric emptying/irritable bowel syndrome.
5. Possible beta-blockade or rarely surgical approach for progressive aortic enlargement.
6. Psychological and/or pain-oriented counseling.

4. Kyphoscoliotic type
   1. Orthopedic management of kyphoscoliosis
   2. Physical therapy for older children, adolescents, and adults
   3. Antimicrobial prophylaxis for patients with mitral valve prolapse
   4. Aggressive control of blood pressure
   5. Improve with large doses of ascorbic acid because vitamin C is a cofactor for the enzyme that is deficient (Pyeritz 2000)
      1. Improve urinary excretion of hydroxylysine
      2. Improve muscle strength and wound healing
5. Vascular type (Pyeritz 2000; Pepin et al. 2015)
   1. The most severe form of EDS
   2. Prompt recognition of the major complications
   3. Difficult to repair ruptured arteries because of the pronounced vascular fragility
   4. Rupture of the bowel, a surgical emergency
   5. Avoid pregnancy because the risk of vascular rupture is especially high during pregnancy
   6. Minimize risk of trauma by avoiding contact sport, heavy lifting, and weight training
   7. Treat high blood pressure aggressively with β-adrenergic blockade
   8. Elective surgical management of vascular disorders in EDS patients using open and endovascular procedure (Brooke et al. 2010)
      1. Associated with good outcomes
      2. Can be safely performed and should not be withheld until rupture or acute symptoms arise
   9. Patient education
      1. Possible complications
      2. Need for close monitoring
      3. Attention to sudden unexplained pain

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Fig. 1 (**a**, **b**) Hyperextensible joints enable a girl and two sisters with EDS to exhibit difficult hyperextensible joint maneuvers

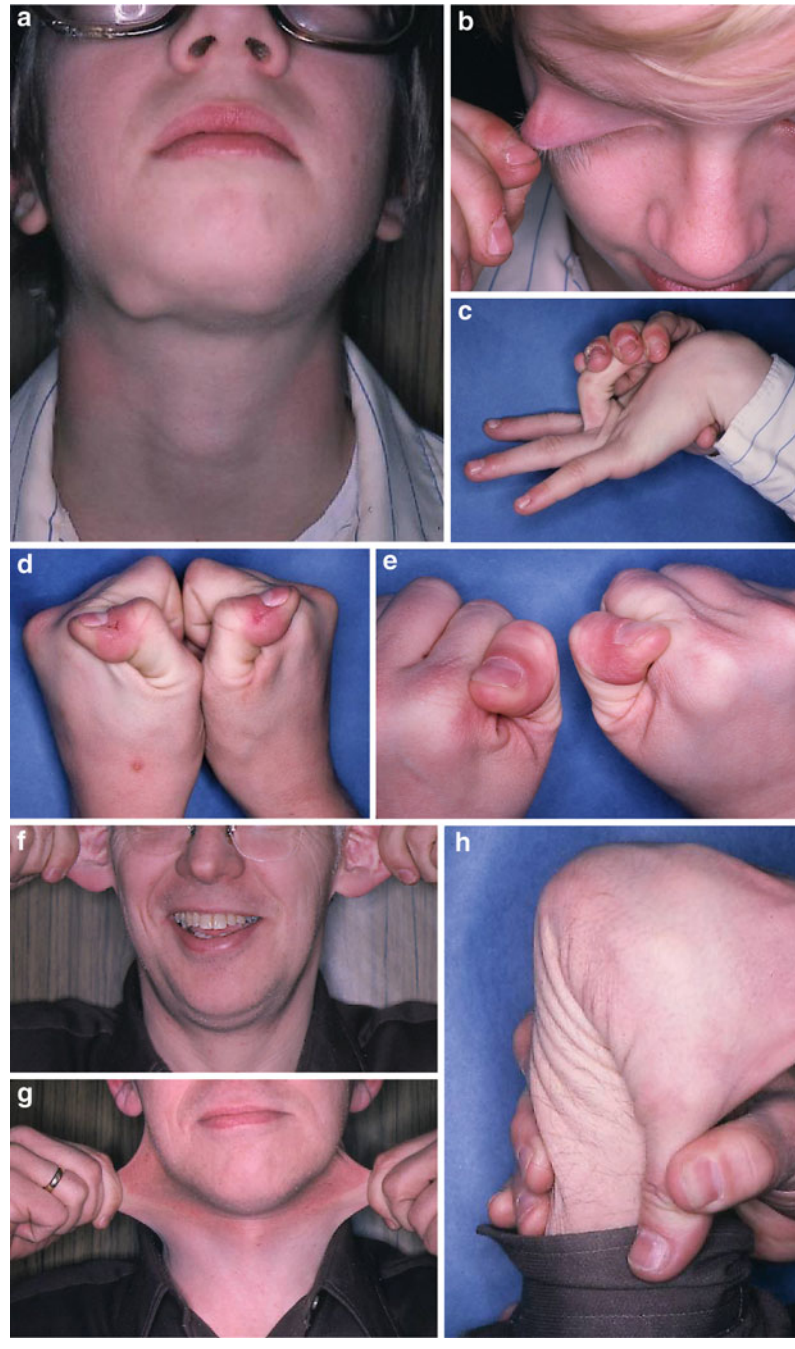

Fig. 2 Familial Ehlers-Danlos syndrome in the son (**a**–**d**), the daughter (**e**), and the father (**f**–**h**) exhibiting hyperextensible joints and hyperelastic skin. The son also has fascia weakness presenting as a hernia on the lower chin

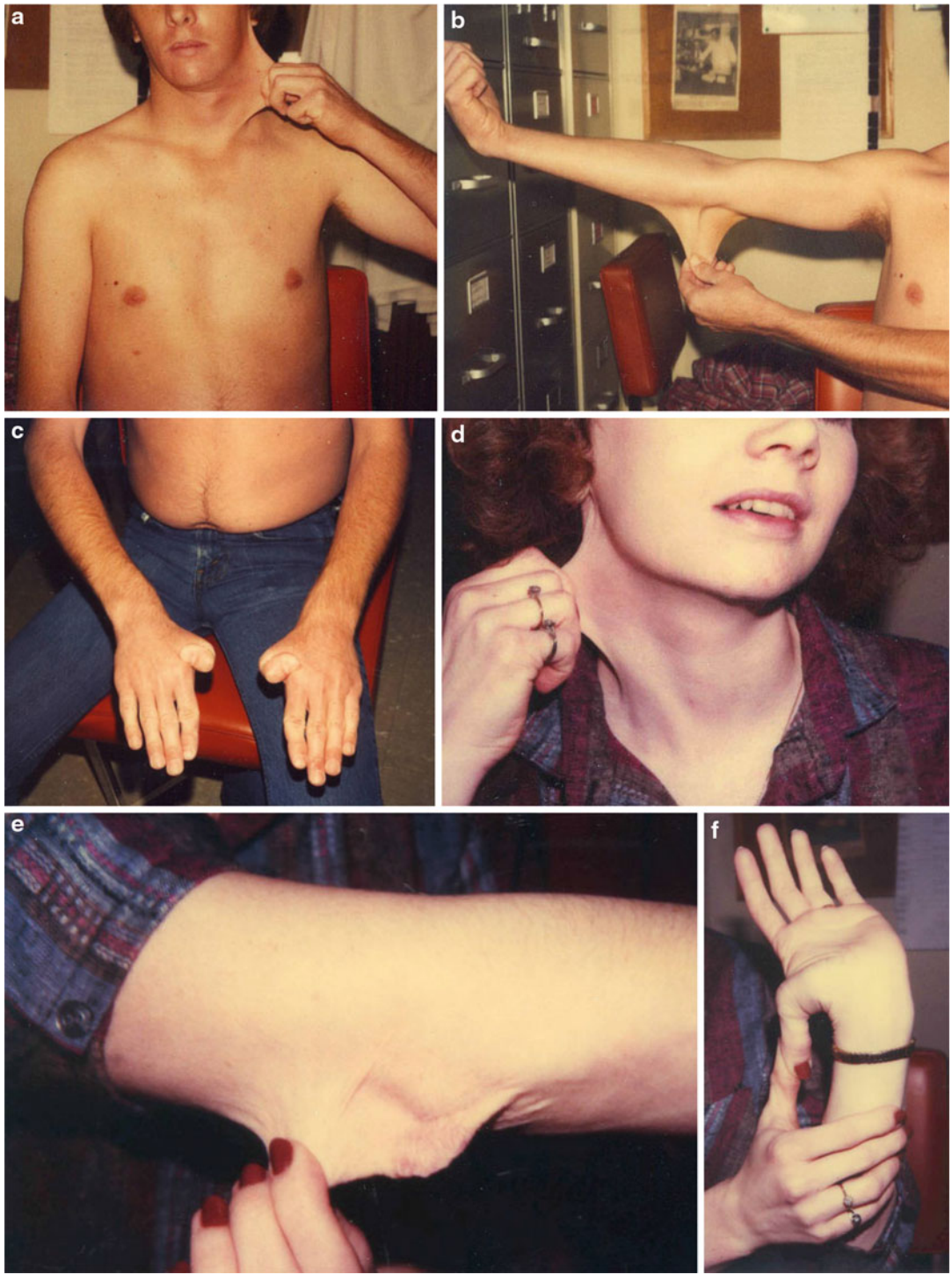

Fig. 3 (**a**–**f**) A male and a female with EDS showing hyperextensible joints and hyperelastic skin

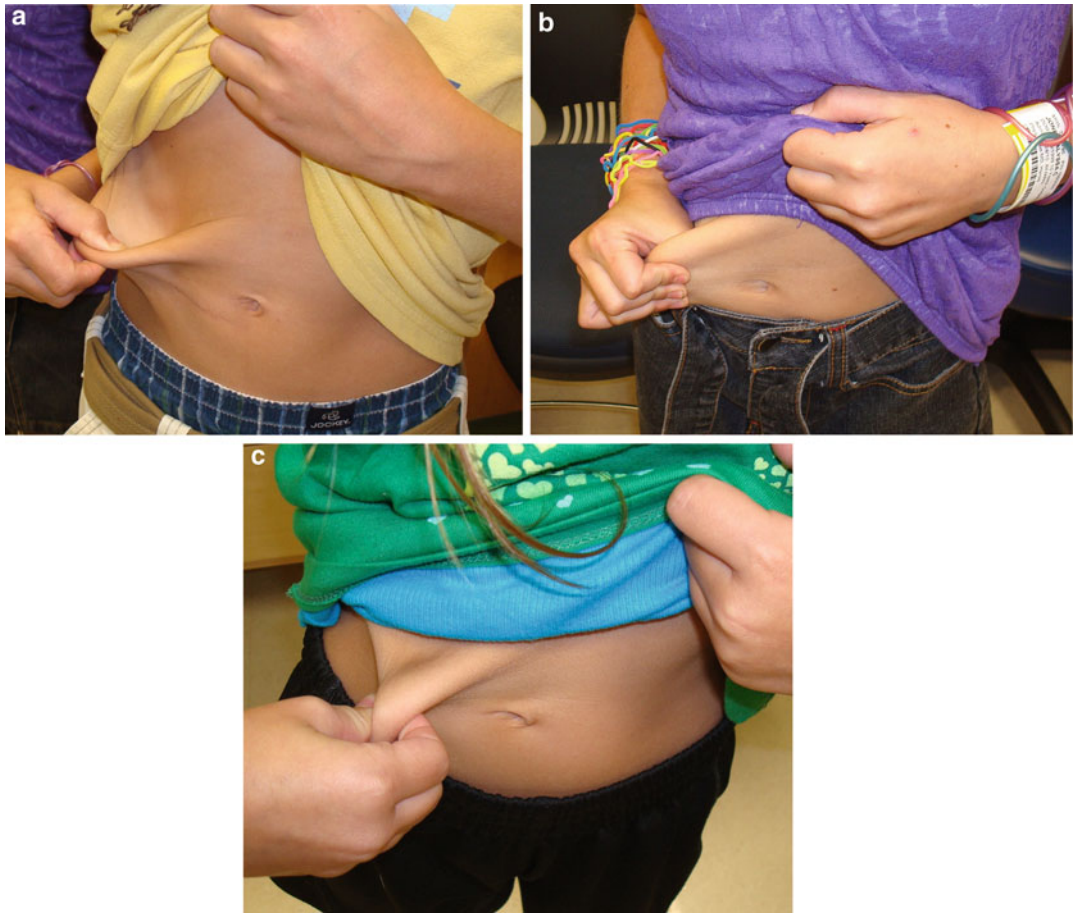

Fig. 4 (**a**–**c**) Three siblings (12-year-old boy, 10-year-old girl, and 7-year-old girl) with Ehlers-Danlos syndrome showing markedly stretchable abdominal walls. Their mother is also affected with a history of hyperextensible joints with subluxations of sternum-collarbone junction, TMJ, hip, and knees

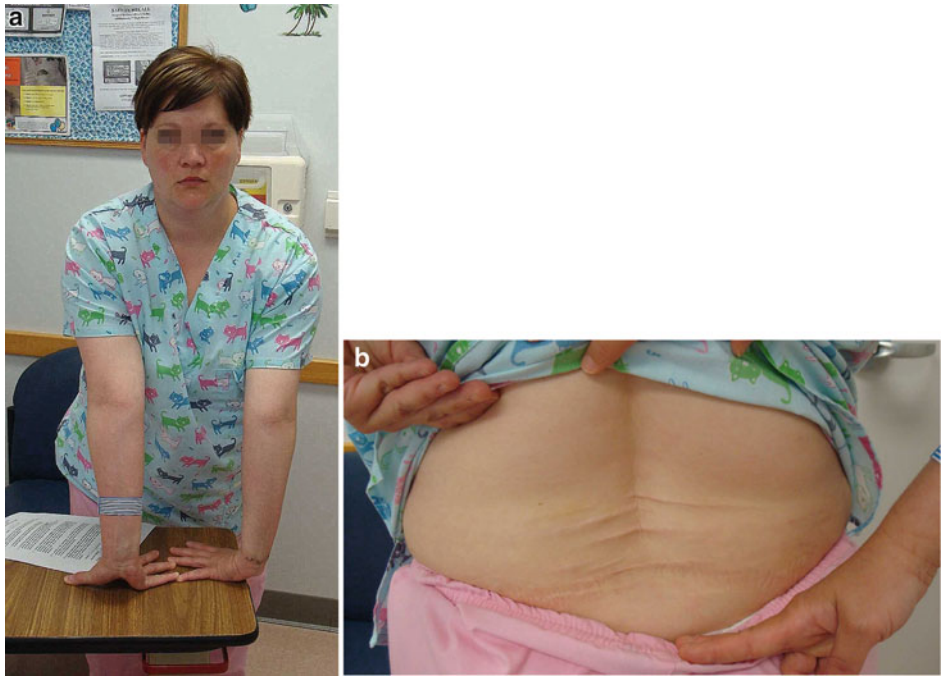

Fig. 5 (**a**, **b**) A 40-year-old female with hypermobile type of Ehlers-Danlos syndrome showing hyperextensible joints and stretch marks of the skin. She suffers from rectal, bladder, and uterine prolapses. She had four placental abruptions and had ventral hernias repaired twice. She had shoulder dislocations three times and patella dislocations more than ten times. She had a history of recurrent articular and abdominal pain and episodic constipations and diarrheas

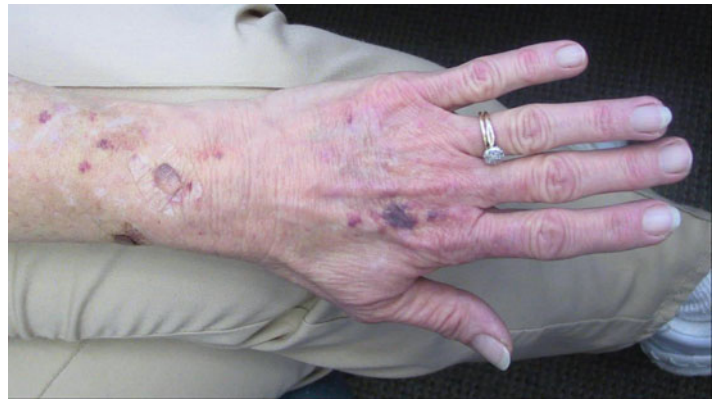

Fig. 6 Typical EDS showing easy bruises and scars of the skin

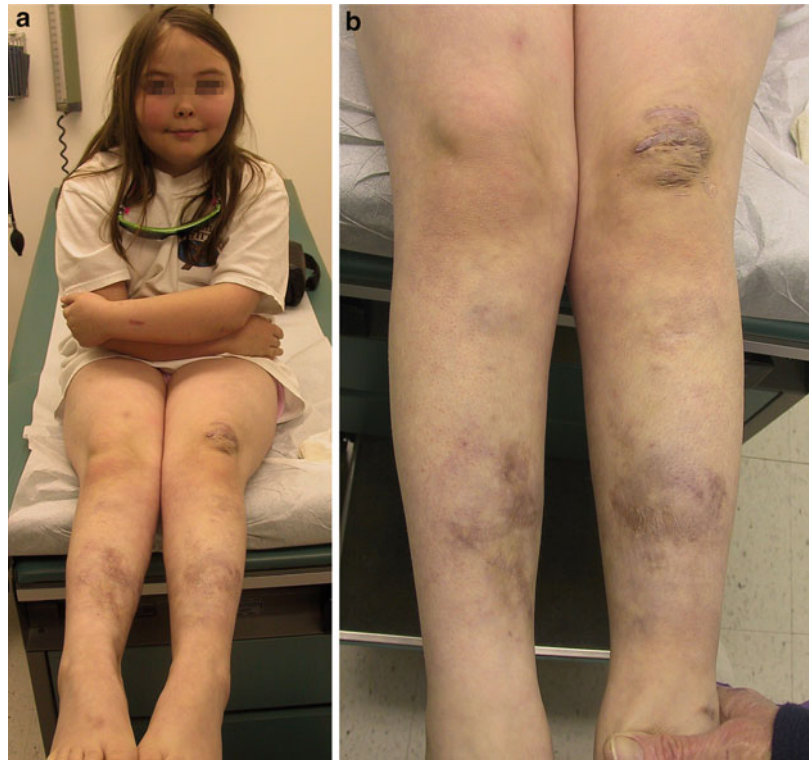

Fig. 7 (**a**, **b**) An 8-year-old girl with Ehlers-Danlos syndrome showing marked scarring of the skin

Fig. 8 A 14-year-old girl, a 10-year-old boy, a 4-year-old half-brother, and their mother were evaluated for Ehlers-Danlos syndrome, hypermobile type. The mother had a history of recurrent articular dislocations (pop-out hips and shoulder joints), chronic and recurrent articular pain with joint hypermobility, loose skin, easy bruising, Raynaud phenomenon, and chronic gastrointestinal discomfort, including chronic recurrent dyspepsia, gastro-esophageal reflux, irritable bowel disease, recurrent unexplained abdominal pain, and constipation/diarrhea episodes. Her three children here and two other older brother and sister also have similar signs and symptoms like those of her mother

Ellis-van Creveld Syndrome

Contents

In 1940, Ellis and van Creveld (Ellis and Creveld 1940) described a syndrome, characterized by ectodermal dysplasia, polydactyly, chondrodysplasia, and congenital heart disease. Ellis-van Creveld syndrome, also called chondroectodermal dysplasia, is relatively common in inbred communities, such as the Amish of Lancaster County where it occurs in 1/5,000 births compared to 1/60,000 births in the general population.

Synonyms and Related Disorders

Chondroectodermal dysplasia

Genetics/Basic Defects

1. Inheritance
   1. Autosomal recessive inheritance (Douglas et al. 1959; da Silva et al. 1980; George et al. 2000)
   2. Parental consanguinity (McKusick et al. 1964; Hill 1977; McKusick 2000) in 30% of cases
2. Basic defect (Arya et al. 2001)
   1. Generalized dysplasia of endochondral ossification
      1. Delayed in the primary centers
      2. Premature in the secondary centers
      3. Leads to short stature with progressive distal shortening of the extremities
   2. Caused by mutations in a novel gene, *EVC1*, which is mapped to chromosome 4p16.1 (Polymeropoulos et al. 1996; Ruiz-Perez et al. 2000)
   3. Caused by mutations in a second gene, called *EVC2*, that gives rise to the same phenotype of the syndrome (Galdzicka et al. 2002)
   4. Molecular heterogeneity (Ali et al. 2010) and possibility of involvement of other genes suggested by more mutations in both *EVC1* and *EVC2* in two thirds of the patients (Tompson et al. 2007)
   5. May be allelic to Weyers acrodental dysostosis

Clinical Features

1. A clinical tetrad (Al-Khenaizan et al. 2001; Arya et al. 2001; Chen 2015)
   1. Chondrodystrophy

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1. The most common feature affecting the tubular bones
2. Disproportionate dwarfism
3. Progressive distal limb shortening
    1. Symmetrical
    2. Affects the forearms and lower legs
2. Polydactyly
    1. A constant finding
        1. Bilateral
        2. Postaxial
    2. Polydactyly of the hands observed in most cases
    3. Polydactyly of the feet observed only in 10% of cases
3. Hidrotic ectodermal dysplasia (up to 93%)
    1. Nails
        1. Hypoplastic
        2. Dystrophic
        3. Friable
        4. Completely absent in some cases
    2. Teeth
        1. Neonatal teeth
        2. Partial anodontia
        3. Small teeth
        4. Delayed eruption
        5. Enamel hypoplasia commonly resulting in abnormally shaped teeth with frequent malocclusion
    3. Occasional sparse hair
4. Cardiac anomalies (50–60%) (Husson and Parkman 1961)
    1. A single atrium (Giknis 1963; Sajeev et al. 2002)
    2. AV canal
    3. Ventricular septal defect
    4. Atrial septal defect
    5. Patent ductus arteriosus
    6. The major cause of shortened life expectancy

2. Other clinical findings
    1. Other oral lesions (Hunter and Roberts 1998; Cahuana et al. 2004)
        1. A fusion of the anterior portion of the upper lip to the maxillary gingival margin
            1. Resulting in the absence of mucobuccal fold
            2. Causing the upper lip to present a slight V-notch in the middle
        2. Multiple labiogingival frenula frequent
        3. Lower alveolar ridge often serrated
    2. Orthopedic manifestations (Weiner et al. 2013)
        1. The shoulder, arm, and elbow
            1. Curvature of the humerus and arm
            2. Cubitus valgus
            3. Radial head subluxation-dislocation
        2. The forearm, wrist, and hand
            1. Enlarged distal radius
            2. Stiffness of the PIP joints
            3. Marked loss of ability to make “fist”
        3. The spine and pelvis
            1. Increased lumbar lordosis
            2. Scoliosis
        4. The hip and thigh
            1. Marked external rotation and markedly limited internal rotation
            2. An overall externally rotated thigh and leg
            3. Contracted iliotibial band and lateral quadriceps
        5. The knee and leg
            1. Severe, profound valgus deformity of the knee
            2. Lateral patellar subluxation
            3. Patellar dislocation
            4. Severe contracture iliotibial band, lateral quadriceps, lateral hamstrings, and lateral collateral ligament
            5. Normal knee ligament stability
            6. Proximal medial tibial exostosis
        6. The ankle and feet
            1. Broad foot with pronation
            2. Overriding the 5th toe
            3. The short third toe and longer fourth toe
    3. Genitourinary anomalies (22%)
        1. Hypospadias
        2. Epispadias
        3. Hypoplastic penis
        4. Cryptorchidism
        5. Vulvar atresia
        6. Focal renal tubular dilation in the medullary region
        7. Nephrocalcinosis

8. Renal agenesis
9. Megaureters

4. CNS
   1. Normal intelligence in most patients
   2. Occasional CNS anomalies or mental retardation

Diagnostic Investigations

1. Radiography (Caffey 1952; Arya et al. 2001)
   1. Essential features
      1. Postaxial polydactyly
      2. Progressively distal shortening of segments (acromesomelia with relative shortening of the distal and middle segment of the limbs and phalanges)
      3. Generalized thickness and coarseness of bones
   2. Other features depending on disease severity and age
      1. Curvature of the humerus
      2. Enlargement of distal ends of the radii and ulnae
      3. Hypoplastic distal phalanges
      4. Short, broad middle phalanges
      5. Fusion of metacarpals
      6. Fusion of the hamate and capitate bones of the wrists
      7. Supernumerary carpal bone centers
      8. Clinodactyly
      9. Synostosis
      10. Wedge-shaped tibial epiphyses
      11. Genu valgum with hypoplasia of the upper lateral tibia
      12. Fibula disproportionately smaller than the tibia
      13. Pelvic dysplasia with low iliac wings and spur-like downward projections at the medial and lateral aspects of the acetabula
      14. The narrow thorax with short ribs
2. Echocardiography for cardiac malformations
3. Histopathology: disorganization of chondrocytes in the physeal growth zone of the long bones (Sergi et al. 2001) and vertebrae in the prenatal period (Qureshi et al. 1993) and retardation of physeal growth zones in the childhood
4. Mutation analysis

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis: feasible as early as the first trimester
   1. Fetoscopy (Bui et al. 1984)
   2. Ultrasonography (Horigome et al. 1997; Guschmann et al. 1999; Tongsong and Chanprapaph 2000; Arya et al. 2001; Dugoff et al. 2001; Baujat and Le Merrer 2007)
      1. Increased nuchal translucency thickness
      2. A narrow chest
      3. Postaxial polydactyly
      4. Short limbs, especially middle and distal segments
      5. Cardiac anomalies such as a single atrium
   3. Molecular genetic testing
      1. Using linked microsatellite markers flanking the *EVC* locus (Torrente et al. 1998; Arya et al. 2001)
      2. Mutation analysis of *EVC1* and *EVC2* genes (www.genetests.org)
      3. Sequencing the EVC and EVC2 genes from DNA extracted from fresh fetal tissue identified p.W215X (inherited from the mother) and P.R677X mutation (inherited from the father) (Peraita-Ezcurra et al. 2012)
   4. Array CGH analysis (D'Ambrosio et al. 2015)
      1. Allows genome analysis with a resolution of <1 Mb, while conventional cytogenetic examination allows for a 5–10 Mb resolution.
      2. Currently, considered to be the best method to detect genomic imbalances in particular submicroscopic rearrangements, but it is not designed to

detect point mutations responsible for monogenic disorders.
3. Array CGH (Agilent 60 K)mon non-cultured amniocytes revealed an 800 kb deletion on 4p16.2 (4979855–5747102) (hg19/GRCh37), including complete deletion of EVC2 gene and partial deletion of EVC gene.

3. Management
   1. Dental cares (Hattab et al. 1998; Cahuana et al. 2004)
      1. Childhood.
         1. To prevent caries by dietary counseling, plaque control, and oral hygiene instruction
         2. Crown or composite buildups for microdonts
         3. Partial dentures to maintain space and improve mastication, esthetics, and speech because of congenitally missing teeth
         4. Orthodontic treatment
      2. Adulthood requires implants and prosthetic rehabilitation to replace congenitally missing teeth.
   2. Cardiac surgery to correct cardiac anomalies
   3. Urologic management for genitourinary anomalies
   4. Orthopedic cares
      1. Polydactyly excision
      2. Surgery for genu valgum

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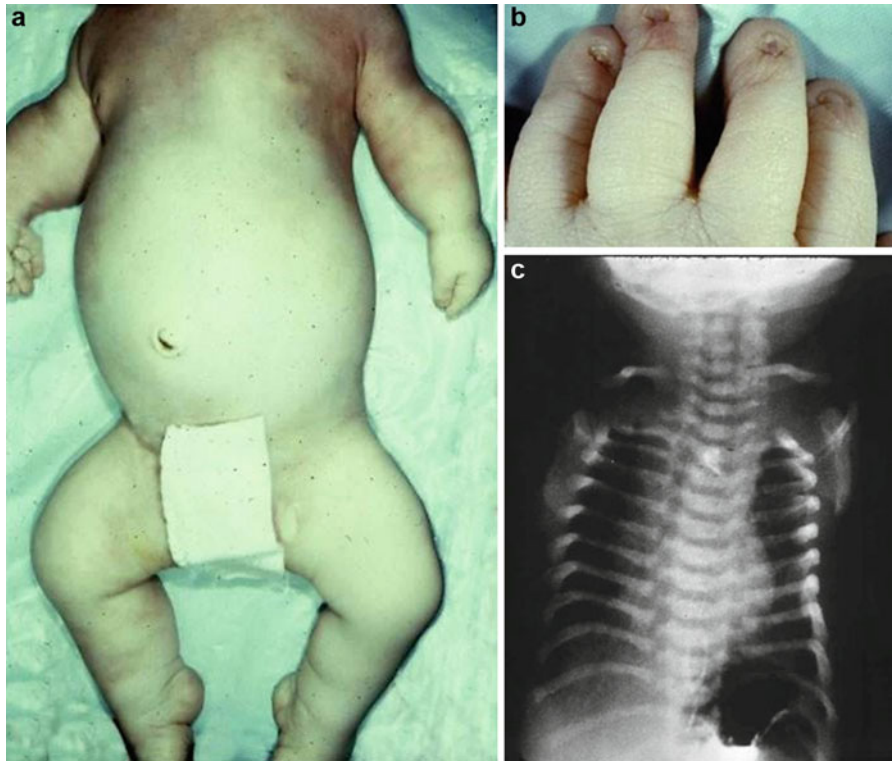

Fig. 1 (**a**–**c**) A neonate with small chest and short extremities. The fingernails are small and deformed. The baby had six fingers on each hand. Radiograph of the chest shows short ribs but the vertebral bodies are normal

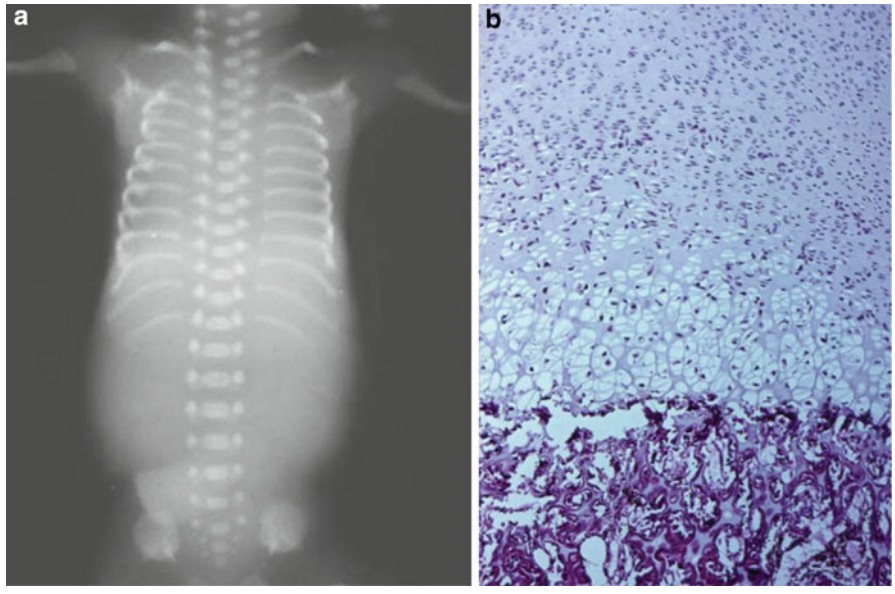

Fig. 2 (**a**, **b**) Radiograph of a fetus with Ellis-van Creveld syndrome showing short ribs and vertically shortened ilia. The vertebral bodies are unremarkable. Photomicrograph of femoral physeal growth zone shows disorganization of chondrocytes. The physeal growth zone of vertebrae showed better columnization

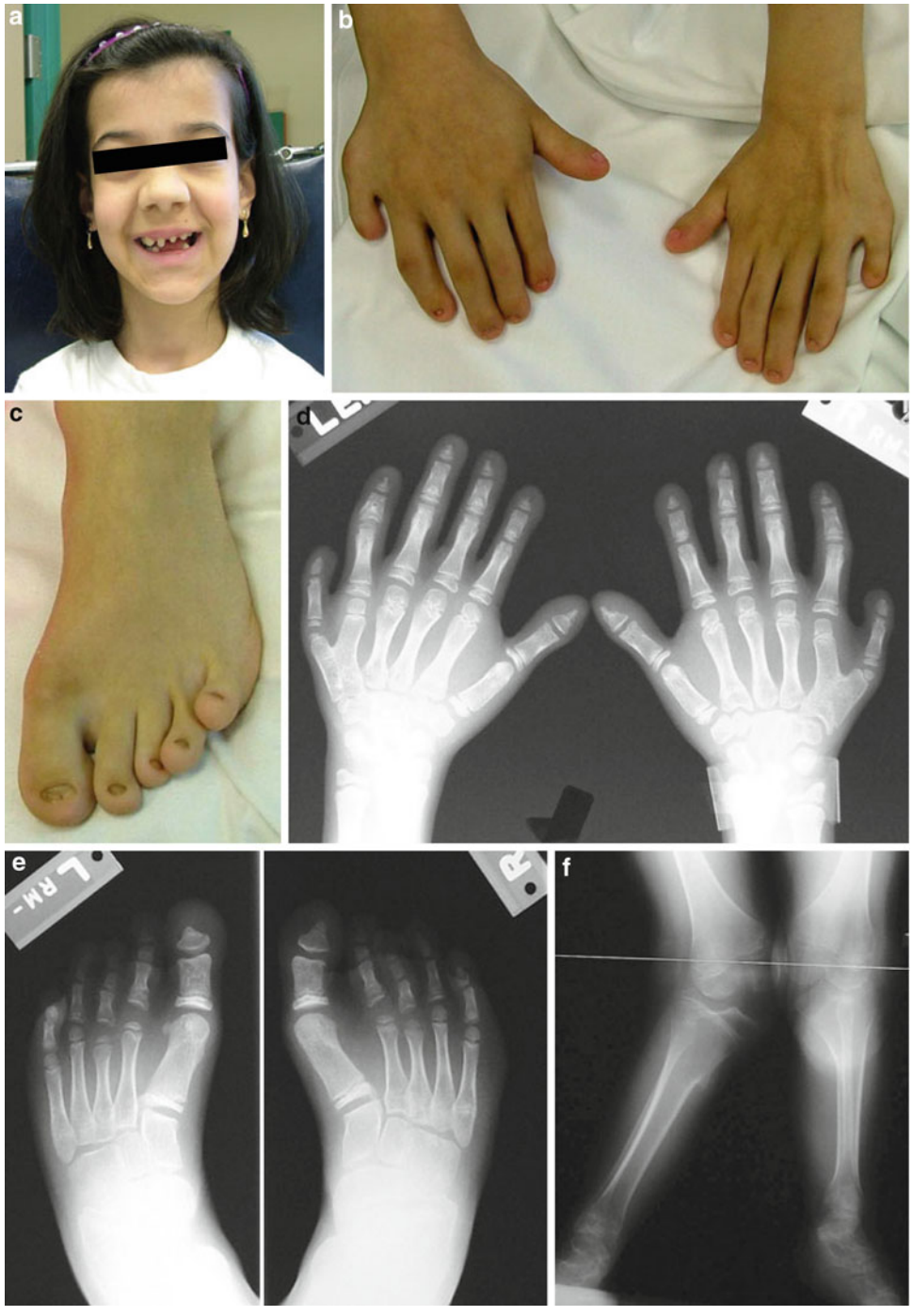

Fig. 3 (**a**–**f**) A 10-year-old Lebanese girl, a product of a consanguineous parents, with Ellis-van Creveld syndrome showing oligodontia and malformed teeth, severe nail hypoplasia of the hands and feet, and broad hands with bilateral postaxial polydactyly. Radiographs show polydactyly, fusion of metacarpals and carpal centers, cone epiphyses of the middle and distal phalanges, and genu valgum

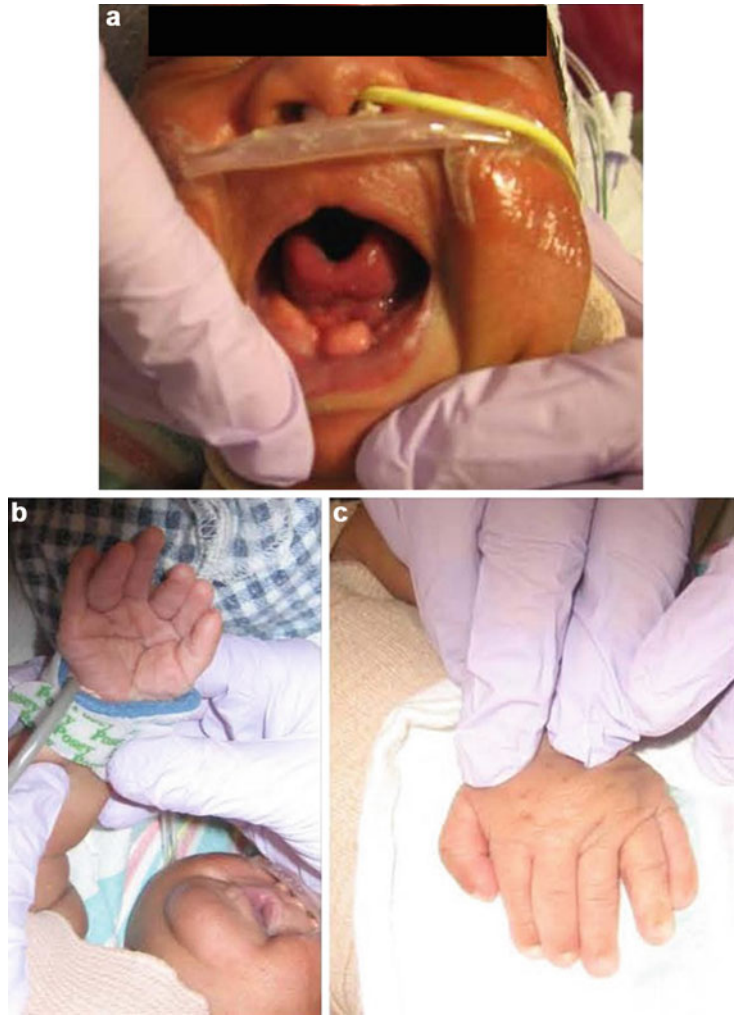

Fig. 4 (**a**–**c**) A 2-day-old male infant with abnormal fetal ultrasound (our OB) showing short limbs and a complex heart defect with a common atrium and AV canal. The infant showed short stature, short extremities, a long narrow chest, some tethering of the internal upper lip to the gingival margin, oral frenula causing clefting of the upper and lower alveolar ridges, and natal teeth on the upper and lower gingiva (**a**). The infant has postaxial polydactyly on both hands, hypoplastic nails on both fingers (**c**) and toes, and distal shortening of the digits of both hands and feet. Cranial and renal ultrasounds were normal. Postnatal echocardiogram showed situs solitus with levocardia, bilateral superior vena cava draining into a common atrium, an AV canal defect, and right ventricular hypertrophy and dilatation. EVC and EVC2 gene analysis showed a homozygous IVS13-9_c.1900del23 in the EVC gene. This 23 nucleotide deletion spans an intron/exon boundary and will result in aberrant mRNA processing. This exact change has been previously reported as a homozygous mutation in a patient with Ellis-van Creveld syndrome (Sund et al. 2009) (Courtesy of Dr. Susonne Ursin)

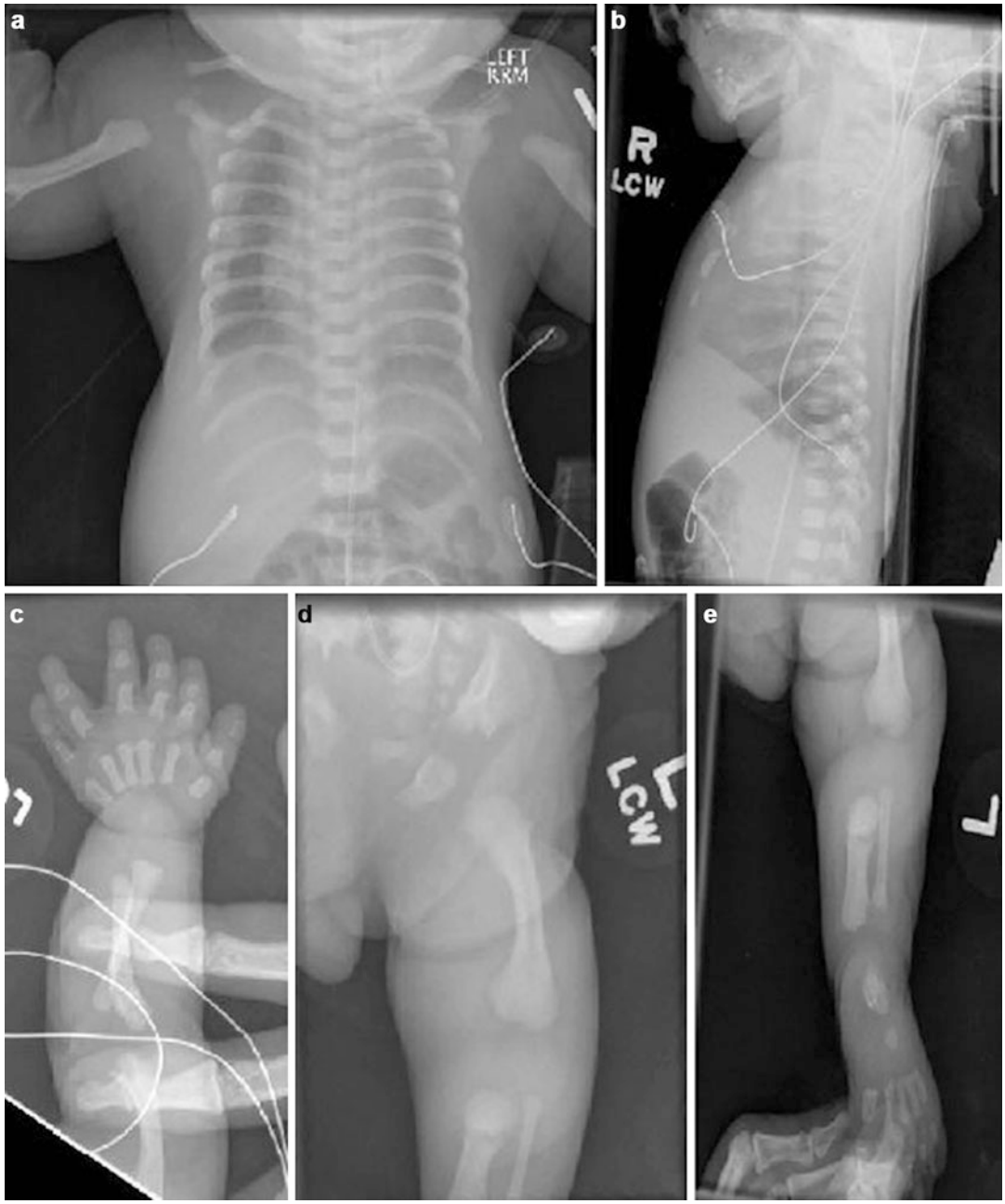

Fig. 5 (**a**–**c**) The radiologic features included a long narrow thorax with short ribs, acetabulum with spurs medially and laterally and narrow sacrosciatic notches, distal humeri with bony spurs, and small mid- and distal phalanges and absent terminal phalanges of all toes and six digits of the hands

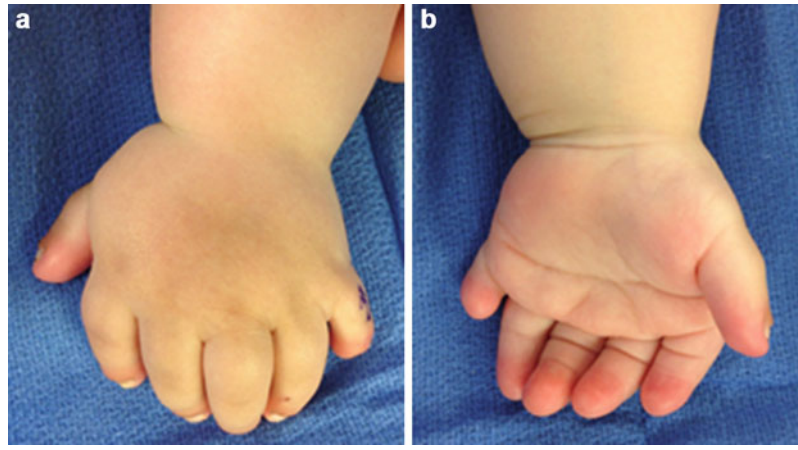

Fig. 6 (**a**, **b**) An 18-month-old boy was evaluated for bilateral postaxial polydactyly of both hands and Ellis-van Creveld syndrome. The boy was born with a birth weight of 3550 g and Apgar scores of 8 and 9 at 1 and 5 min, respectively. He was delivered at 41 weeks via C-section due to breech presentation. He was admitted to NICU for evaluation of atrial septal defect and respiratory distress and pulmonary hypertension. He lives with his parents in the Amish community. Family history revealed that the father's cousin has Ellis-van Creveld syndrome. He was short for his age with a slightly large head and mesomelic shortening of his lower and upper extremities. He had short and plump hands with bilateral postaxial polydactyly, type A (**a**, **b**). The toenails appeared to be hypoplastic (Contributed by Dr. Grace Guo)

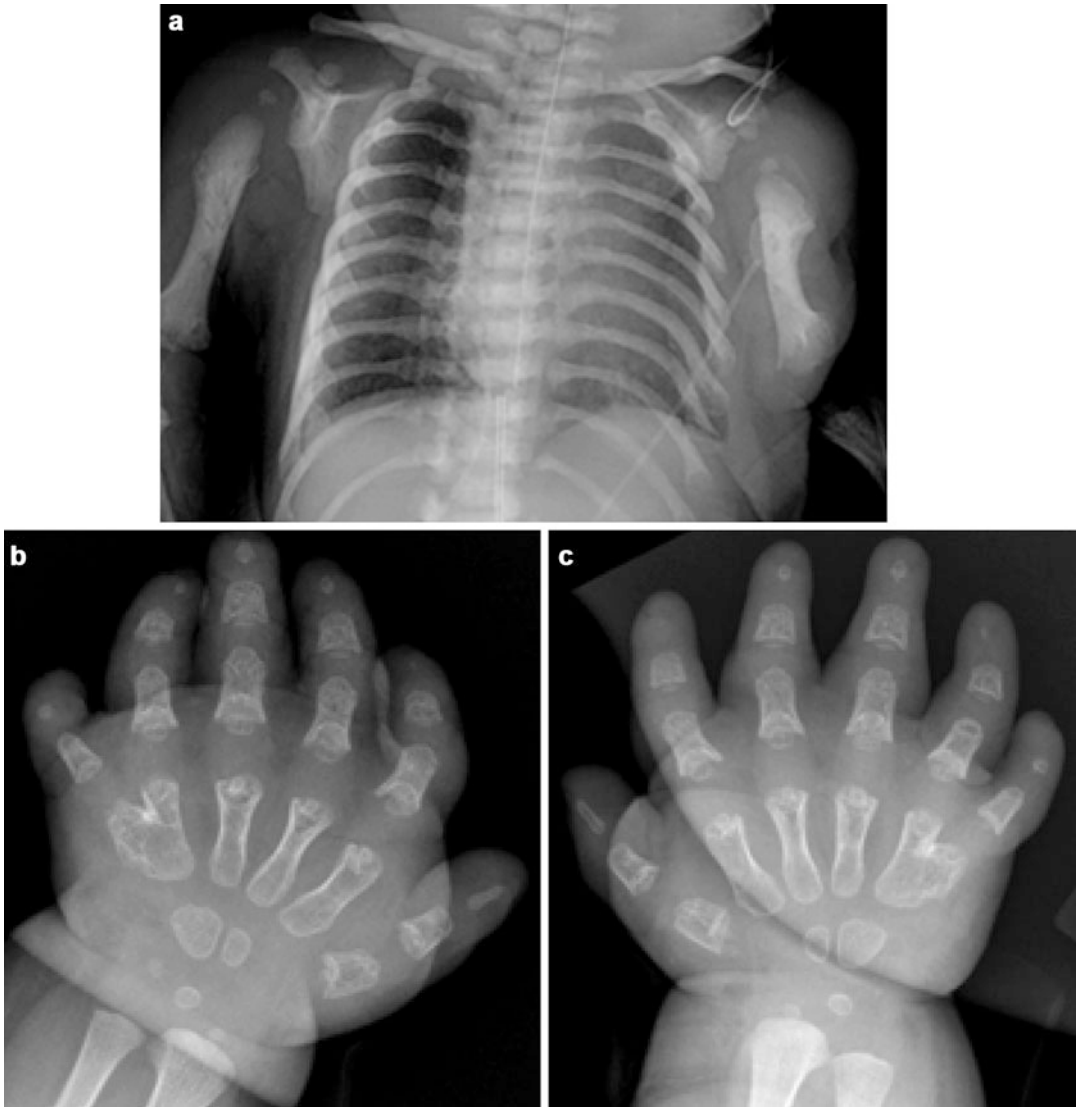

Fig. 7 (**a**–**c**) Chest radiography at 3 weeks age (**a**) showed a small rib cage with short ribs and small scapulae bilaterally. The humeri were hypoplastic and deformed. Radiography of hands showed six rays bilaterally. The phalanges were short and thickened with irregular metaphyses. Distal phalanges were hypoplastic. The fifth and sixth metacarpals of both hands were fused proximally. The patient's clinical and radiographic features were classic for Ellis-van Creveld syndrome (Contributed by Dr. Grace Guo)

Emanuel Syndrome

Contents

Emanuel syndrome (ES) is an unbalanced translocation syndrome that usually arises through a 3:1 meiosis I malsegregation during gametogenesis in a balanced translocation phenotypically normal carrier (Shaikh et al. 1999). ES is a rare inherited chromosomal abnormality syndrome with over 100 cases reported (Fraccaro et al. 1980; Zackai and Emanuel 1980; Lin et al. 1986; Choudhary et al. 2013).

Synonyms and Related Disorders

Derivative 11;22 syndrome; Derivative 22 syndrome; Partial trisomy 11;22; Supernumerary der (22)t(11;22) syndrome

Genetics/Basic Defects

1. Etiology, caused by chromosome imbalance consisting of either of the following (Emanuel et al. 2015):
    1. A derivative chromosome 22 [der(22)] as a supernumerary chromosome with the following karyotype:
        1. 47,XX,+der(22)t(11;22)(q23;q11) in females
        2. 47,XY,+der(22)t(11;22)(q23;q11) in males
    2. Rarely, a balanced (11;22) translocation as well as the supernumerary derivative chromosome
2. The supernumerary der(22) chromosome is easily identified by routine G-band analysis at the 500–550 band level.

Clinical Features

1. Affected children: usually identified in the newborn period as the offspring of a balanced (11;22) translocation carrier
2. A distinctive phenotype (Fraccaro et al. 1980; Zackai and Emanuel 1980; Lin et al. 1986; Hou 2013; Carter et al. 2009; Zaki et al. 2012; Choudhary et al. 2013; Emanuel et al. 2015):
    1. Growth and development
        1. Pre- and postnatal growth retardation
        2. Failure to thrive

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_283

3. Severe intellectual disability
4. Delayed speech and language development (more commonly)

2. Craniofacial features
   1. Microbrachycephaly
   2. Prominent forehead
   3. Downslanting palpebral fissures
   4. Broad and flat nasal bridge
   5. Long pronounced philtrum
   6. Abnormal auricles
   7. Preauricular pits/or tags (76%)
   8. Cleft or high-arched palate (50%)
   9. Micrognathia (60%)
   10. Angular mouth pits
   11. Bifid uvula
   12. Deafness
   13. Otitis media
3. CNS
   1. Microcephaly most commonly present
   2. Seizures
4. Congenital heart defects (60%)
   1. Atrial septal defect
   2. Ventricular septal defect
   3. Tetralogy of Fallot
   4. Patent ductus arteriosus
5. Gastrointestinal
   1. Diaphragmatic hernia
   2. Anal atresia
   3. Inguinal hernias
   4. Biliary atresia
   5. Micropenis (64%)
   6. Cryptorchidism (46%)
6. Renal: kidney abnormalities (36%)
7. Musculoskeletal
   1. Most commonly central hypotonia
   2. Congenital hip dislocation
   3. Arachnodactyly
   4. Club foot and joint
   5. Syndactyly of the toes
   6. Delayed bone age
   7. Hyperextensibility of joints
8. Immunological: congenital immunological deficiency

3. Mortality and survival:
   1. High mortality rate in the first months of life due to life-threatening congenital malformations.
   2. With improved palliative care, survival chances improve and survival into adulthood has been well documented (Emanuel et al. 2015).
4. Differential diagnosis:
   1. Fryns syndrome
   2. Smith-Lemli-Opitz syndrome (please see the chapter of "► Smith–Lemli–Opitz Syndrome")
   3. Pallister-Killian syndrome (please see the chapter of "► Pallister–Killian Syndrome")
   4. Kabuki syndrome (Kapoor 2015) (please see the chapter of "► Kabuki Syndrome")
   5. Wolf-Hirschhorn syndrome (please see the chapter of "► Wolf–Hirschhorn Syndrome")
   6. Other chromosomal abnormalities

Diagnostic Investigations

1. Chromosome analysis: to detect supernumerary der(22)
   1. Supernumerary marker chromosomes (SMCs) are frequent findings in cytogenetic studies, with 13% of SMCs derived from chromosome 22 (Crolla et al. 2005).
   2. This chromosome imbalance consists of either a derivative chromosome 22 [der(22)] as a supernumerary chromosome with the following karyotype: 47,XX,+der(22)t(11;22)(q23;q11) in females or 47,XY,+der(22)t(11;22)(q23;q11) in males rarely (Carter et al. 2009).
2. FISH testing: to detect duplication of 22q11 and 11q23 (Emanuel et al. 2015)
   1. Using probes N25 and TUPLE1 mapping to 22q11.2 and using 11q subtelomeric probe.
   2. In the rare instance in which one of the parents is not a balanced translocation carrier, commercially available FISH probes for the 22q11.2 deletion and for the telomere of 11q can identify the supernumerary chromosome in the karyotype as being derived from chromosomes 11 and 22.
3. Chromosome microarray analysis (array CGH): to detect copy number variations of chromosome 11 and chromosome 22

4. Deletion/duplication analysis: to detect duplication 22q11 (Emanuel et al. 2015)
    1. Testing that identifies exonic or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA.
    2. Included in the variety of methods that may be used are quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

Genetic Counseling

1. Recurrence risk (Emanuel et al. 2015)
    1. In more than 99% of cases, one of the parents of a proband with Emanuel syndrome is a balanced carrier of a t(11;22)(q23;q11.2) and is phenotypically normal.
    2. In most cases, a carrier parent has inherited the t(11;22) from one of his or her parents.
    3. When one of the parents of a proband is a carrier of the balanced t(11;22), possible outcomes of future pregnancies of the parents include:
        1. Normal chromosomes
        2. Supernumerary der(22) syndrome
        3. Balanced t(11;22) carrier
        4. Spontaneous abortion as a result of supernumerary der(22) or another meiotic malsegregant
    4. Risks vary depending on whether the mother or father of a proband is the balanced translocation carrier (Fraccaro et al. 1980; Zackai and Emanuel 1980):
        1. The risk of having a live-born infant with supernumerary der(22) is higher if the mother carries a balanced t(11;22) than if the father carries a balanced t(11;22).
        2. The overall risk of having a live-born infant with supernumerary der(22) when a parent carries a balanced t(11;22) is estimated to be between 1.8% and 5.6%.
        3. The overall risk of having a spontaneous abortion with supernumerary der(22) or another meiotic malsegregant when a parent carries a balanced t(11;22) is estimated to be between 23% and 37%.
    5. Patient's offspring: unlike to reproduce due to severe cognitive impairment.
2. Prenatal diagnosis
    1. Tertiary monosomy resulting from the 3:1 segregation is compatible with embryonic survival into the first trimester (Jobanputra et al. 2005).
    2. Prenatal diagnosis for pregnancies at increased risk is possible if the chromosome abnormality has been confirmed in the family (Emanuel et al. 2015).
3. Preimplantation genetic diagnosis: successfully performed on several occasions (Van Assche et al. 1999), may be an option for some families at increased risk
4. Management (Emanuel et al. 2015)
    1. Treatment of manifestations
        1. Gastroesophageal reflux, anal atresia (or stenosis), inguinal hernias, cardiac defects, cleft palate, hip dysplasia, other skeletal complications, hearing loss, cryptorchidism and/or micropenis, refractive errors, and strabismus or other ophthalmologic issues
        2. Physical, occupational, and speech therapies
    2. Prevention of secondary complications: attention to the airway during sedation and/or operative procedures in an institution with pediatric anesthesiologists
    3. Surveillance: regular developmental assessments and periodic reevaluation by a medical geneticist
    4. Female carriers of a balanced t(11;22)
        1. Possible association for premenopausal breast cancer (Lindblom et al. 1994; Jobanputra et al. 2005).
        2. Other studies not confirming such association (Kurahashi et al. 2000; Carter et al. 2009).
        3. Enhanced breast cancer surveillance may be warranted in female carriers of

a balanced t(11;22) only if there is a family history of breast cancer (Wieland et al. 2006; Emanuel et al. 2015).

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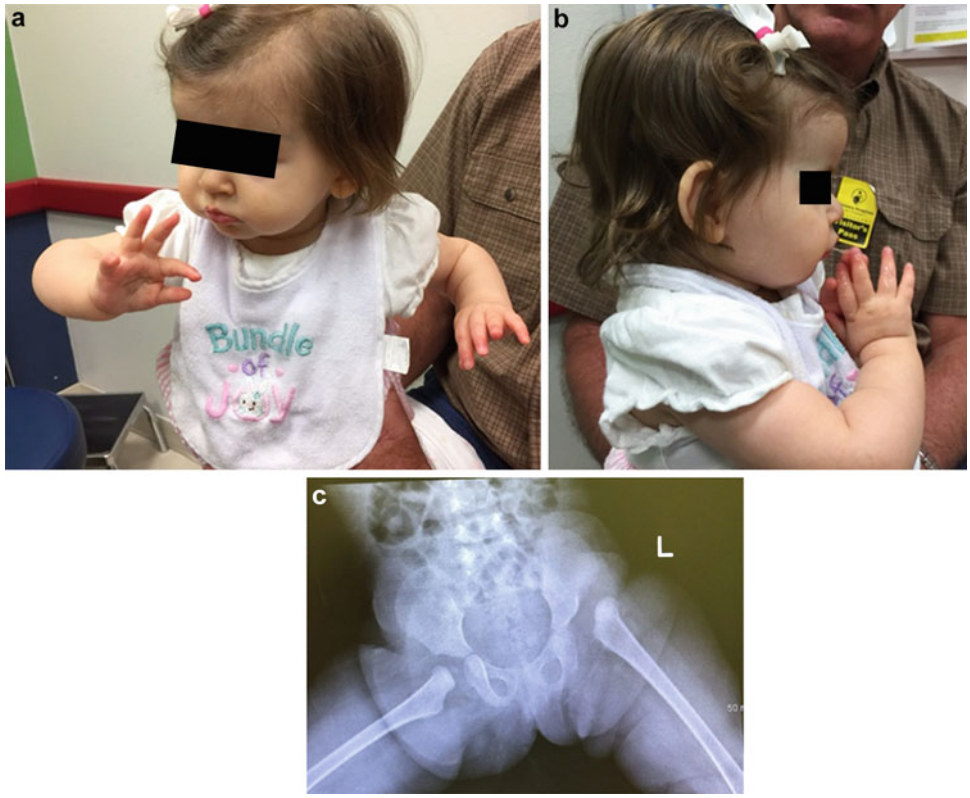

Fig. 1 (**a**–**c**) This 20-month-old Caucasian female (**a**, **b**) was evaluated for multiple congenital anomalies, consisting of developmental delay, microcephaly, prominent forehead, depressed nasal bridge, large ears, cleft palate, atrial septal defect, mitral valve defect, kyphosis, and left hip subluxation (**c**). Chromosome microarray analysis showed a terminal 18.3 megabase duplication from 11q23.3 to 11q25 and a pericentromeric 3.4 megabase duplication from 22q11.1 to 22q11.21. Metaphase FISH studies using probes within the duplicated interval (RP11-1125D12 and TUPLE1) demonstrated that both of the duplicated regions are present on a supernumerary marker chromosome (performed at Mayo Clinic laboratories). This marker chromosome is likely a derivative chromosome 22 from an 11;22 translocation (47,XX,t(11;22)(q23;q11.2)), which is associated with Emanuel syndrome (reviewed by Emanuel et al. (2015)) (Courtesy of Drs. David Yates, Jennifer Woerner, and Ghali Ghali)

Enchondromatosis

Contents

Enchondromas are benign cartilaginous growth in the intramedullary region of the bones, predominantly affecting the metaphyses of long bones (Silve and Jüppner 2006). When two or more bones are affected with enchondromas, the condition is called multiple enchondromatosis. Maffucci first described the syndrome of multiple enchondromas and subcutaneous hemangiomas in 1881. Eighteen years previously, Ollier (1898) described multiple enchondromatosis. The prevalence of enchondromatosis is estimated to be 1 in 100,000 (Silve and Jüppner 2006). Enchondromatosis encompasses several different subtypes of which Ollier disease and Maffucci syndrome are the most common (Superti-Furga et al. 2012; Cerny et al. 2013).

Synonyms and Related Disorders

Dysspondyloenchondromatosis; Genochondromatosis; Maffucci syndrome (enchondromatosis with soft tissue hemangiomas); Metachondromatosis; Metaphyseal chondromatosis with 2-hydroxyglutaric aciduria; Multiple enchondromatosis; Ollier disease/syndrome (enchondromatosis); Spondyloenchondrodysplasia

Genetics/Basic Defects

1. Inheritance (Superti-Furga et al. 2012; Amyere et al. 2014)
    1. Ollier disease (OD)
        1. Autosomal dominant or sporadic
        2. Caused by somatic or germ line *PTHR1* (3p22p21.1) mutations (Hopyan et al. 2002; Couvineau et al. 2008)
        3. Also caused by somatic mutations in *IDH1* and *IDH2* (Amary et al. 2011; Pansuriya et al. 2011)
    2. Maffucci syndrome (MS)
        1. Sporadic.
        2. Caused by somatic *IDH1 and IDH2* mutations (Amary et al. 2011; Pansuriya et al. 2011).
        3. No *PTHR1* mutations have been detected in MS (Amyere et al. 2014).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Metachondromatosis
    1. Autosomal dominant.
    2. Caused by loss of function mutations in the *PTPN11* gene (12q24.1) (Sobreira et al. 2010; Bowen et al. 2011).
    3. The mutations are heterozygous in the germ line but switch to homozygosity within the tumor suppressor gene.
4. Spondyloenchondrodysplasia: caused by recessive mutations in *ACP5* (Lausch et al. 2011; Girschick et al. 2015)
    1. Autosomal recessive
    2. Gene: TRAP (19p13) (Briggs et al. 2011)
5. Enchondromatosis with irregular vertebral lesions: sporadic (Spranger et al. 1978)
6. Generalized enchondromatosis
    1. Sporadic
    2. Gene: dupl PTHLH (12p11p23) (Spranger et al. 1978)
7. Dysspondyloenchondromatosis: a variant of "type 2 collagenopathy"

2. Basic Defect and Pathogenesis
    1. Enchondromas believed to be a part of a generalized mesodermal dysplasia.
    2. Appearance of enchondromas close to the epiphysis can severely affect the progressive development of a bone, resulting in distortion in the shape and length of the bone.
3. Proposed Origin of Enchondroma Formation
    1. Endochondral bone ossification: a highly regulated process, requiring the progression of undifferentiated mesenchymal cells into hypertrophic chondrocytes and the subsequent replacement of a cartilaginous matrix by mineralized bone.
    2. Development of enchondromas in the metaphysis of long tubular bones in close proximity to the growth plate.
    3. Consequently, enchondromas resulted from abnormalities in signaling pathways controlling the proliferation and differentiation of chondrocytes, leading to the development of intraosseous cartilaginous foci.
    4. Osteochondromatosis possibly results from abnormal regulation of proliferation and terminal differentiation of chondrocytes in the adjoining growth plate, since enchondromas are usually present in close proximity to, or in continuity with, growth-plate cartilage (Hopyan et al. 2002).
        1. Parathyroid hormone-related protein (PTHRP) delays the hypertrophic differentiation of proliferating chondrocytes.
        2. Indian hedgehog (IHH) promotes chondrocytes proliferation.
        3. Identification of a mutant PTH/PTHRP type I receptor (PTHR1) in human enchondromatosis that signals abnormally in vitro and causes enchondroma-like lesions in transgenic mice.
            1. The mutant receptor constitutively activates hedgehog signaling.
            2. Excessive hedgehog signaling is sufficient to cause formation of enchondroma-like lesions.
    5. Loss of chromosomes (chromosomes 6 and 3), deletions, amplifications, gains, and genomic copy number neutral structural changes of subtle genes (Hopyan et al. 2002; Rozeman et al. 2006; Kumar et al. 2015).
    6. Hereditary nature of the disorder reported:
        1. Generalized enchondromatosis observed in a son of the father who presented with mild skeletal dysplasia but without evidence of enchondromas.
        2. A heterozygous mutation (R150C) in the PTH/PTHrP receptor (*PTHR1* gene) was inherited from the father in one of these cases (Hopyan et al. 2002).
        3. Heterozygous mutations in PTHR1 that impair receptor function participate in the pathogenesis of Ollier disease in some patients (Couvineau et al. 2008).

Clinical Features

1. Ollier syndrome (Spranger type I)
    1. Nonhereditary cartilage dysplasia of bone
        1. A prototype of enchondromatosis.
        2. Enchondromas appear as radiolucent defects that originate in the metaphyses, grow slowly, and can

attain considerable expansion while remaining centered within the bone of origin (as contrasted to exostoses and metachondromatosis).
3. A form characterized by enchondromas located mainly at the extremities (hand).
4. Consisting of multiple, asymmetrically distributed, intraosseous cartilaginous foci and subperiosteal deposition of cartilage, either exclusively or predominantly involving one side of the body.
5. Can be symmetric lesions (Khoo et al. 2008; Choh and Choh 2009).
6. Multiple enchondromas as described in Maffucci syndrome.
7. Enchondromas in infancy and early childhood:
   1. Quite innocuous
   2. Appearing as small radiolucent defects
8. Characteristic lesions develop as the skeletal growth progresses:
   1. Localized asymmetric impairment of growth
   2. Asymmetric shortening and bowing of extremity parts (especially forearm and/or lower leg)
9. No increase in size of the lesions after the cessation of the normal growth.

2. Taut-elastic skin over hyaline cartilage distensions
3. Marked asymmetry of swellings with local growth deficiency
4. Firm, indolent, rounded distensions continuous with bone on one or more fingers or toes
5. Kyphoscoliosis
6. Joint impairment
7. Spontaneous fractures in affected area (Shapiro 1982)
8. Tumors associated with Ollier disease (Kumar et al. 2015):
   1. Rare malignant (chondrosarcoma) transformation (Liu et al 1987; Schwartz et al. 1987; Bovée et al. 2000)
   2. Osteosarcoma (Liu et al. 1987; Braddock and Hadlow 1966)
   3. Central nervous system tumors:
      1. Chondrosarcoma-like parasellar chondrosarcoma
      2. Glioma, glioblastoma multiforme (Ranger and Szymczak 2009)
      3. Astrocytoma (Schwartz et al. 1987)
      4. High-grade anaplastic astrocytoma (Braddock and Hadlow 1966; Rawlings et al. 1987)
      5. Oligoastrocytoma (Filiz 2006)
      6. Oligodendroglioma (Chang and Prados 1994)
   4. Ovarian tumors
      1. Juvenile granulosa cell tumor (Tamimi and Bolen 1984; Vaz and Turner 1986; Gell et al. 1998; Leyva-Carmona et al. 2009; Rietveld et al. 2009)
      2. Sertoli-Leydig cell tumor (Weyl-Ben Arush and Oslander 1991)
   5. Leukemia
      1. Chronic myeloid leukemia (Au et al. 2004)
      2. Acute myelogenous leukemia (White et al. 2008)
   6. Breast adenoma (Weyl-Ben Arush and Oslander 1991)
   7. Lung tumor: non-small-cell lung cancer (Sendur et al. 2010)
   8. Fibromatosis (deep): extra-abdominal desmoid tumor (Al-Ismail et al. 2002)
9. Major orthopedic manifestations (Fang et al. 2009)
   1. Asymmetrical limb shortening and deformity
   2. Swelling and deformity of the hands or feet
   3. Pathological fracture
10. Prognosis: difficult to assess
    1. In general, cases with early onset have more severe prognosis.
    2. Localized cartilaginous changes, especially in a very young child, may induce major shortening of a

lower extremity leading to limb asymmetry; in contrast, patient with numerous lesions may have a better prognosis.
3. Early development of enchondromas in the phalanges may lead to major finger deformities.
4. Neural compressions: less frequently observed than in hereditary multiple exostosis.
5. Malignant transformation of enchondromas into chondrosarcomas usually occurs in young adults. The estimated incidence of malignant transformation is 5–50% of the cases.
6. Association of Ollier disease with other tumors, such as ovarian juvenile granulosa tumor, has been reported (Tamimi and Bolen 1984; Vaz and Turner 1986).

2. Maffucci syndrome (Spranger type II) (Lewis and Ketcham 1973; Chen and Harrison 1978; Gutman et al. 1978; Kaplan et al. 1993; Superti-Furga et al. 2012)
   1. Age of onset
      1. Bony or soft tissue abnormalities at birth in 27% of cases
      2. Average age of onset: 4 years (ranging from birth to 30 years of age)
   2. Skeletal lesions: multiple enchondromas
      1. Can occur anywhere in the body
      2. Most commonly in the hands, followed by tibia/fibula, foot, femur, humerus, radius/ulna, ribs, pelvis, scapula, and head
      3. Common long bone involvement
      4. Kyphoscoliosis caused by direct involvement of the spine
      5. Progressive skeletal deformities:
         1. Enlarged fingers.
         2. Bowed legs.
         3. Asymmetric limb shortening.
         4. Pathological fractures.
      6. High incidence (23%) of malignancies (Ben-Itzhak et al. 1988), especially chondrosarcomas (15%) which lead to greater tissue destruction.
      7. Vascular malignancies may occur occasionally.
   3. Vascular lesions: cutaneous (Suringa and Ackerman 1970), subcutaneous, and sometimes visceral hemangiomas
      1. Occur anywhere in the body.
      2. Most commonly in the hands, followed by foot, arm, leg, trunk, and head/neck (Lowell and Mathog 1979).
      3. Hemangiomas also reported in the leptomeninges, eyes (Johnson et al 1990) pharynx, tongue, trachea, and intestines.
      4. Appear as blue subcutaneous nodules that sometimes can be emptied by pressure or by elevating the lesions above the level of the heart.
      5. Unilateral or bilateral lesions.
      6. Phlebitis often results from thrombi forming within the hemangiomatous vessels.
      7. Characteristic calcified thrombi.
      8. Histologic types of hemangiomas:
         1. Venous: most often
         2. Capillary
         3. Mixed venous/capillary type
      9. Lymphangiomatosis, a rare aspect of the mesodermal dysplasia in Maffucci syndrome (Loewinger et al. 1977).
      10. Spindle cell hemangiomatosis as a component of Maffucci syndrome (Fernández-Aguilar et al. 2004).
   4. Neoplastic changes
      1. Overall malignancy rate: 37% (Kaplan et al. 1993), 52–57.1% (Herget et al. 2014)
      2. Chondrosarcoma (15%) (Sun et al. 1985; Albregts and Rapini 1995; Abdelmalek and Stanko 2008)
         1. The neoplasm most commonly associated with Maffucci syndrome (Schwartz et al. 1987).
         2. Average age of onset is 40 years (ranging from 13 to 69 years of age).
         3. The most common sites: pelvis, shoulder girdle, distal femur, and proximal tibia (Goto et al. 2003).
      3. Malignant astrocytoma
      4. Ovarian tumors
      5. Pancreatic tumors

6. Hemangiosarcoma
7. Lymphangiosarcoma
8. Other neoplasms

5. Normal intelligence
6. Short stature
7. Minimally affected individuals:
    1. No major functional impairment
    2. Unrestricted employment
    3. Moderate cosmetic deformity only
    4. Reconstructive or corrective surgery, limited to one or two major procedures with acceptable final results
    5. Ablative surgery, restricted to amputation of a finger or a toe
8. Moderately affected individuals:
    1. Significant functional impairment
    2. Self-supporting and able to work most of the time
    3. Ambulatory
    4. Reconstructive surgery or amputation and prosthesis helpful
    5. Ablative surgery restricted to potentially functional (transfemoral or transhumeral) amputation
9. Severely affected individuals:
    1. Severe functional impairment
    2. Inability to work
    3. Chronic invalidism
    4. No surgical rehabilitation possible
    5. Forequarter or hindquarter amputation required

3. Differential diagnosis: other types of enchondromatosis (Spranger et al. 1978; Kozlowski and Masel 2002; Bovée 2008; Ghatan et al. 2010; Pansuriya et al. 2010; Superti-Furga et al. 2012)
    1. Metachondromatosis (Spranger type III)
        1. An autosomal dominant disorder.
        2. Caused by loss of function mutations in the PTPN11 gene (Sobreira et al. 2010; Bowen et al. 2011).
        3. A rare disorder exhibiting synchronous, both multiple osteochondromas and enchondromas in children, with prominent calcification of short tubular bones.
        4. Painless swelling of the hands and feet.
        5. Lesions associated with metachondromatosis may cause a variety of complications due to mass effects; however, they are often asymptomatic, cause cosmetic concern, and, importantly, most regress spontaneously (Fisher et al. 2013).
        6. Normal intelligence.
        7. Short stature.
        8. Radiographic features intermediate between exostosis and enchondromatosis.
    2. Spondyloenchondrodysplasia (Spranger type IV): irregularly distributed discrete enchondromas of long tubular bones, generalized severe platyspondyly, and mild or no involvement of hands and feet (Schorr et al. 1976; Menger et al. 1989; Halal and Azouz 1991)
    3. Enchondromatosis with irregular vertebral lesions (Spranger type V): multiple enchondromas of tubular and flat bones, generalized irregular dysplasia of vertebral bodies, and mild or no involvement of hands or feet
    4. Cheirospondyloenchondromatosis, formerly generalized enchondromatosis (Spranger type VI): characterized by multiple enchondromas, severe hand and foot involvement, mild platyspondyly, and erosions of iliac crests
    5. Dysspondyloenchondromatosis (Springer type VII) (Freisinger et al. 1993; Kozlowski et al. 1994)
        1. Characterized by multiple appendicular enchondromas with hemivertebrae, dwarfism, and limb-length discrepancy
        2. Genetic heterogeneity
            1. Caused by *COL2A1* mutations (Nakane et al. 2011)
            2. Without *COL2A1* mutation (Tran Mau-Them et al. 2014)
    6. Metaphyseal chondromatosis with 2-hydroxyglutaric aciduria (Talkhani et al. 2000; Honey et al. 2003; Bayar et al. 2005; Vissers et al. 2011; Choo et al. 2012)

7. Genochondromatosis I (Le Merrer et al. 1991)
   1. Enchondromatosis with celery type of metaphyseal lesions
   2. Characteristic thickening of the clavicles
   3. Regressive without any complications
8. Genochondromatosis II (Kozlowski and Jarret 1992)
   1. Enchondromatosis with celery type of metaphyseal lesions
   2. Moderately severe hand involvement with long dense streaks and more irregular radiolucent channels
   3. Regress without any complications
9. A new variant of generalized enchondromatosis (Ollier syndrome) (Ghatan et al. 2010)
   1. "Extreme" enchondromatosis appears to be the rarest of all of the variants.
   2. Slow progressive growth of the cartilage tumors.
   3. Develops severe bilateral extremity and spine involvement.
   4. Normal intelligence.
10. Dysplasia epiphysealis hemimelica (tarso-epiphysial aclasis) (Trevor disease) (Oestreich et al. 2002)
    1. A developmental disorder with cartilaginous overgrowth of a portion of one or more epiphyses
    2. Exostosis of epiphyseal growth centers and their equivalents that grow solely by enchondral ossification with no membranous ossification in the lesions
       1. Apophyses
       2. Carpal bones
       3. Tarsal bones
       4. Sesamoids including the patella
    3. Predominantly affects the lower extremity on one side of the body, usually restricted to either the medial (most frequent) or lateral side of the limb (hemimelica)
11. Hereditary multiple exostoses (Pannier and Legeai-Mallet 2008) (see chapter "▶ Hereditary Multiple Exostoses")
    1. An autosomal dominant disorder
    2. A genetically heterogeneous disorder associated with mutations in *EXT1* or *EXT2* genes, which are both tumor suppressor genes
    3. Clinically characterized by the development of benign tumors, multiple osteochondromas (exostoses), growing outward from the metaphyses of long bones
    4. The most important criteria to distinguish enchondromas from osteochondromas seen in hereditary multiple exostoses (radiographic distinction) (Silve and Jüppner 2006):
       1. Osteochondromas are located at the bone surface.
       2. Enchondromas are located in the center of bones.
12. Epiphyseal-metaphyseal enchondromatosis (Gabos and Bowen 1998): the lesions develop extensively within the epiphysis with direct extension across the epiphyseal growth plate into the metaphysis

Diagnostic Investigations

1. Diagnosis of Ollier disease (Silve and Jüppner 2006).
   1. Based on clinical and conventional radiological evaluations
   2. Histological analysis
      1. Limited role
      2. Mainly used if malignancy is suspected
   3. Additional studies such as scintigraphy, ultrasound, and MRI
      1. Not useful for establishing the diagnosis
      2. Indicated for the evaluation and surveillance of lesions that become symptomatic, such as pain and increase in size

2. Radiography (Kaufman 1973).
    1. Enchondromas
        1. Lesions usually arise within the medullary cavity, replacing the normal cancellous bone with the abnormal cartilage.
        2. Lytic lesions initially contain calcifications in a punctate pattern.
        3. Advanced lesions assume a ground glass appearance.
        4. Predilection for the metaphysis or diaphysis.
        5. Bone often expands but with intact cortex.
        6. Often with a scalloped border.
        7. Pathological fractures not uncommon.
        8. Multiple asymmetric enchondromas of long and flat bones (characteristic ovoid or pyramid shaped, linear translucent defects in metaphyses).
    2. Massive metaphyseal enlargement in any bones, particularly metacarpals and fingers
    3. Enchondromatosis with destruction and calcification
    4. Streaks of unossified cartilage in the metaphyses, sometimes extending into the diaphyses
    5. Madelung deformity
    6. Shortening of extremities
    7. Spinal deformity
    8. Occasional malignant degeneration
3. Major radiographic features (Fang et al. 2009).
    1. Oval/elongated radiolucent lesions, often with longitudinal striations
    2. Erosion of the cortices and subsequent calcification of the lesion producing a diffusely speckled appearance typical of enchondromas
    3. Long bones and small bones of hands and feet typically the most commonly affected sites
    4. Enchondromas almost exclusively in the metaphyseal region in long bones, possibly extending to the diaphysis
    5. Epiphysis affected at later age after closure of the growth plate
    6. Affected areas substantially enlarged and shortened cortical thinning associated with pathological fracture
4. Bone scan.
    1. Exhibiting intense and increased uptake
    2. To locate polyostotic lesions
5. CT scan.
    1. To delineate the extent of bone involvement
    2. A good diagnostic tool to demonstrate the high attenuation coefficient (classic in bone affected by fibrous dysplasia)
6. MRI (Herget et al. 2014).
    1. To delineate the extent of bone involvement
    2. Enchondromas, lobulated lesion with (Unger et al. 1988):
        1. Low to intermediate signal intensity on T1-weighted images
        2. High signal intensity on T2-weighted images
        3. High signal intensity on gradient-recalled echo images similar to articular cartilage
    3. Malignant progression of an enchondroma is evident in most cases if one of the following is present:
        1. Cortical destruction
        2. Moth-eaten or permeative osteolysis
        3. Spontaneous pathological fracture
        4. Periosteal reaction
        5. Edema surrounding the tumor
        6. Soft tissue mass
7. F-18 FDG PET-CT imaging may prove to be useful in detecting malignant transformation of enchondromas in Maffucci syndrome (Makis et al. 2010).
8. Bone scintigraphy: recommended for initial staging of chondrosarcomas (Hogendoorn et al. 2010).
9. Histopathology.
    1. Gross view of enchondromas: usually shows multiple oval-shaped or round cartilaginous nodules in osseous portions of the bone
    2. Individual nodules
        1. Limited at their periphery by woven or lamellar bone

2. Separated from each other by intertrabecular marrow spaces
3. Cartilaginous tumor matrix: usually solid with myxoid changes, manifesting as frayings of the matrix
4. Characteristics of enchondromas and chondrosarcomas
   1. Presence of a striking heterogeneity and diversity in the degree of cellularity and chondrocyte phenotype.
   2. Because of the increased cellularity, the distinction between enchondroma and grade *I* chondrosarcoma in the context of enchondromatosis is extremely difficult or even impossible; the diagnosis therefore relies on the combination of radiographic (cortical destruction, soft tissue extension), clinical, and histological criteria.
10. Fine needle aspiration cytology.
    1. Workup of soft tissue tumors
       1. An outpatient procedure
       2. Minimal risk of complications
       3. Can easily be performed from different parts of a large tumor
    2. Workup of bone tumors: comparable to cutting needle biopsy

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased
   2. Patient's offspring: not increased unless in rare familial cases
2. Prenatal diagnosis: bone lesions unlikely to manifest in the prenatal period
3. Management (Flach et al. 2001)
   1. Requires no treatment in the absence of clinical problems.
   2. Relief of symptoms.
   3. Early detection of malignancies.
      1. Suspect malignancy change if skeletal or soft tissue lesions enlarge or become painful without antecedent trauma
      2. Biopsy
4. Surgery indicated in case of complications.
   1. Pathological fractures
   2. Growth defect
   3. Malignant transformation
5. Operative procedures.
   1. Corrective osteotomy
   2. Epiphysiodesis
   3. Hemiepiphysiodesis
   4. Physeal stapling
   5. Lengthening of an arm or leg (Märtson et al. 2005)
   6. Curettage and packing with bone graft material
   7. Sclerotherapy, irradiation, and surgery for the vascular lesions
6. Serial surgery for distortion of knees and unequal leg length.
7. Limb lengthening, either gradual bone grafting or callus distraction: the most common method of correcting deformities in the lower limb.
8. Amputation in suspected malignancy with severe deformity of the limb due to intraosseous cartilaginous foci.
9. Radiotherapy (Le et al. 2003): provides palliative benefit in patients with inoperable chondrosarcoma.
10. Annual surveillance of the enchondromas recommended for children and adults.
11. Periodic surveillance of the brain and abdomen for occult lesions indicated in patients who have enchondromatosis.
12. Long-term consideration to address the potential for malignant changes.
13. Interdisciplinary efforts of health-care professionals from medicine, nursing, physical and occupational therapy, recreational therapy, and social services. Long-term consideration must address the potential for malignant changes.

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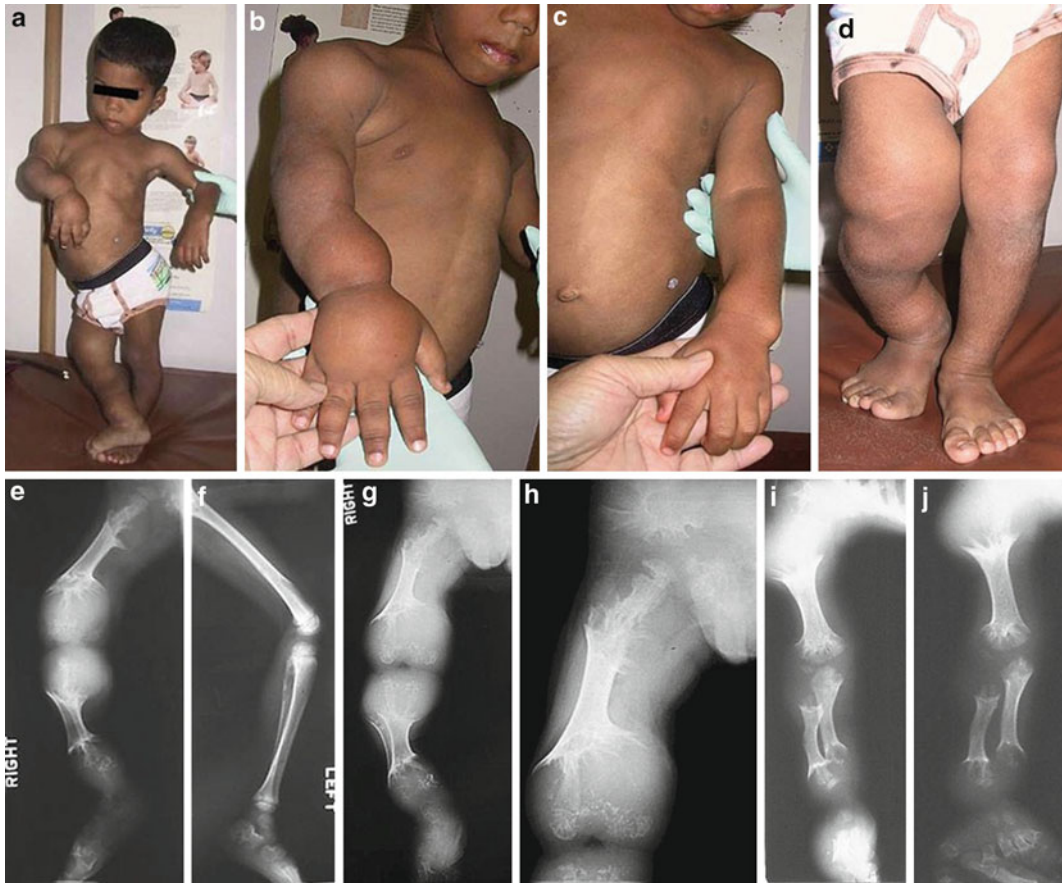

Fig. 1 (**a**–**j**) A 4-year-old boy with Ollier syndrome showing short stature, scoliosis, and severe limb deformities (**a**). The *right* limb (**b**, **d**) was affected by larger lesions with more prominent limb shortening. Marked swellings were evident on the *right* wrist and fingers. The *left* hand (**c**) showed Madelung deformity. The radiographs (**e**–**j**) showed massive metaphyseal enchondromatous lesions in the right upper and lower extremities. Streaks of radiolucency due to the abnormal cartilage extended into the diaphyses. The left femur, tibia, and fibula also showed lytic lesions

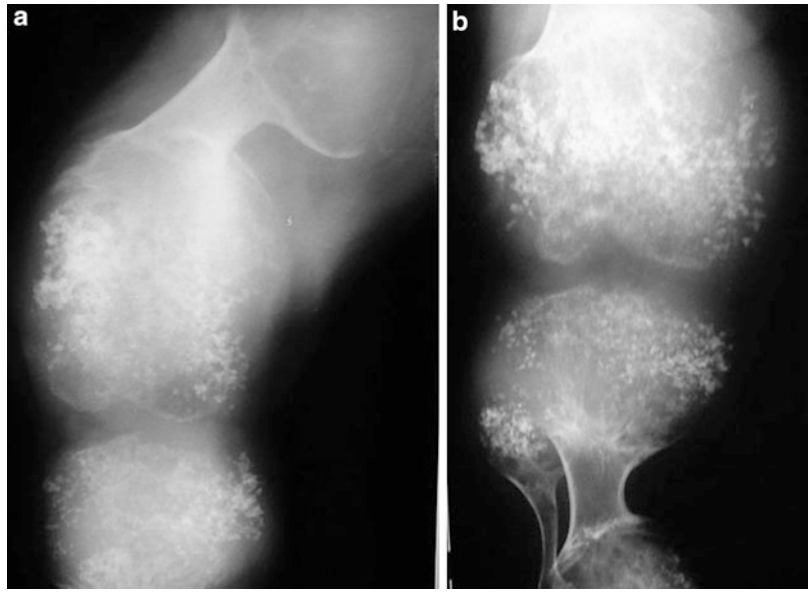

Fig. 2 (**a**, **b**) Radiographs of the right lower leg of the previous boy at 16 years of age showed large deforming enchondromas involved in the proximal and distal parts of the femur, tibia, and fibula (**a**, **b**). This case fits well to the "extreme enchondromatosis" (Ollier syndrome) described by Ghatan et al. 2010

Fig. 3 A 4-year-old boy was seen because of swelling of phalangeal joints of multiple fingers on both hands with occasional joint pain. No vascular malformation was detected. Clinical and radiographic findings are consistent with Ollier disease

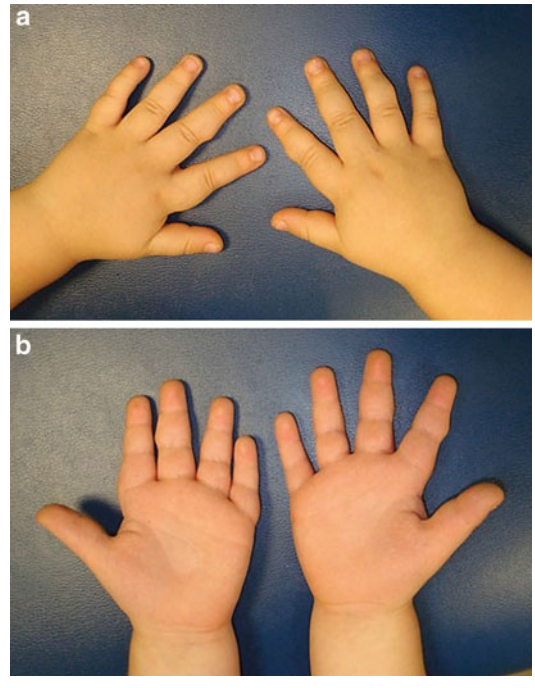

Fig. 4 (**a**, **b**) Close-up view of both hands showing multiple joint swelling on multiple fingers (**a**, **b**)

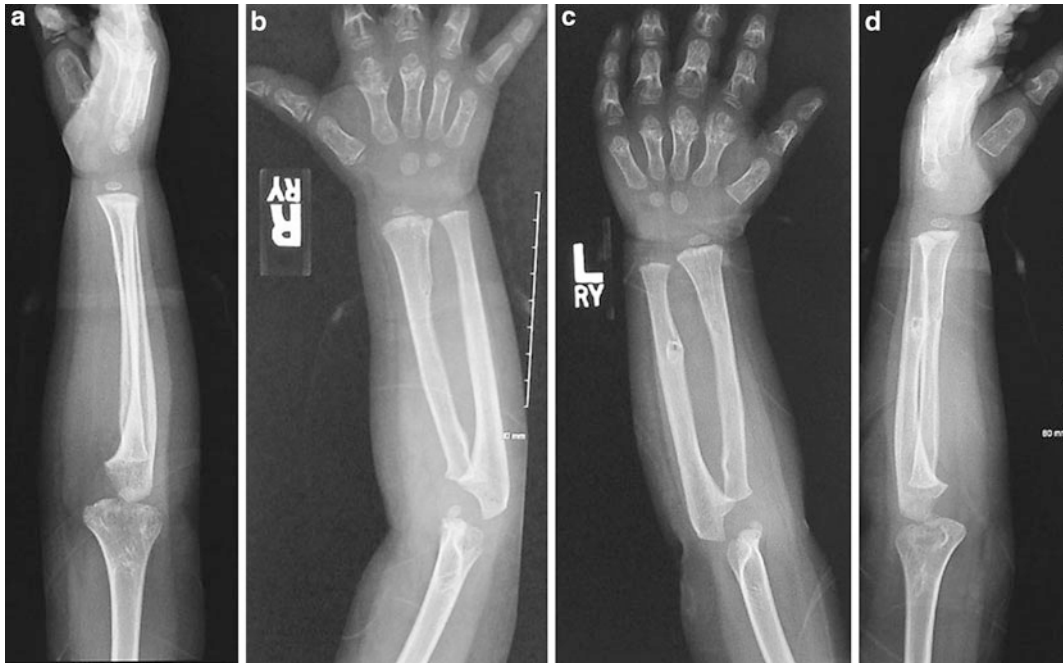

Fig. 5 (**a**–**d**) Radiographs of both forearms and hands (**a**–**d**) showed multiple enchondromas involving phalanges and metacarpals of both hands and an enchondroma involving the midshaft of the left ulna

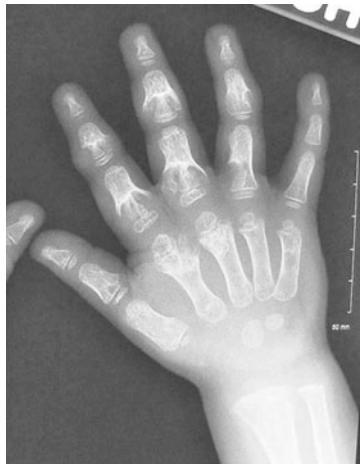

Fig. 6 Right hand radiograph showed multiple enchondromas (multiple well-defined osteolytic lesions with endosteal scalloping, cortical thinning, and bony expansion) involving proximal metaphyses of the second to fourth middle and proximal phalanges and the distal metaphyses of the second to third metacarpals

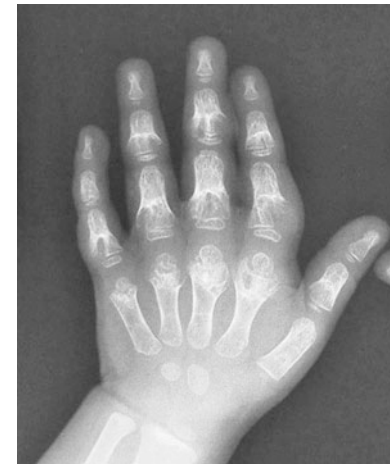

Fig. 7 Left hand radiograph showed multiple enchondromas involving proximal metaphyses of the second to fourth middle phalanges and the second to fifth proximal phalanges

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a rare group of inherited disorders of skin fragility, characterized by a reduced resistance of the skin and mucous membranes to trauma, manifesting as blistering or erosion of the skin and the epithelial lining of other organs. Epidermolysis bullosa can be classified into three major types, namely, the simplex, the junctional, and the dystrophic types, based on the level of the epidermis or basement membrane zone in which blister is formed.

All types and subtypes of EB are rare. The overall incidence and prevalence of the disease within the USA is approximately 19 per one million live births and 8 per one million population, respectively (Fine 2010).

Synonyms and Related Disorders

Dominant dystrophic EB; Dystrophic EB; EB with congenital localized atrophy of skin (Bart syndrome) Epidermolysis bullosa simplex; Inherited EB; JEB gravis; JEB Herlitz; JEB non-Herlitz; JEB-mitis; JEB-pyloric atresia; Junctional epidermolysis bullosa (JEB); Kindler syndrome; Recessive dystrophic EB, severe generalized

Genetics/Basic Defects

1. Epidermolysis bullosa simplex (EBS) (Eady 2001; Mitsuhashi and Hashimoto 2003; Fine 2010)
    1. Autosomal dominant (AD) simplex type EB (most common type)
        1. Caused by mutations in the cytoskeleton structural proteins, keratin 5 (*KRT5*) and keratin 14 (*KRT14*) genes, leading to disruption of basal cells and the formation of bullae in the basal and parabasal cell zone
        2. Keratins 5 and 14: expressed exclusively in basal cell layer of epidermis keratinocytes and essential for the maintenance of normal structural integrity
        3. Disease severity correlates with the location within the keratin gene mutation
            1. Mutations in highly conserved genetic sequences leading to severe disease
            2. Mutations in less critical keratin gene regions manifesting as milder, more localized symptoms: Koebner variant (generalized blistering but no mucosal or nail changes) and Weber-Cockayne form (blistering is confined primarily to the easily traumatized palms and soles)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Autosomal recessive (AR) simplex types (rare type)
    1. Mutation in exon 1a of *PLEC*, leading to disruption of plectin isoform 1a, causes autosomal recessive skin-only epidermolysis bullosa simplex (Gostyńska et al. 2015)
    2. EBS with muscular dystrophy due to abnormal plectin, a protein involved in hemidesmosome formation (currently also classified as a subtype of hemidesmosomal epidermolysis bullosa)
    3. EB without muscular dystrophy in patients homozygous for *KRT14* gene abnormalities
    4. Skin fragility syndrome (a form of ectodermal dysplasia but can also be classified as acantholytic EB simplex variant) with formation of acantholytic vesicles within the epidermis due to plakophilin 1 (*PKP1*) gene mutations
    5. Lethal acantholytic epidermolysis bullosa (McGrath et al. 2010)
        1. The first case report (Jonkman et al. 2005): Recessive mutations in *DSP* leading to truncation of the complete desmoplakin C-terminus (intermediate filament binding); loss of the intermediate filament binding domain of desmoplakin in both isoforms caused loss of keratin insertion of desmosomes which still had an inner and an outer dense plaque
        2. A novel homozygous deletion in *DSP* gene, encoding desmoplakin, in two infants born to same consanguineous parents (Bolling et al. 2010): Novel recessive *DSP* mutation predicted to result in truncation as well
2. Junctional epidermolysis bullosa (JEB) (Dank et al. 1999; Pulkkinen et al. 1994)
    1. Inheritance: autosomal recessive in most cases
    2. Herlitz type (epidermolysis bullosa letalis or JEB gravis)
        1. Caused by mutations in laminin 5 gene
        2. Associated with premature death
    3. Non-Herlitz type (generalized atrophic benign EB or JEB-mitis)
        1. Caused by mutation in laminin 5 and type XVII collagen (*COL17A1*) genes
        2. Generally associated with a good prognosis
    4. Junctional epidermolysis associated with pyloric atresia (Chung and Uitto 2010)
        1. Caused by mutations in a hemidesmosomal component, $\alpha_6\beta_4$ integrin (*ITGA6*, *ITGB4*) (Vidal et al. 1995) and *PLEC1*
        2. Currently also classified as a subtype of hemidesmosomal epidermolysis bullosa
3. Dystrophic epidermolysis bullosa
    1. Inheritance: either autosomal dominant or autosomal recessive
    2. Molecular basis: abnormalities of collagen VII
        1. Caused by mutations in type VII collagen gene. *COL7A1* gene mutations have been identified in most cases in both recessive (Salas et al. 1998) and dominant forms
        2. Type VII collagen is a major component of the anchoring fibrils that tether the basement membrane structure and overlying epidermis to its dermal foundation
        3. Severity of the phenotype dictated by missense mutation that alters a glycine residue in dominant dystrophic epidermolysis bullosa versus a nonsense or frameshift mutations in recessive dystrophic epidermolysis bullosa
4. Kindler syndrome
    1. Inherited in an autosomal recessive manner
    2. Pathogenesis of Kindler syndrome involves loss-of-function mutations in a newly recognized actin cytoskeleton-associated protein, now known as fermitin family homolog 1 and encoded by the gene *FERMT1* (Jobard et al. 2003)
5. Main types and subtypes of hereditary epidermolysis bullosa (Fine et al. 2014; Laimer et al. 2015)
    1. Epidermolysis bullosa simplex, EBS (intradermal [epidermolytic] blisters)

1. Suprabasal EBS (cytolysis of suprabasal keratinocytes)
    1. Acral peeling skin syndrome (AR) (*TGM5*)
    2. Superficial EBS (AD)
    3. Acantholytic EBS (includes variants formerly termed lethal acantholytic EBS and lethal congenital EBS) (AR) (*DSP*, *JUP*)
2. Skin fragility syndromes (very rare variants)
    1. Desmoplakin deficiency (skin fragility/woolly hair syndrome) (AR) (*DSP*)
    2. Plakoglobin deficiency (AR) (*JUP*)
    3. Plakophilin deficiency (skin fragility/ectodermal dysplasia syndrome) (AR) (*PKP1*)
3. Basal EBS (cytolysis of basal keratinocytes)
    1. Localized EBS (formerly type Weber-Cockayne) (AD) (*KRT5*, *KRT14*)
    2. Generalized severe EBS (formerly type Dowling-Meara, herpetiform EBS) (AD) (*KRT5*, *KRT14*)
    3. Generalized intermediate EBS (formerly EBS, generalized other; non-Dowling-Meara; EBS, type Koebner) (AD) (*KRT5*, *KRT14*, *COL17A1*)
    4. EBS with mottled pigmentation (AD) (*KRT5*)
    5. EBS with migratory circinate erythema (AD) (*KRT5*)
    6. Autosomal recessive EBS K14 (AR) (*KRT14*)
    7. Trauma-induced skin blistering (AR) (*EXPH5*)
    8. EBS with muscle dystrophy (AR) (*PLEC1*)
    9. EBS with pyloric atresia (AR) (*PLEC1*, *ITGA6*, *ITGB4*)
    10. EBS type Ogna (AD) (*PLEC1*)
    11. Autosomal recessive EBS, BP230 deficiency (AR) (*DST*)
    12. Autosomal recessive EBS, exophilin-5 deficiency (AR) (*EXPH5*)
2. Junctional epidermolysis bullosa, JEB (junctional [lucidolytic] blisters) within the basement membrane zone
    1. Generalized JEB
        1. Generalized severe JEB (previously type Herlitz) (AR) (*LAMA3*, *LAMB3*, *LAMC2*)
        2. Generalized intermediate JEB (formerly type non-Herlitz; JEB, generalized other; GABEB) (AR) (*LAMA3*, *LAMB3*, *LAMC2*)
        3. JEB with pyloric atresia (AR) (*ITGA6*, *ITGB4*)
        4. JEB, late onset (formerly progressive) (AR) (*COL17A1*)
        5. Localized JEB (AR) (*COL17A1*)
        6. JEB with respiratory and renal involvement (previously EB congenital nephrotic syndrome-interstitial lung disease) (AR) (*ITGA3*)
    2. Localized JEB
        1. Localized JEB (previously localized JEB, non-Herlitz) (AD) (*COL17A1*)
        2. JEB inversa (AR) (*LAMA3*, *LAMB3*, *LAMC2*)
        3. JEB, laryngo-onycho-cutaneous syndromes (AR) (*LAMA3A*)
3. Dystrophic epidermolysis bullosa, DEB (dermolytic blistering below the lamina densa) (Shinkuma 2015)
    1. Dominant DEB
        1. Generalized dominant DEB (formerly type Pasini, Cockayne-Touraine) (AD) (COL7A1)
        2. Acral dominant DEB (AD, AR) (*COL7A1*)
        3. Pretibial dominant DEB (AD, AR) (*COL7A1*)
        4. Dominant DEB pruriginosa (AD, AR) (COL7A1)
        5. Dominant DEB, nails only (AD) (*COL7A1*)
        6. Dominant DEB, bullous dermolysis of the newborn (AD, AR) (*COL7A1*)
    2. Recessive DEB (Soro et al. 2015)
        1. Generalized severe DEB (formerly type Hallopeau-Siemens) (AR) (*COL7A1*)

2. Generalized intermediate DEB (formerly type non-Hallopeau-Siemens; RDEB, generalized other) (AR) (*COL7A1*)
3. Recessive DEB inversa (AR) (*COL7A1*)
4. Localized recessive DEB (formerly acral recessive DEB) (AR) (COL7A1)
5. Pretibial recessive DEB (AD, AR) (COL7A1)
6. Recessive DEB pruriginosa (AR) (*COL7A1*)
7. Recessive DEB (centripetal variant) (AR) (*COL7A1*)
8. Recessive DEB, bullous dermolysis of the newborn (AR) (*COL7A1*)
9. Kindler syndrome (intraepidermal, junctional, or sub-lamina-densa blisters (AR) (*FERMT1* (*KIND1*)))

4. Recently identified autosomal recessive EB variants (McGrath 2015)
   1. Mutations in either *DST-e* (coding for epidermal dystonin, also known as the 230 kDa bullous pemphigoid antigen, BP230)
   2. *EXPH5* (coding for exophilin-5, also known as Slac2-b)
   3. *ITGA3* (coding for the integrin alpha-3 subunit)

Clinical Features

1. Classification of the major EB subtypes was discussed in great detail in the 2008 consensus report on diagnosis and classification (Fine et al. 2008), which was based on the recommendations of an international panel of EB experts, superceding two previously recommended classification schemes (Fine et al. 1991, 2000)
2. Epidermolysis bullosa simplex (Pai and Marinkovich 2002; Pfendner and Bruckner 2011)
   1. General characteristics
      1. The most common heritable blistering process
      2. Intraepidermal blistering at the level of the basal cell
      3. Typical healing of blisters without scarring
      4. Little involvement of other organ systems
      5. Extent and severity of disease improves with age
   2. EBS Koebner type
      1. Commonly involves hands, feet, and extremities
      2. Onset at birth to early infancy
      3. Often present with palmar-plantar hyperkeratosis and erosions
      4. Mildly involves nails, teeth, and oral mucosa
   3. EBS Weber-Cockayne type
      1. Relatively mild variant of EBS
      2. Commonly involves palms and soles only after a clearly identifiable traumatic event
      3. May not present until adulthood
      4. Hyperhidrosis of the palms and soles
      5. Most common complications involve secondary infections of blistering lesions on the feet
   4. EBS Dowling-Meara type (EBS-DM)
      1. A more severe subtype of EBS
      2. Involves a more generalized distribution of blisters occurring at, or shortly after, birth
      3. Pronounced inflammation with milia formation in infancy
      4. Spontaneous blisters occurring in groups on the trunk and proximal extremities
      5. Usually healing without scarring later in life
      6. Hyperkeratosis may develop at age 6 or 7 years
      7. Unlike the previous two subtypes, heat does not appear to exacerbate blistering
   5. EBS with mottled pigmentation
      1. Skin fragility: evident at birth and clinically indistinguishable from EBS-DM
      2. Over time, progressive brown pigmentation interspersed with hypopigmented spots develops on the trunk and

extremities, with the pigmentation disappearing in adult life
3. Focal palmar and plantar hyperkeratoses may occur

6. Lethal acantholytic epidermolysis bullosa (Jonkman et al. 2005; Bolling et al. 2010; McGrath et al. 2010)
1. Striking phenotypic findings
1. Extensive nonbullous epidermal dislodgment
2. Universal alopecia
3. Anonychia
4. Rapid postnatal demise
2. Malformed ears
3. Cardiac enlargement and dysfunction in utero

3. Junctional epidermolysis bullosa (Dank et al. 1999)
1. General characteristics
1. Blistering at the level of the lamina lucida
2. More severe blistering process
3. Presenting spontaneously or at sites of trauma with generalized blistering
2. Herlitz or junctional epidermolysis letalis
1. The commonest form of JEB formerly known as "lethal JEB"
2. Characterized by generalized blistering at birth
3. Extensive dental enamel hypoplasia
4. Tracheolaryngeal involvement leading to a hoarse cry, cough, and/or other respiratory difficulties
5. Gastrointestinal involvement and genitourinary involvement leading to infection and obstructive sequelae
6. Rarely survives beyond 6 months secondary to chronic anemia, failure to thrive, and sepsis
7. Rare survivors: develop exuberant granulation tissue at sites of erosion, especially at the perioral region
3. Non-Herlitz junctional epidermolysis bullosa
1. Early clinical course similar to that found in Herlitz type JEB
2. Often survives infancy
3. May improve clinically with age
4. Rare and mild pulmonary involvement
5. Scalp, nail, and tooth abnormalities common
6. Prominent nonhealing periorificial lesions
7. Erosions in the mucous membranes resulting in strictures
4. Generalized atrophic benign epidermolysis bullosa
1. Generalized cutaneous blistering at birth
2. Blisters heal with a distinctive atrophic appearance
3. Blisters confined to sites of trauma
4. Alopecia
5. Dental anomalies
6. Rare severe nail and mucosal involvement
5. Junctional epidermolysis associated with pyloric stenosis/atresia (Chang et al. 1983; Dank et al. 1999; Pfendner and Lucky 2013)
1. A syndromic association of skin fragility and congenital gastrointestinal atresia, most frequently pyloric, although duodenal atresia with skin fragility has also been reported
2. Often with severe skin blistering and extensive multisystem mucosal blistering
3. Presence of pyloric and/or duodenal atresia: vomiting and abdominal distension resulting from complete obstruction of the gastric outlet
4. Often with urologic abnormalities
1. Hydronephrosis
2. Nephritis
5. Many patients die during infancy

4. Dystrophic epidermolysis bullosa
1. General characteristics
1. Clinical hallmarks (Bruckner-Tuderman 2010)
1. Trauma-induced blisters
2. Healing with scarring
2. Sub-lamina densa blistering
3. Characterized by dermolytic blisters resulting in scarring and milia formations
4. Dystrophic scarring follows cutaneous blistering

5. Congenital localized absence of skin (Bart's syndrome) may be the presenting sign of epidermolysis bullosa (Wojnarowska et al. 1983)

2. Dominantly inherited dystrophic epidermolysis bullosa
   1. Mild phenotype
   2. Present with generalized blistering at birth or during infancy
   3. Blistering at sites of maximal trauma
   4. Healing with scarring and small keratinaceous cysts (milia)
3. Transient bullous dermolysis of the newborn (Hansen et al. 1999)
   1. An uncommon variant
   2. Blistering at sites of trauma that heals after several months without scarring
   3. Variable mucous membrane and nail involvement
4. Recessively inherited dystrophic epidermolysis bullosa: Hallopeau-Siemens type (the most severe form)
   1. Excessive fragile skin leading to blisters with minimal trauma
   2. Extensive scarring leading to contractures and fusion of digital web spaces (pseudosyndactyly, "mitten deformities") that require surgical correction
   3. Extremely itching and painful skin
   4. Regular mucosal blistering leading to eating and swallowing disorders and ocular abnormalities
   5. Tendency to growth retardation and anemia
   6. Devastating complications unique to recessively inherited dystrophic epidermolysis bullosa
      1. Increased propensity for cutaneous malignancy at sites of scarring (>40% of patients develop malignancy by age 30 years)
      2. Aggressive nature of malignancy (squamous cell carcinoma)
5. Kindler syndrome (Sawamura et al. 2010)
   1. Autosomal recessive inheritance
   2. A subtype of EB
   3. The pathogenesis of Kindler syndrome involves loss-of-function mutations in a newly recognized actin cytoskeleton-associated protein, now known as fermitin family homolog 1 and encoded by the gene *FERMT1* (Jobard et al. 2003)
   4. Trauma-induced blistering
   5. Poikiloderma
   6. Skin atrophy
   7. Mucosal inflammation
   8. Varying degrees of photosensitivity
6. Differential diagnosis of inherited EB (in neonates and small children) (Fine 2010)
   1. Inherited or congenital disorders
      1. Epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythro-derma)
      2. Ichthyosis bullosa of Siemens
      3. Peeling skin syndrome
      4. Pachyonychia congenita
      5. Congenital porphyrias
      6. Acrodermatitis enteropathica
      7. Incontinentia pigmenti
      8. Ectodermal dysplasia (ED)
      9. AEC syndrome (Hay-Wells syndrome)
      10. Congenital absence of skin (cutis aplasia)
      11. Congenital erosive dermatosis with reticulate supple scarring
   2. Acquired disorders
      1. Immunobullous disorders
         1. EB acquisita
         2. Linear IgA dermatosis
         3. Bullous pemphigoid
         4. Cicatricial pemphigoid
         5. Neonatal herpes gestationis
         6. Pemphigus
      2. Infectious diseases
         1. Herpes simplex
         2. Staphylococcal scalded skin syndrome
         3. Bullous impetigo
      3. Other diseases or conditions
         1. Bullous mastocytosis
         2. Traumatic blisters (sucking; other)

Diagnostic Investigations

1. Level of blister formation in each major EB type (Fine 2010)
    1. EB simplex: intraepidermal
    2. Junctional EB: intra-lamina lucida
    3. Dystrophic EB: sub-lamina densa
    4. Kindler syndrome: multiple levels (intra-lamina lucida and sub-lamina densa)
2. Radiographs: distended stomach, filled with air in junctional EB with pyloric atresia
3. EM of skin biopsy (Pai and Marinkovich 2002)
    1. A gold standard of laboratory diagnosis
        1. To determine the level at which blistering occurs
        2. To obtain additional information on the morphology of various basement membrane zone components
    2. Epidermolysis bullosa simplex
        1. Cytolysis of the basal cells
        2. Distinctive clumping of the keratin tonofilaments
    3. Junctional epidermolysis bullosa: rudimentary hemidesmosomes
    4. Dystrophic epidermolysis bullosa: absent or altered anchoring fibrils
    5. Hemidesmosomal epidermolysis bullosa: separation at the level of hemidesmosome just inside the basal keratinocytes
4. Transmission electron microscopy findings among selected EB subtypes (Fine 2010)
    1. EB simplex (suprabasal) (EBS)
        1. EB simplex superficialis: subcorneal cleavage
        2. Lethal acantholytic EB:
            1. Suprabasal cleavage
            2. Acantholysis
            3. Perinuclear retraction of keratin filaments
        3. EBS, plakophilin deficiency:
            1. Mid-epidermis cleavage
            2. Perinuclear retraction of keratin filaments
            3. Small suprabasal desmosomes
    2. EBS (basal)
        1. EBS, localized: basal keratinocyte cleavage
        2. EBS, Dowling-Meara
            1. Basal keratinocyte cleavage
            2. Clumped keratin filaments
        3. EBS, generalized other: basal keratinocyte cleavage
        4. EBS, autosomal recessive
            1. Basal keratinocyte cleavage
            2. Absent or reduced keratin filaments within basal keratinocytes
    3. Junctional EB (JEB)
        1. JEB, Herlitz
            1. Intra-lamina lucida cleavage
            2. Markedly reduced or absent hemidesmosomes
            3. Absent subbasal dense plates
            4. Absent anchoring filaments
        2. JEB, non-Herlitz
            1. Intra-lamina lucida cleavage
            2. Hemidesmosomes may be normal or reduced in size and number
        3. JEB with pyloric atresia
            1. Intra-lamina lucida cleavage
            2. Small hemidesmosome plaques with attenuated subbasal dense plates
    4. Dominant dystrophic EB (DDEB)
        1. DDEB, generalized
            1. Sub-lamina densa cleavage
            2. Normal or reduced numbers of anchoring fibrils
        2. DDEB, bullous dermolysis of the newborn
            1. Sub-lamina densa cleavage
            2. Electron-sense stellate shaped bodies within basal keratinocytes
            3. Reduced numbers of anchoring fibrils
    5. Recessive dystrophic EB (RDEB)
        1. RDEB, severe generalized
            1. Sub-lamina densa cleavage
            2. Absent or rudimentary appearing anchoring fibrils
        2. RDEB, generalized other (generalized mitis)
            1. Sub-lamina densa cleavage

2. Reduced or rudimentary appearing anchoring fibrils

5. Immunofluorescent microscopy (Pai and Marinkovich 2002)
   1. Provide additional information on the level of blistering
   2. Provide important clue to the underlying molecular defects
   3. Antibodies against intracellular hemidesmosomal component such as BP230 and a lamina densa protein such as type IV collagen
      1. Samples from EBS: both antibodies localized to the floor of the blister
      2. Samples from JEB
         1. Antibodies against BP230 localized to the roof of the blister
         2. Antibodies against type IV collagen localized to the floor
      3. Samples from DEB: both antibodies localized to the roof of the blister
   4. Samples lacking staining with antibodies specific to laminin 5 support a JEB diagnosis
   5. Samples lacking staining with antibodies specific to type VII collagen support a DEB diagnosis
   6. Absence of staining for BP180 supports a diagnosis of generalized atrophic benign epidermolysis bullosa
6. Laboratory approach to epidermolysis bullosa (Castiglia and Zambruno 2010)
   1. At first use of immunofluorescence epitope mapping (IFM) and transmission electron microscopy (TEM) examination of a skin biopsy to determine the level of skin cleavage and the presence of morphologic alterations of epithelial adhesion structures and the defective expression of specific protein components
   2. IFM and TEM enable definition of the major EB type and, in most cases, the subtype and identification of the protein component targeted by the mutations
   3. These analyses define the candidate genes for mutation screening and they must precede molecular testing, which should be primarily considered when:
      1. Prenatal or preimplantation diagnosis is being planned
      2. The mode of genetic transmission cannot be delineated from the family pedigree in combination with IFM and TEM findings
      3. Gene-replacement therapy protocol is foreseen
   7. Linkage analysis of linked markers within or flanking the particular EB gene in families in which the inheritance pattern is known
   8. Mutation detection for all forms of epidermolysis bullosa
      1. Mutation analysis
      2. Sequence analysis
   9. Genetic testing for EB: the perfect application for NGS technology, as there are many candidate genes (some of which are very complex), large deletions are relatively rare, and if the phenotype is consistent with the inherited form of EB (neonatal onset and a fragile skin phenotype), mutations are reliably disclosed (Takeichi et al. 2013, 2015; Poulter et al. 2014; Nagai et al. 2015; Pfendner 2015)
   10. Lethal acantholytic epidermolysis bullosa (Bolling et al. 2010)
      1. Electron microscopy
         1. Loss of keratin filament insertion and
         2. Loss of the inner dense plaque
      2. A panel of antibodies directed against the desmoplakin C-terminus and the N-terminus/rod domain for immunofluorescence microscopy on a representative fresh frozen skin sample can provide an early diagnosis

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal dominant
         1. 50% if a parent is affected
         2. Low recurrent risk when the parents are clinically unaffected
         3. Low recurrent risk but greater than that of the general population because

of the possibility of germline mosaicism when the disease-causing mutation cannot be detected in the DNA of either parent
4. Parental germline mosaicism have been reported in both EBS (Nagao-Watanabe et al. 2004) and DEB (Rouan et al. 1998; Cserhalmi-Friedman et al. 1999, 2001; van den Akker et al. 2015)

2. Autosomal recessive
1. Carrier status of parents needs to be confirmed by molecular genetic testing because germline mosaicism and uniparental isodisomy have been reported (Takizawa et al. 2000; Cserhalmi-Friedman et al. 2002; Fassihi et al. 2005)
2. Recurrence risk: 25%

2. Patient's offspring
1. Autosomal dominant
1. A 50% risk of inheriting the mutation
2. A 75% risk of having at least one mutation in the rare instance in which both parents have an autosomal dominant mutation such as in consanguineous union
2. Autosomal recessive: recurrence risk not increased unless the spouse is a carrier or affected

2. Prenatal diagnosis (Eady 2001; Fassihi and McGrath 2010)
1. Fetal skin biopsy with EM analysis and/or immunohistochemistry with following drawbacks
1. Drawbacks
1. Fetal biopsy can only be obtained fairly late in gestation ($\geq$17 weeks)
2. A relatively high rate of miscarriage
3. Fetal status can only be determined by an expert in the ultrastructure of fetal skin who is qualified to make the diagnosis
2. An alternative option for rare families in which mutations cannot be identified and linked markers are not available to be used for prenatal diagnosis
2. Fetal skin biopsy at 20 weeks' gestation in a woman at risk for a child with the lethal skin-blistering disorder junctional epidermolysis bullosa (Herlitz) confirmed an affected fetus (McGrath et al. 1995)
3. Prenatal diagnosis of EB letalis made by electron microscopy of a biopsy specimen of fetal skin obtained under direct vision by fetoscopy at 18 weeks gestation (Rodeck et al. 1980)
4. Villous trophoblasts, sampled during the first trimester, display immunoreactivity to $\alpha_6\beta_4$ integrin and plectin, thereby permitting diagnosis/exclusion of EB associated with pyloric atresia through tissue diagnosis (D'Alessio et al. 2008)
5. Mutation detection on fetal DNA obtained by amniocentesis or CVS for all forms of epidermolysis bullosa (Pfendner et al. 2003)
1. Before any prenatal test, samples from both parents and any previous affected siblings are analyzed for pathogenic mutations
2. In autosomal recessive EB, ideally both parents must be shown to be heterozygous carriers of the pathogenic mutation (s)
3. The possibility of de novo mutations, nonpaternity, and uniparental disomy (the inheritance of both copies of a chromosome pair from just one parent) should be excluded before considering the suitability of the prenatal test
6. Gene diagnosis and prenatal genetic diagnosis of a case of dystrophic epidermolysis bullosa family caused by gonadosomatic mosaicism for the *COL7A1* mutation p. Gly2043Arg in the pregnant mother (Shen et al. 2015)
7. Linkage analysis by linked markers within or flanking the *COL7A1* gene in several DEB families in which the inheritance pattern was known
8. Probability of parental germline mosaicism should always be kept in mind, and the option of prenatal diagnosis should be discussed (Cserhalmi-Friedman

et al. 2001, 2002; van den Akker et al. 2015)
9. Preimplantation genetic diagnosis, an alternative to first-trimester prenatal diagnosis
    1. Involves in vitro fertilization, usually by intracytoplasmic sperm injection
    2. Followed by the biopsy of a single cell from the eight-cell blastocysts (embryo)
    3. Using complex polymerase chain reaction analysis to determine whether DNA from the single cell caries the parental mutations

3. Management (Herod et al. 2002; Bello et al. 2003; Hachem et al. 2014; Soro et al. 2015)
    1. A multidisciplinary team approach, tailored to the severity and extent of skin involvement
    2. Blister management and dressing technique
        1. Avoidance of trauma as a primary goal
        2. Puncture fresh blisters with a sterile needle and drain blister fluid with the blister roof left in situ so that the blister fluid cannot extend
        3. Use white petrolatum-impregnated gauzes, hydrogels, fenestrated silicone dressings, or absorbent foam silicone dressings for open wounds
        4. Keep intravenous lines in place by using soft roller-gauze bandages
        5. Avoid dressing with adhesive tapes
        6. Prevention and treatment of infections
    3. Prevention and treatment of complications (Pai and Marinkovich 2002)
        1. Change dressing regularly
            1. To control blistering and infection
            2. To prevent the debilitating contractures secondary to bullae formation in dystrophic EB
        2. Physiotherapy
            1. To maintain mobility
            2. To decrease contracture formation
        3. Corrective surgery recommended for digital fusion (mitten pseudosyndactyly) and contractures
        4. Nutritional support
    5. Gastrointestinal management
        1. Dilatation of esophageal strictures
        2. Colonic interposition for advanced cases of strictures
        3. Gastrostomy tube insertion to provide nutrition
        4. Laxatives and increased dietary fiber for constipation, anal fissures, and perianal ulceration
    6. Care for eye lesions (Tong et al. 1999)
        1. Ophthalmic complications: most severe in the dystrophic recessive and junctional subtypes
        2. Moisture chambers and ocular lubricants
        3. Treat corneal erosions with antibacterial ointments and use of cycloplegic agents to reduce ciliary spasms and provide comfort
    7. Oral care
        1. Good oral hygiene
        2. Gentle cleaning of the mucosal surfaces with normal saline rinses
        3. Softest brush for regular cleansing
4. Pain management (Herod et al. 2002)
    1. Acute phase: experience considerable pain and discomfort caused by the expanding and often tense bulla
    2. Chronic wounds: experience considerable pain caused by chronic wounds with denuded areas of skin and by therapeutic procedures
    3. Analgesics
        1. Combination of paracetamol and ibuprofen or diclofenac for dressing changes associated with small wounds
        2. Potent analgesia and sedation required for large dressing changes (oral morphine solution and midazolam)
5. Management of anesthesia and surgery: should be undertaken in specialized centers familiar with the many complex aspects of EB care
6. Outcome after surgical repair of junctional epidermolysis bullosa-pyloric atresia syndrome (Dank et al. 1999): The poor

prognosis of this condition must be considered when decisions are made regarding surgical correction. Attempting surgical correction may be warranted in individual circumstances, but withholding surgical intervention and providing palliative support is an acceptable alternative. However, successful repair of PA was performed after appropriate stabilization in three children with long-term survival (Hayashi et al. 1991)

7. Tumor detection in recessively inherited DEB
8. Advanced therapy to treat hard to heal wounds
    1. Cultured keratinocytes
    2. Acellular dermal allograft plus ultrathin autografts
    3. Living dermal skin substitute
    4. Living bilayered skin equivalents
        1. Composite cultured skin (CCS)
        2. Graft skin
        3. Dermagraft
9. Feasibility of ex-vivo gene therapy in generalized non-Herlitz JEB (Mavilio et al. 2006)
10. Clinical trials based on the use of (i) allogenic fibroblasts for local RDEB wound care (Petrof et al. 2013; Venugopal et al. 2013) and (ii) allogenic hematopoietic stem cell/mesenchymal cell transplantation for severe RDEB forms (Tolar and Wagner 2013) have been recently described. In particular, hematopoietic stem cells transplantation has been reported to result in significant disease improvement, but not cure, in the majority of treated patients
11. Grafting of gene-corrected skin stem cells: still the most promising approach for permanent treatment of chronic wounds in EB patients (Murauer et al. 2015)

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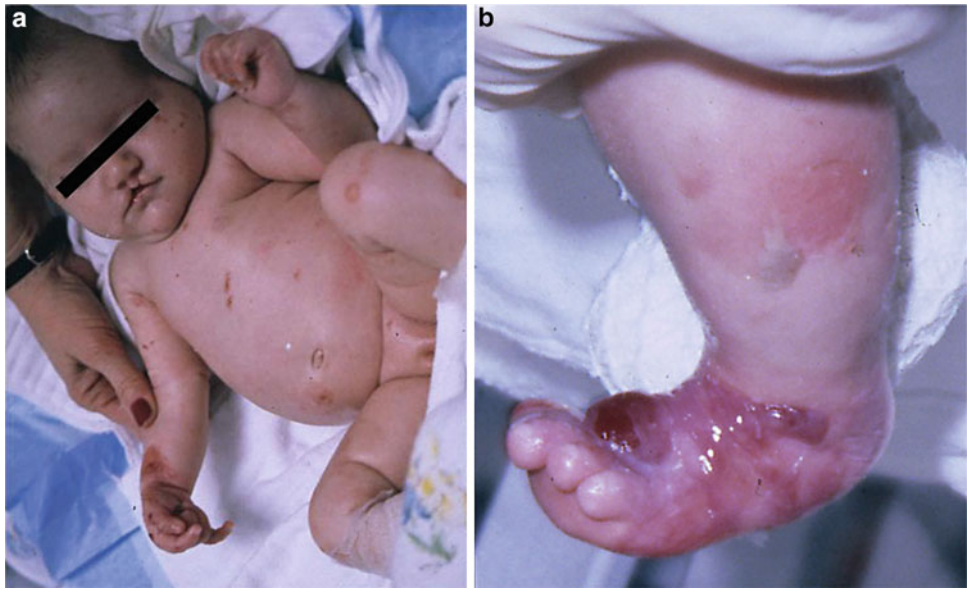

Fig. 1 (**a**, **b**) An infant (**a**) with epidermolysis bullosa showing large blisters on the foot (**b**) and smaller blisters on other part of the body (**a**)

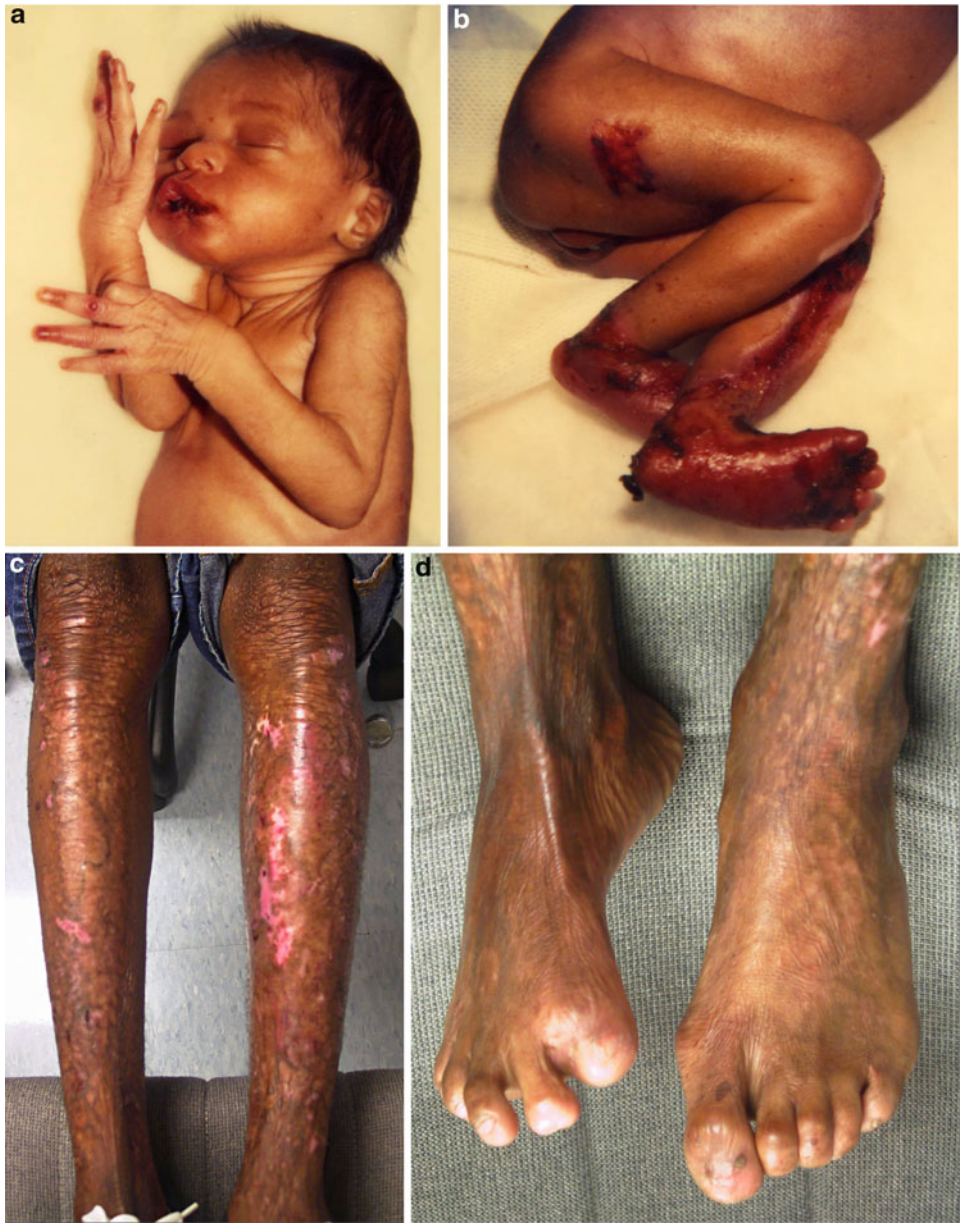

Fig. 2 (**a**–**d**) A 19-year-old female with recessively inherited dystrophic epidermolysis bullosa (Hallopeau-Siemens type) who was born with generalized blisters involving skin and mucosa, especially blisters and skin sloughing on the fingers and legs (**a, b**). She showed excessive fragile skin leading to blisters with minimal trauma (**c**), excessive scarring leading to contractures of the right foot, and fusion of first and second toe on the right foot requiring surgical separation. She also had syndactyly of the second, third, and fourth toes of the left foot. The lesions were extremely itchy and painful and more severe on the lower extremity (**c, d**). At the time of these photos, the patient still had swallowing difficulty secondary to blistering lesion in the throat

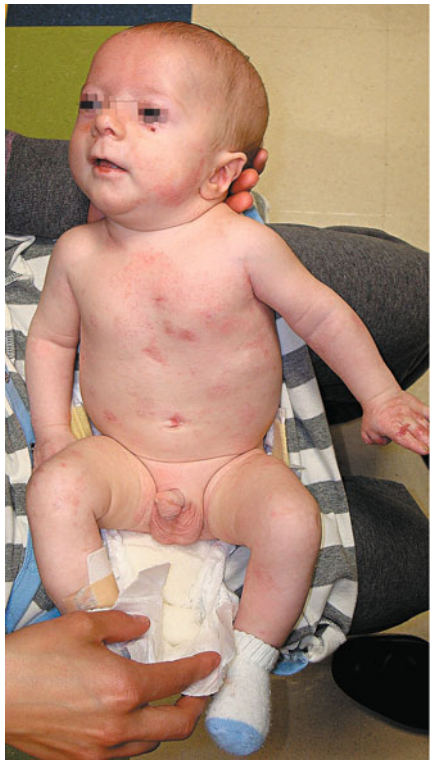

Fig. 3 This infant was born with blisters on his hands, fingers, ankles, feet, toes, and oral mucosa, and part of the body. A biopsy of the lesion was consistent with dystrophic epidermolysis bullosa. In addition, he had a single umbilical artery, esophageal atresia, a single kidney, penile hypospadias, and unilateral preaxial polydactyly. At 12-weeks of age, he still showed scars on the oral mucosa and the chest and dystrophic lesions on the fingers

Epidermolytic Palmoplantar Keratoderma

Contents

Epidermolytic palmoplantar keratoderma (EPPK), first described by Vörner in 1901 (Vörner 1901), may be the most common form of diffuse keratoderma and is characterized by keratosis restricted to the palms and soles. The disease is also known as keratosis palmaris et plantaris familiaris. The estimated incidence is at least 4.4 per 100,000 in Northern Ireland (Covello et al. 1998).

Synonyms and Related Disorders

Keratosis of Greither; Keratosis palmaris et plantaris; Localized epidermolytic hyperkeratosis; Vörner type palmoplantar keratoderma

Genetics/Basic Defects

1. Inheritance:
    1. Autosomal dominant
    2. Highly penetrant
2. Cause
    1. Keratin 9 (K9)
        1. A type 1 keratin gene (*KRT9*, located at 17q12-q21) (Reis et al. 1992, 1994; Stevens et al. 1996), a type 1 keratin expressed exclusively in the suprabasal keratinocytes of the palmoplantar epidermis
        2. Over 20 distinct pathogenic mutations in KRT9 have been identified in various ethnic kindreds with EPPK (Coleman et al. 1999; He et al. 2004; Chen et al. 2009; Liu et al. 2012; Liang et al. 2014)
    2. Mutations in keratin 1 gene (*KRT1*) underlie mild EPPK (Terron-Kwiatkowski et al. 2002, 2006)
3. Disorders of keratin genes (Knöbel et al. 2015)
    1. Mutations in *KRT5* or *KRT14*
        1. Various subtypes of epidermolysis bullosa simplex (EBS)
        2. EBS generalized severe (formerly EBS Dowling-Meara): considered the most debilitating form of EBS with extensive blistering from birth (Fine et al. 2014)
        3. EBS localized (formerly Weber-Cockayne): the mildest form with onset in childhood and predominantly confined to palms and sole
        4. Rare variants including autosomal recessive EBS
    2. *KRT1* or *KRT10* mutations
        1. Autosomal dominant: epidermolytic ichthyosis (also known as epidermolytic

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hyperkeratosis), bullous congenital ichthyosiform erythroderma (characterized by erythroderma, hyperkeratosis, and blistering of the upper skin layer) (Arin 2009; Oji et al. 2010), ichthyosis hystrix of Curth-Macklin (*KRT1* mutations, characterized by generalized or localized verrucous or spiky hyperkeratosis without blistering (Arin 2009)), and congenital reticular ichthyosiform erythroderma (KRT10 mutation, characterized by small patches of normal skin within erythroderma that increase in size over time)
    2. Autosomal recessive *KRT10* mutations (Gutierrez et al. 2013)
3. *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, or *KRT17* mutations: pachyonychia congenita (characterized by a painful and debilitating plantar keratoderma, variable hypertrophic nail dystrophy, oral leukokeratosis, and epidermal cysts) (Wilson et al. 2014)
4. *KRT9* mutations
    1. Palmoplantar keratoderma
    2. Epidermolytic palmoplantar keratoderma (Chamcheu et al. 2011; Lane and McLean 2004)

Clinical Features

1. Characteristic hyperkeratosis (Covello et al. 1998)
    1. Early onset: present at birth or during the first months of life
    2. Diffuse thick yellowish hyperkeratosis, distinctly limited to the palms and soles, with sharply bordered erythematous margins (virtually diagnostic of EPPK) (Chamcheu et al. 2011)
    3. The absence of associated features
2. Differential diagnosis (Lucker et al. 1994; Corden and McLean 1996; Ratnavel and Griffiths 1997; Lee et al. 2008)
    1. Diffuse hereditary PPK without associated features (Hatsell et al. 2001; Kingsbery 2014)
        1. Diffuse nonepidermolytic PPK (NEPPK)
            1. NEPPK: an autosomal dominant disorder.
            2. Clinically difficult to distinguish between EPPK and NEPPK.
            3. Histologically, EPPK shows epidermolysis of keratinocytes in the suprabasal layers, a characteristic not observed in NEPPK.
            4. In mild cases of EPPK, diagnosis can still be problematic as detection of epidermolysis can be difficult.
        2. Progressive PPK
            1. Hyperkeratosis extends onto the dorsa of the hands and the feet with characteristic involvement of the Achilles tendon.
            2. Hyperhidrosis common.
            3. Intrafamilial phenotypic variation common.
            4. Course of the disease: worsens during childhood, becomes static after puberty, and improves in the fifth decade of life.
        3. Gamborg-Nielsen PPK
            1. An autosomal recessive disorder.
            2. Severe form of PPK delineated in two families with six patients in Sweden.
            3. Thick, diffuse keratoderma with knuckle pads.
            4. Occasional keratosis on the dorsa of the hands.
            5. Mutilating changes due to constricting bands surrounding the fingers have been described.
    2. Diffuse hereditary PPK with associated features
        1. Mal de Meleda
            1. Described initially in inhabitants of the Adriatic Island of Meleda (Mljet)
            2. An autosomal recessive disorder

3. Diffuse, thick keratoderma with prominent erythematous border extending onto the dorsa of the hands and the feet
4. Constricting bands around digits resulting in spontaneous amputation
5. Well-circumscribed psoriasis-like plaques or lichenoid patches on the knees and the elbows
6. Hyperhidrosis
7. Periorbital erythema and hyperkeratosis
8. Nail changes (koilonychias, subungual hyperkeratosis)
9. Other associated features (lingua plicata, syndactyly, hair on the palms and the soles, high-arched palate, left handedness)

2. Vohwinkel PPK mutilans
   1. An autosomal dominant disorder
   2. Honeycomb-like keratosis of the palms and soles in infancy
   3. Constricting fibrous bands on the digits, leading to progressive strangulation and autoamputation
   4. Starfish-shaped keratosis on the dorsa of the fingers and the knees
   5. Other associated features (alopecia, deafness, spastic paraplegia, myopathy, ichthyosiform dermatosis, and nail abnormalities)
3. Olmsted mutilating PPK with periorificial keratotic plaques (Olmsted syndrome) (Da Rosa Santos et al. 1997; Tao et al. 2008)
   1. An autosomal dominant disorder
   2. Onset in the first year of life
   3. Symmetric, sharply circumscribed PPK, surrounded by erythema with flexion deformities of the digits, leading to constriction and spontaneous amputation (Poulin et al. 1984)
   4. The presence of hyperkeratotic plaques with a periorificial pattern (Atherton et al. 1990; Lucker and Steijlen 1994)
   5. Onychodystrophy
   6. Universal congenital alopecia
   7. Oral leukokeratosis
   8. Joint hyperlaxity
4. PPK with sclerodactyly
   1. An autosomal dominant disorder
   2. Sclerodactyly
   3. Diffuse keratoderma more marked on the soles than the palms
   4. Nail abnormalities
   5. Hypohidrosis
   6. Associated with squamous cell carcinoma
5. PPK with periodontitis
   1. An autosomal recessive disorder.
   2. Diffuse transgrediens palmoplantar dermatosis.
   3. Periodontosis, unless treated, results in severe gingivitis and loss of teeth by age 5 years.
   4. Increased susceptibility to infection.
   5. Scaly, erythematous lesions often observed over the knees, the elbows, and the interphalangeal joints.
   6. Hyperhidrosis with malodor.
6. Clouston hidrotic ectodermal dysplasia
   1. Diffuse, papillomatous PPK
   2. Nail dystrophy
   3. Universal sparsity of hair
   4. Other associated features (sensorineural deafness, polydactyly, syndactyly, finger clubbing, mental retardation, dwarfism, photophobia, and strabismus)
7. Diffuse NEPPK and sensorineural deafness
   1. An autosomal dominant disorder.
   2. Diffuse palmoplantar hyperkeratosis.
   3. Associated with a slowly progressive, bilateral, high-frequency hearing loss.
   4. Deafness precedes the skin changes.

3. Focal (nummular) PPK without associated features
   1. Focal NEPPK
      1. An autosomal dominant disorder

2. Palmar keratosis with a nummular, linear, membranaceous, fissured, or periungual configuration
3. Plantar keratosis with a nummular appearance, localized to pressure points

2. Focal epidermolytic PPK
   1. An autosomal dominant disorder
   2. Nummular keratotic lesions, located mainly on plantar pressure points
   3. Painful lesions
3. Siemens PPK areata/striata
   1. An autosomal dominant disorder
   2. Marked variable phenotypic expression
   3. Marked erythema initially, followed by islands of linear hyperkeratosis

4. Focal (nummular) hereditary PPK with associated features
   1. Oculocutaneous tyrosinemia (tyrosinemia type II)
      1. Focal, painful PPK
      2. Bilateral, pseudoherpetic corneal ulceration, leading to corneal scarring and glaucoma
      3. Mental retardation
      4. Occasional hyperkeratotic lesions on the elbows, knees, and tongue
      5. Hyperhidrosis
      6. Occasional bullous lesions
   2. Pachyonychia congenita
      1. Autosomal recessive disorder
      2. Localized areas of hyperkeratosis on the palms and the soles
      3. Discoloration and thickening of the nails
   3. Keratosis palmaris and plantaris with carcinoma of the esophagus
      1. Autosomal dominant disorder
      2. Age of onset: 5–15 years
      3. Focal PPK
      4. Increased susceptibility to developing carcinoma of the esophagus (38-fold increase)
      5. Variable oral leukokeratosis and follicular keratosis
   4. Focal palmoplantar and oral mucosa hyperkeratosis
      1. Autosomal dominant disorder
      2. Focal PPK, especially on weight-bearing areas
      3. Oral hyperkeratosis
      4. Increased severity with age
      5. Subungual and circumungual hyperkeratosis

5. Papular PPK without associated features
   1. Keratosis palmoplantaris punctata
      1. Autosomal dominant disorder
      2. Asymptomatic, tiny hyperkeratotic papules present on the palmoplantar surface
      3. The absence of associated features in most patients
      4. Spastic paralysis, ankylosing spondylitis, facial sebaceous hyperplasia reported
      5. Possible association with gastrointestinal malignancy
   2. Acrokeratoelastoidosis
      1. Autosomal dominant disorder
      2. Round or oval, yellowish, hyperkeratotic papules that can appear umbilicated
      3. Distribution of the lesions: along the border of the palms and the soles
      4. Associated hyperhidrosis
   3. Focal acral hyperkeratosis
      1. Autosomal dominant disorder
      2. Condition similar to acrokeratoelastoidosis
      3. Insidious onset in childhood, reaching maximum in early life
      4. Race: African origin

6. Papular PPK with associated features
   1. Rare single pedigree syndromes
      1. Syndrome of cystic eyelids, punctate PPK, hypotrichosis, and hypodontia (Schöpf-Schulz-Passarge syndrome)
      2. Punctate PPK with ankylosing spondylitis
      3. Punctate PPK with facial sebaceous hyperplasia
      4. Punctate PPK with spastic paralysis
      5. PPK with lipomata
   2. Punctate PPK and cancer

7. Acquired palmoplantar keratoderma
    1. Inflammatory and reactive dermatoses
        1. Hyperkeratotic eczema
        2. Psoriasis
        3. Reiter syndrome
        4. Lichen planus
        5. Pityriasis rubra pilaris
        6. Lupus erythematosus
        7. Callosities
        8. Darier disease
    2. Infective causes
        1. Dermatophytes
        2. Viral (human papillomavirus) warts mimicking keratoderma
        3. AIDS-related psoriasis with discrete keratotic pustular keratoderma
        4. Late secondary syphilis in patients with HIV with diffuse, symmetric keratoderma or papular PPK
        5. Yaws
        6. Leprosy
    3. Drugs
        1. Chronic arsenic exposure with multiple, irregular, warty keratosis
        2. Lodine: manifestation of drug hypersensitivity
    4. Cutaneous features of systemic disease
        1. Myoedema with hyperkeratosis
        2. Diabetes with discrete plantar keratosis
        3. Cutaneous T cell lymphoma with subungual hyperkeratosis
    5. Haxthausen keratoderma climactericum
        1. Onset in the 40s
        2. Initial lesion: pressure areas on the soles
        3. Erythema and hyperkeratosis with fissuring making walking painful
        4. Minimal pruritus
        5. Discrete and centrally confined palmar involvement
    6. Keratoderma associated with internal malignancy
        1. Keratoderma as a paraneoplastic phenomenon, such as acrokeratosis paraneoplastica of Bazex associated with squamous cell carcinoma of the upper gastrointestinal tract and acanthosis palmaris associated with gastric or pulmonary malignancy in 90% of cases
        2. Keratoderma as evidence of predisposition to malignancy such as late-onset punctate keratoderma associated with cutaneous and internal malignancy
    8. Syndromes with PPK as associated features
        1. Basal cell nevus syndrome
        2. Congenital bullous ichthyosiform erythroderma
        3. Congenital nonbullous ichthyosiform erythroderma
        4. Darier disease
        5. Epidermodysplasia verruciformis
        6. Epidermolysis bullosa herpetiformis
        7. Ichthyosis vulgaris
        8. Incontinentia pigmenti
        9. Keratitis, ichthyosis, and deafness (KID) syndrome
        10. Lamellar ichthyosis

Diagnostic Investigations

1. Histology and ultrastructures: cytolysis of keratinocytes and abnormal aggregation of tonofilaments in the suprabasal layers of the epidermis (Navsaria et al. 1995)
2. Molecular genetic analysis
    1. *KRT9* mutation analysis
        1. Sequencing of entire coding region
        2. Sequencing of select exons
        3. Targeted mutation analysis
    2. *KRT1* mutation analysis for patients with no mutations in *KRT9*

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased unless a parent is affected in which case there is a 50% risk
    2. Patient's offspring: 50%

2. Prenatal diagnosis
    1. Not usually requested because of mild nature of the disease
    2. Possible to pregnancy at risk, provided the disease-causing mutation has been identified in the proband
    3. KRT9 gene mutation as a reliable indicator in the prenatal diagnosis of EPK (Ke et al. 2014)
    4. Accomplished in a Chinese kindred affected by EPPK for detection of c. T470C (p.M157T) of the keratin 9 gene from fetal DNA obtained by amniocentesis (Chen et al. 2009)
3. Management
    1. Topical keratolytics
    2. Topical retinoids such as tretinoin

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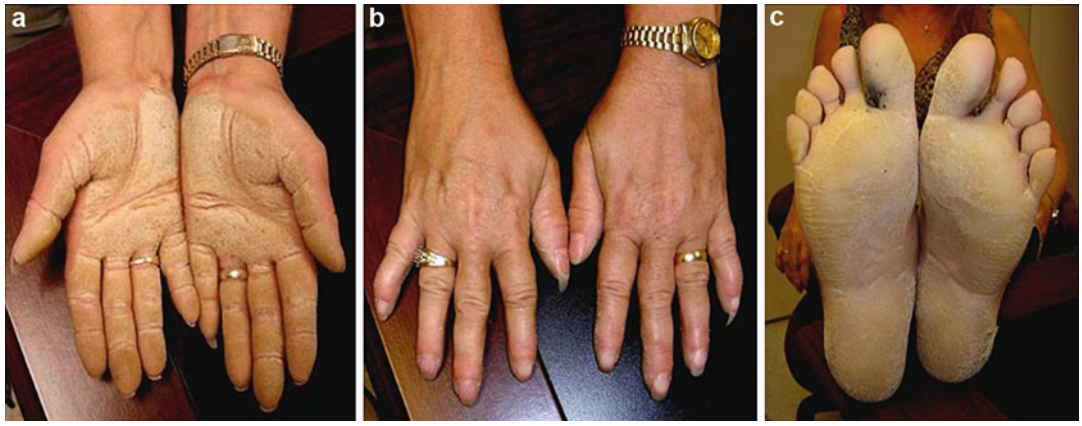

Fig. 1 (**a**–**c**) A 47-year-old woman with epidermolytic palmoplantar keratoderma showing diffuse keratoderma affecting both the palms and the soles. The keratoderma had erythematous border at the margins of both palms and soles and was completely restricted to the palms and soles. The dorsa of the hands and soles were spared. This patient has multiple affected relatives in several generations

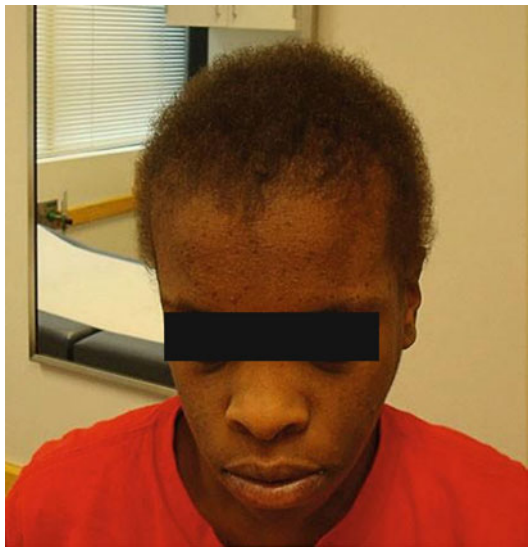

Fig. 2 This 17-year-old girl was seen for hyperkeratosis of the palms and soles associated with severe nail hyperplasia of the toes. She has mental retardation and short stature. Clinically, she has type IV epidermolytic palmoplantar keratoderma with pachyonychia congenita

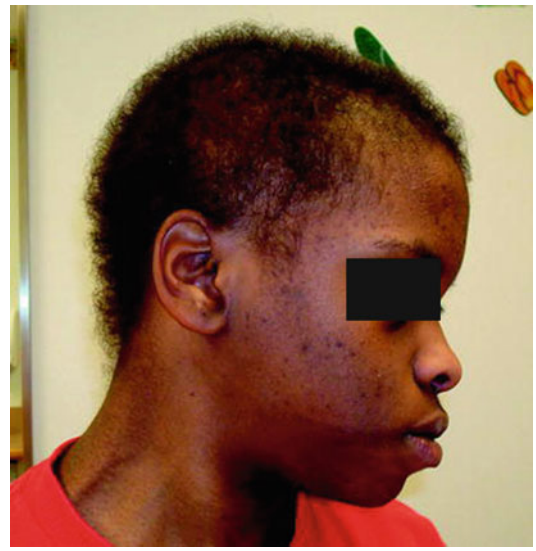

Fig. 3 She has marked midfacial hypoplasia

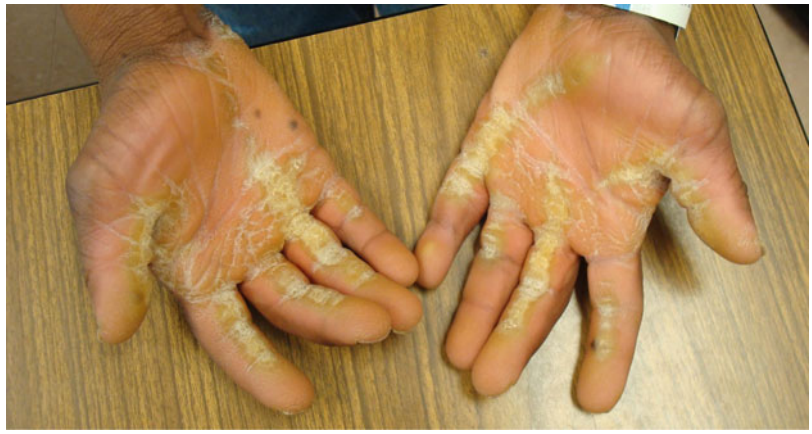

Fig. 4 Diffuse *thick* yellowish hyperkeratosis was noted on her palms. Her soles also have same *thick* yellowish hyperkeratosis

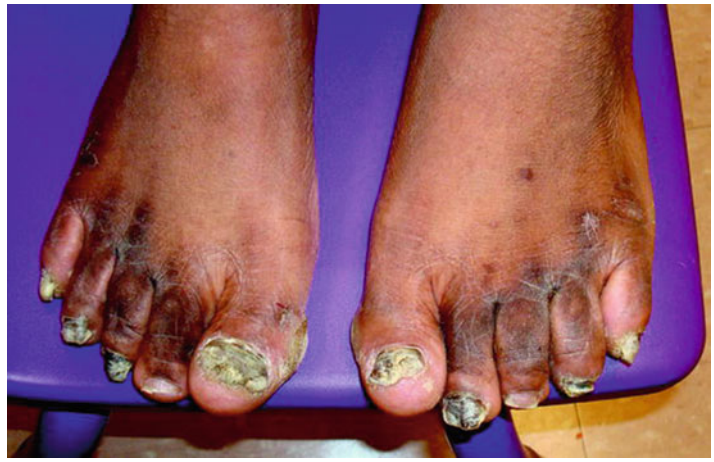

Fig. 5 Her toenails show subungual keratinous mass pushing the nail bed upward

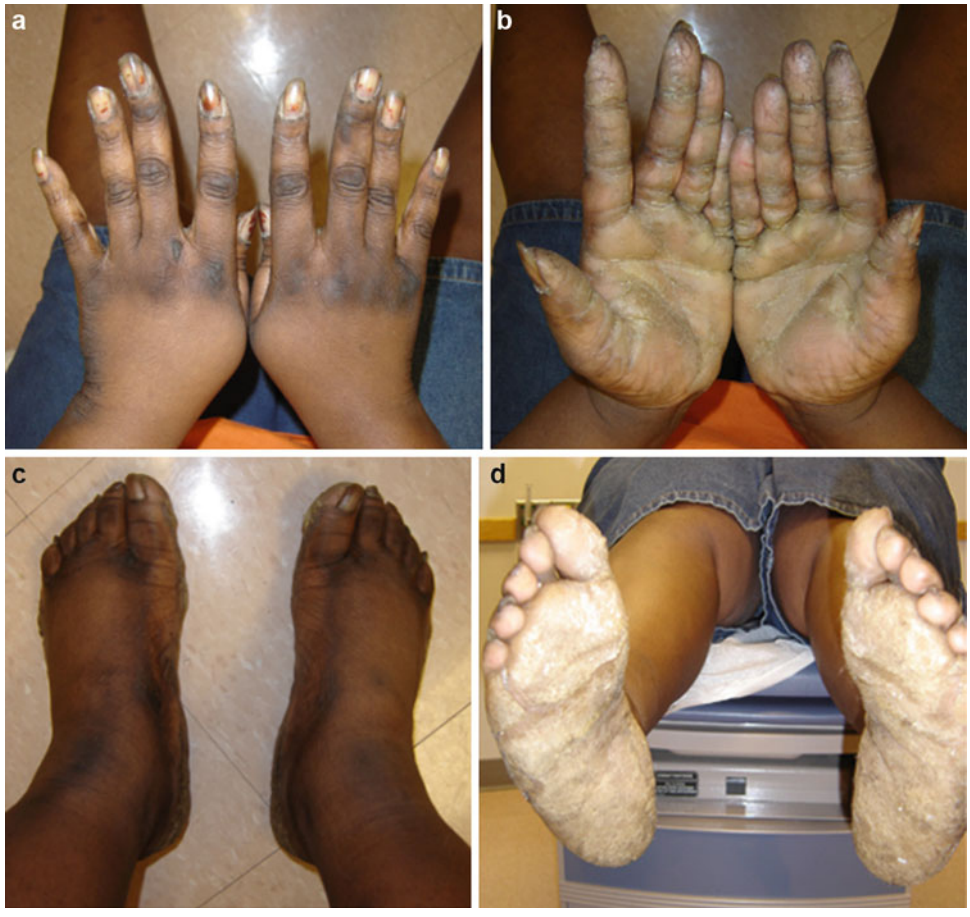

Fig. 6 (**a**–**d**) An African-American female presented with epidermolytic palmoplantar keratoderma affecting both the palms (**a**, **b**) and soles (**c**, **d**)

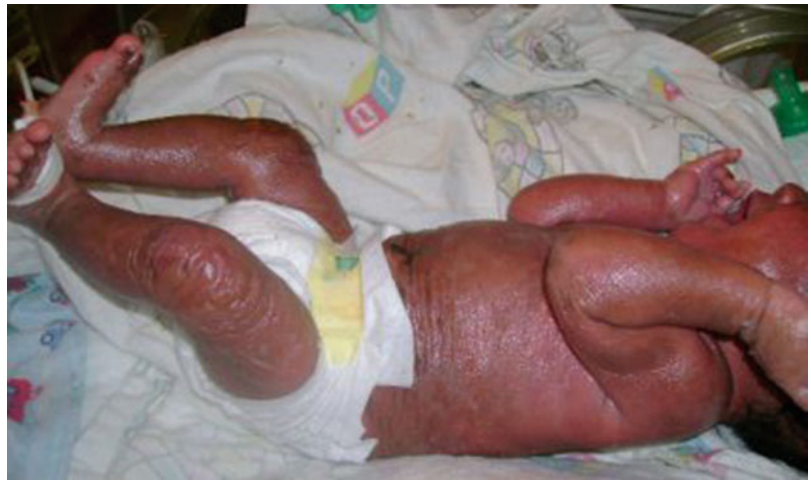

Fig. 7 This newborn was suspected to have epidermolytic hyperkeratosis. *KRT10* mutation hot spot analysis showed a heterozygous T>G (L153P) mutation in exon 1 of the *KRT10* gene. The presence of the L153P mutation in the *KRT10* gene confirms the clinical diagnosis of epidermolytic hyperkeratosis

Faciogenital (Faciodigitogenital) Dysplasia

Contents

Faciogenital dysplasia (FGDY) was first described by Aarskog in 1970 (Aarskog 1970) as a familial syndrome of short stature associated with facial and genital anomalies. The occurrence of ligamentous laxity was emphasized by Scott in 1971 (Scott 1971). The syndrome is also known as Aarskog syndrome, Aarskog-Scott syndrome, and faciodigitogenital syndrome (Sugarman et al. 1973).

Synonyms and Related Disorders

Aarskog syndrome; Aarskog-like syndrome; Aarskog-Scott syndrome

Genetics/Basic Defects

1. Aarskog-Scott syndrome (Orrico et al. 2010)
    1. X-linked recessive inheritance (Archibald and German 1975; Berman et al. 1974, 1975; Escobar and Weaver 1978; Bawle et al. 1984) with occasional partial expression in the heterozygote
    2. X-linked dominant with full male–female expression (Tyrkus et al. 1980)
    3. The *FGDY1* gene (Schwartz et al. 2000): mapped to the pericentromeric region of the X chromosome (Stevenson et al. 1994) by the observation of an X;8 translocation in an affected mother and son (Pasteris et al. 1997) (breakpoint at Xp11.21) (Glover et al. 1993); encoding a guanine nucleotide exchange factor (Estrada et al. 2001) that specifically activates the P21 GTPase Cdc42, a member of the Rho (Ras homology) family of GTPase proteins (Pasteris et al. 1994; Zheng et al. 1996; Gorski et al. 2000)
    4. Caused by mutations in the *FGDY* gene (*FGDY1*) affecting multiple skeletal structures including craniofacial bones, vertebrae, ribs, long bones, and phalanges
    5. First case of deletion of *FGD1* gene: reported in a boy with Aarskog-Scott syndrome (Bedoyan et al. 2009)
    6. Unusual facies, joint hypermobility, genital anomaly, and short stature (Bartsocas and Dimitriou 1975)
2. Aarskog syndrome: autosomal dominant (Grier et al. 1984; van de Vooren et al. 1983)
3. Aarskog-like syndrome (faciodigitogenital syndrome): autosomal dominant (Teebi et al. 1988)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_83

Clinical Features

1. Typical triad of the syndrome (Furukawa et al. 1972; Funderburk and Crandall 1974; Berry et al. 1980; Porteous and Goudie 1991; Aten et al. 2013)
    1. Facial appearance (Nielson 1988)
        1. Rounded facies
        2. Prominent metopic ridge
        3. Widow's peak hair anomaly
        4. Ocular hypertelorism
        5. Ptosis
        6. Antimongoloid obliquity of palpebral fissures
        7. Small and short nose
        8. Anteverted nares
        9. Broad nasal bridge
        10. Broad long philtrum
        11. Maxillary and mandibular hypoplasia
        12. Slight crease below lower lip
        13. Low-set ears with fleshy earlobes and incomplete outfolding of upper helices
        14. Wide phenotypic variability with severe craniofacial dysplasia (Volter et al. 2014)
    2. Digital anomalies
        1. Hands
            1. Short and broad hands
            2. Hypermobility of fingers
            3. Cutaneous syndactyly (interdigital webbing)
            4. Clinodactyly with hypoplasia of middle phalanges
            5. Transverse palmar crease
        2. Feet
            1. Short and broad feet
            2. Bulbous toes
            3. Metatarsus varus
            4. Hypoplasia of the middle or terminal phalanges
    3. Genital abnormalities
        1. Shawl scrotum (scrotal folds encircling the base of the penis): most frequently responsible for ascertainment (Duncan et al. 1977)
        2. Cryptorchidism
        3. Phimosis
        4. Hypoplasia
        5. Renal hypoplasia
2. Growth
    1. Failure to thrive
    2. Delayed puberty
    3. Slight to moderate (disproportionate acromelic) short stature (71%)
3. Intelligence and behavioral disorders (Logie and Porteous 1998)
    1. Most individuals with normal intelligence: hyperactive and attention deficits present in 61% of these individuals, which usually regress after 12–14 years of age
    2. Individuals with subnormal to mentally retarded (30%): hyperactive and attention deficits present in 84% of these individuals
4. Dental abnormalities (Halse et al. 1979; Reddy et al. 1999)
    1. Hypodontia
    2. Retarded dental eruption
    3. Orthodontic problems
5. Ocular features (Kirkham et al. 1975; Brodsky et al. 1990)
    1. Strabismus
    2. Nystagmus
    3. Amblyopia
    4. Bilateral blepharoptosis
    5. Astigmatism
    6. Hyperopia
    7. Anisometropia
    8. Corneal enlargement
    9. Deficient ocular elevation
    10. Blue sclera
    11. Posterior embryotoxon
    12. Ophthalmoplegia (Melnick and Shields 1976)
    13. Tortuosity of the retinal vessels (Pizio et al. 1994)
6. Musculoskeletal anomalies
    1. Cervical vertebral anomalies
    2. Spina bifida occulta
    3. Mild pectus excavatum

4. Genu recurvatum
5. Joint restriction
6. Prominent umbilicus
7. Inguinal hernias
8. Myopathy and distal arthropathy (Al-Semari et al. 2013)

7. Other rare signs
    1. Congenital heart defects (Fernandez et al. 1994)
    2. Gastrointestinal obstruction and volvulus in a few patients
    3. Rare perinatal occurrence of severe cerebrovascular accidents, resulting in severe neurological deficit with spastic hemiplegia (Fryns and Descheemaker 1995)
8. Phenotypic variability: wide between mother and sons and between sibs (Teebi et al. 1993)
9. Clinical variability and changing phenotype with age (Fryns 1992)
10. Carrier females often present with minor manifestations of disorder, especially relatively short stature and subtle craniofacial anomalies (Fryns et al. 1978; Hoo 1979; Pasteris et al. 1997)

Diagnostic Investigations

1. Ophthalmic examination
2. Radiography (Lizcano-Gil et al. 1994)
    1. Ocular hypertelorism
    2. Short tubular bones with widened metaphysis
    3. Brachydactyly
    4. Clinodactyly of fifth fingers
    5. Hypoplastic middle phalanges
    6. Mild interdigital webbing
    7. Cubitus valgus
    8. Splayed toes with bulbous tips
    9. Metatarsus adductus
    10. Broad flat feet
    11. Cervical vertebral anomalies
        1. Odontoid hypoplasia
        2. Fused cervical vertebrae
        3. Spina bifida occulta
    12. Scoliosis
    13. Additional pairs of ribs
    14. Retarded bone age
3. Mutation analysis: by sequencing entire coding region of *FGD1* gene available clinically
4. Application of exome sequencing in a diagnostic setting should give a significant increase in the detection of pathogenic variants by partially covering the intron–exon flanking regions. Ultimately, only full-genome sequencing will guarantee that all possible regions are taken into account (Aten et al. 2013)

Genetic Counseling

1. Recurrence risk for X-linked recessive inheritance (Aarskog-Scott syndrome)
    1. Patient's sib: 50% risk of having affected brothers if the mother is a carrier; otherwise recurrence risk is not increased
    2. Patient's offspring: 50 of his daughters to be carriers; no increased risk to his sons
2. Prenatal diagnosis
    1. Ultrasonography (Sepulveda et al. 1999): possible with a positive family history of a previously affected child by demonstrating hydrops, ocular hypertelorism, short long bones, vertebral defects, and digital anomalies in a male fetus
    2. Mutation analysis of fetal DNA from amniocytes or CVS provided the mutation has been previously identified in the proband
3. Management
    1. Supportive management
    2. Ophthalmological evaluation of the ocular problems for treatable causes of visual loss
    3. Surgery for cryptorchidism and inguinal hernia
    4. Reports of growth hormone treatment indicate a positive effect on growth and adult height in treated patients (Petryk et al. 1999)

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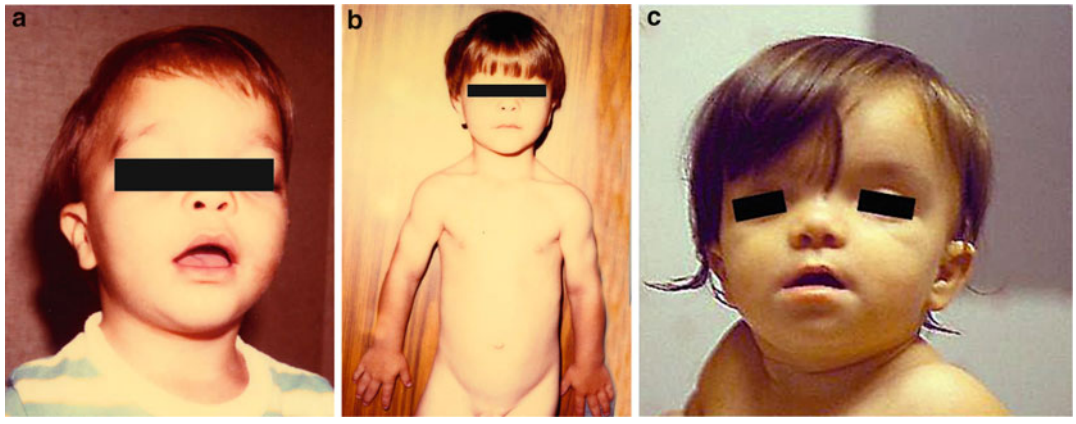

Fig. 1 (**a**–**c**) Two patients (*top* two photos (**a**, **b**) are same patient, **c**) with faciogenital dysplasia showing short stature, round face, broad forehead, hypertelorism, mild ptosis, short nose with anteverted nostrils, long philtrum, low-set ears, and broad hands with webbing of fingers

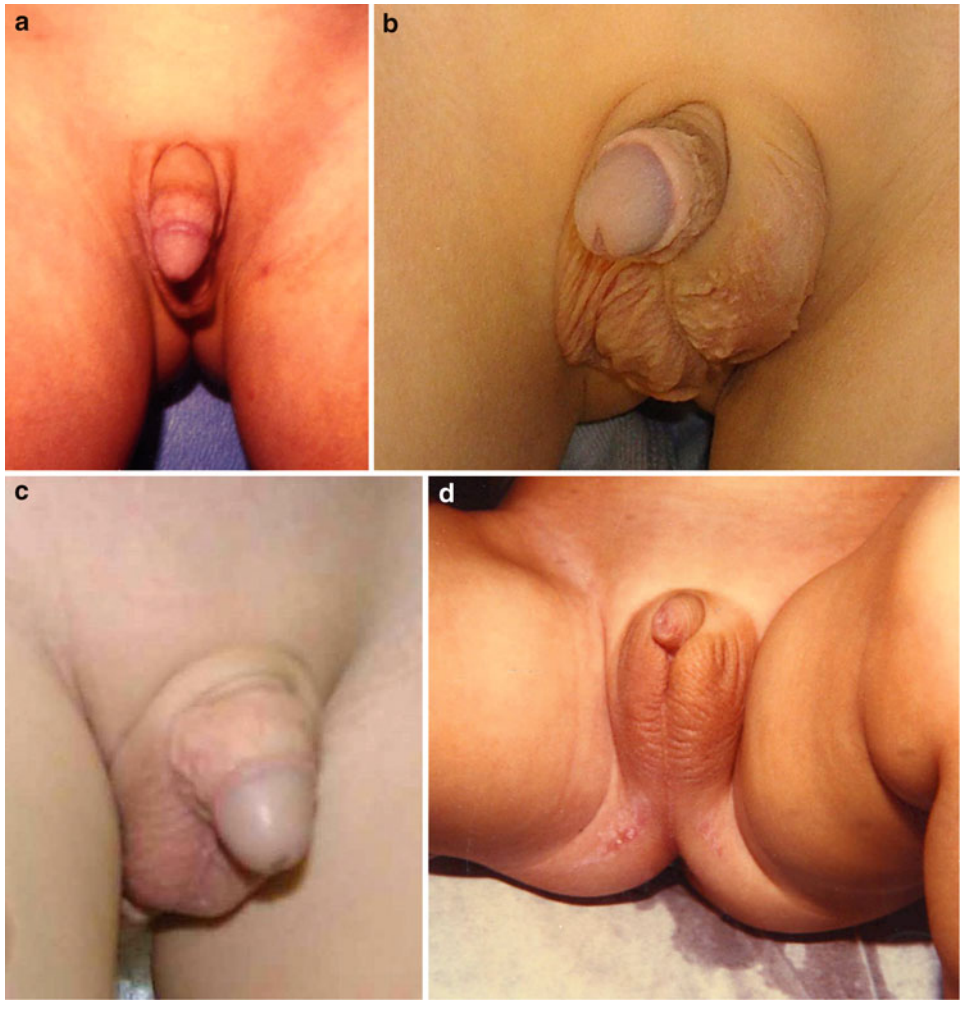

Fig. 2 (**a**–**d**) Shawl scrotums observed in four patients (**a**-**d**) with faciogenital dysplasia

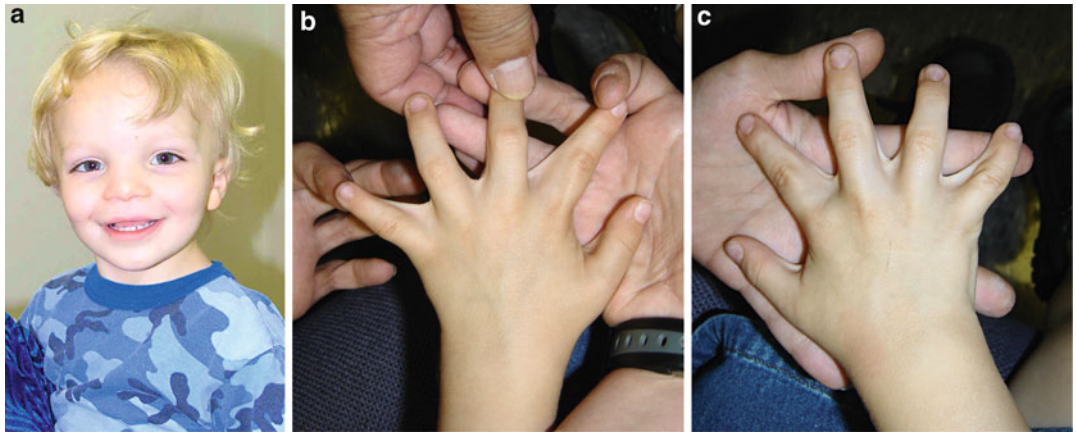

Fig. 3 (**a**–**c**) A 3-year-old boy with faciogenital syndrome showing typical facial features (round face, prominent metopic ridge, ocular hypertelorism, low-set ears) (**a**) and digital anomalies (short and broad hands and cutaneous syndactyly) (**b**, **c**)

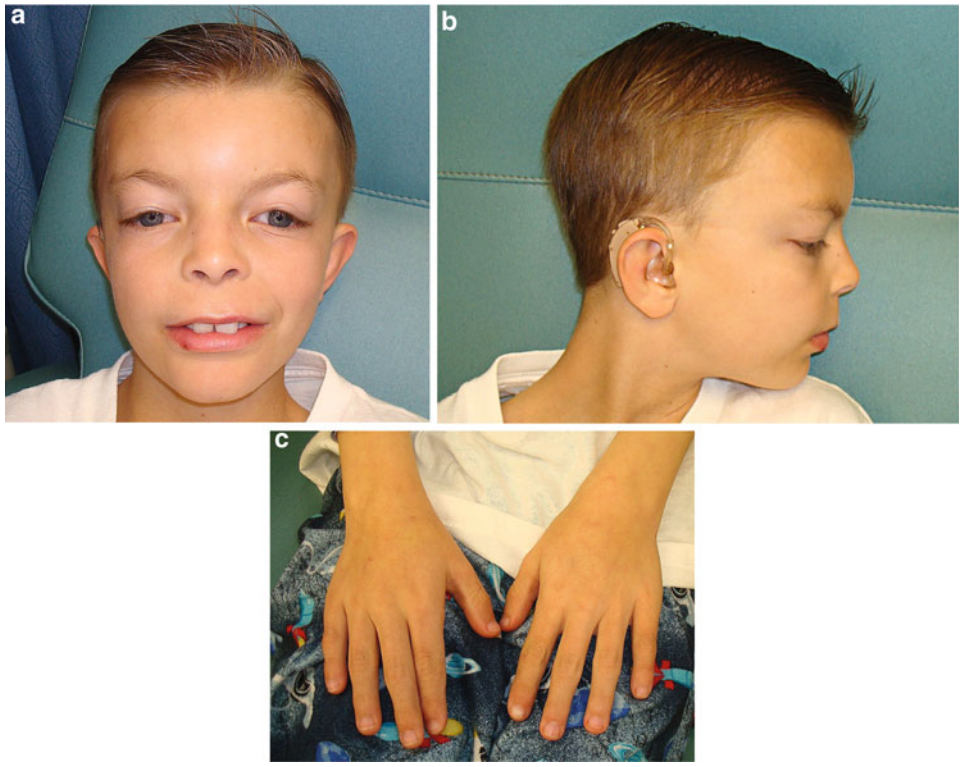

Fig. 4 (**a**–**c**) A 12-year-old boy was evaluated for short stature. On physical examination, he had ocular hypertelorism, ptosis, antimongoloid palpebral fissures, long philtrum (**a**, **b**), short and broad hands, and shawl scrotum. DNA sequencing identified a one basepair insertion at nucleotide 527 of the *FGDI* gene (c.527insC). This change is expected to cause a shift in the reading frame resulting in a truncated protein. This result is consistent with a diagnosis of Aarskog syndrome. In addition, he had sensorineural hearing loss. DNA sequence analysis indicated normal GJB2, connexin 26 (Cx26) gene

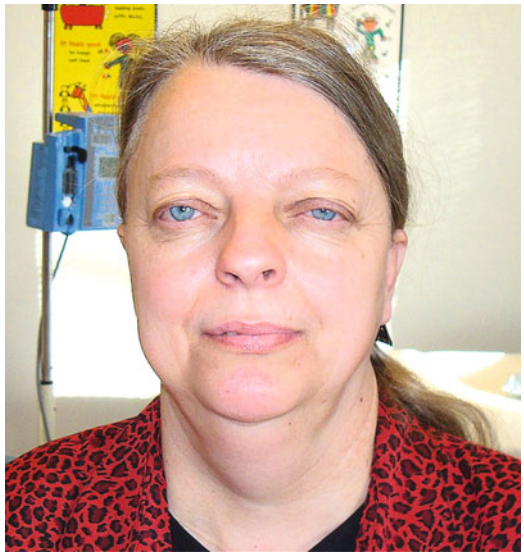

Fig. 5 His mother showed ocular hypertelorism, ptosis, and a long philtrum. She may represent a carrier with partial expression. Unfortunately, *FGS1* gene sequencing was not performed

Facioscapulohumeral Muscular Dystrophy

Contents

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common neuromuscular disorder after Duchenne muscular dystrophy and myotonic dystrophy (Upadhyaya and Cooper 2002). It is characterized by progressive weakness and atrophy of the facial and shoulder girdle muscles. The other muscles are also involved. Its prevalence is estimated to be 1 in 20,000 in Europe (Lunt and Harper 1991).

Genetics/Basic Defects

1. Inheritance
    1. Autosomal dominant
    2. Almost complete penetrance (95%)
2. FSHD1
    1. *FSHD1 gene*: mapped to the subtelomeric region of chromosome 4q35.
    2. Closely linked to the highly polymorphic locus D4F104S1.
    3. Deletion of 3.3 kb tandemly repeated D4Z4 within the *Eco*RI fragment on chromosome 4q35 (van Deutekom et al. 1996): associated with the disease in 85–95% of FSHD families (Lunt et al. 1995).
    4. The deletion is pathogenic only when it is hypomethylated and resides in a 4qA161 allele (Lemmers et al. 2007).
    5. Candidate genes for FSHD not yet elucidated.
    6. Nature of the precise mutation: still unknown.
    7. Approximately 5% of FSHD families fail to exhibit linkage to 4q35, presumably indicating the presence of a second *FSHD1* locus (Upadhyaya et al. 1999).
    8. Germline mosaicism in 4q35 FSHD1A occurring predominantly in oogenesis (Köhler et al. 1996).
    9. Evidence of anticipation and association of deletion size with severity in FSHD (Tawil et al. 1996).
3. FSHD2 (Sacconi et al. 2015)
    1. A small proportion of patients (around 5–10%) with features of FSHD do not harbor a contraction of the 4q35 D4Z4 array, and they often have a complex pattern of inheritance. The molecular basis of this second form of FSHD is termed FSHD2.
    2. FSHD2 gene *SMCHD1*: a modifier of disease severity in families affected by DSHD1 (Sacconi et al. 2013)
4. Genotype-phenotype correlation
    1. Patients with a large gene deletion

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Tendency to have a higher chance of exhibiting severe clinical phenotypes (Tawil et al. 1998)
2. Higher chance of central nervous system abnormalities

2. Patients with small *Eco*RI fragments
   1. Tendency to have earlier-onset disease
   2. More rapid progression
3. Correlation between the size of the disease-associated 4q35-*Eco*RI fragment and the following parameters:
   1. Age at onset of symptoms.
   2. Age at loss of ambulation.
   3. Muscle strength as measured by quantitative isometric myometry.
4. Prognosis varies with the length of the p13E-11 fragment (i.e., the number of *Kpn*I repeat units spared by the deletion) (Ricci et al. 1999).
   1. Patients with very short fragments (1–2 *Kpn*I repeats left): 100% probability of developing a severe form of the disease.
   2. Patients carrying fragments of 16–20 kb (3–4 *Kpn*I repeats left): probability decreases to 54%.
   3. Patients carrying fragments larger than 20 kb (>4 repeats left): probability drops to 21% or less and also they are compatible with asymptomatic conditions in adult age.
5. De novo mutations
   1. Association with smaller *Eco*RI fragments (on average) than those segregating in families
   2. Tendency of patients with de novo mutations to have findings the more severe end of the phenotypic spectrum
6. Reduced penetrance in females bearing the FSHD small fragment as compared to the penetrance in males with the FSHD small fragment
7. Germinal mosaicism (Upadhyaya et al. 1995)

5. Categories of FSHD (Padberg and van Engelen 2009)
   1. Severe disease, infantile form, onset usually before the age of 10 years with one to three residual D4Z4 repeats
   2. Moderate disease or classical phenotype with four to seven repeats and with a widely variable course, encompassing a large percentage of asymptomatic carriers older than 50 years and 60% lower limb involvement with 20% wheelchair use after this age
   3. Mild disease with eight to ten residual D4Z4 repeats, probably with frequent nonpenetrant gene carriers and muscle involvement limited to the upper limbs

Clinical Features

1. Marked clinical variability
   1. Age at onset
      1. Usually between the first and second decade
      2. Progress gradually over time
   2. Pattern of muscle involvement
      1. Progressive weakness and atrophy of the facial and shoulder girdle muscles
      2. Other muscles affected in a specific order
         1. Abdominal muscles involved first
         2. Followed by foot-extensor and upper arm muscles
         3. Finally involving pelvic girdle and lower arm muscles
   3. Intrafamilial variability
   4. Interfamilial variability
   5. Phenotype ranging from almost asymptomatic forms to more severe wheelchair-bound forms
2. A distinctive distribution of progressive muscular weakness involving the following muscles (Kissel 1999)
   1. Facial muscles
      1. Typically involved:
         1. Orbicularis oculi
         2. Orbicularis oris
      2. Clinical signs
         1. Often asymmetric involvement
         2. Facial weakness
         3. Unable to turn up the corners of the mouth when smiling
         4. Difficulty in whistling

5. Unable to purse lips
6. Sleeping with eyes partially open, the most common early sign
7. Bury eyelashes when attempting to close eyelids tightly
8. Sparing of extraocular, eyelid, and bulbar muscles

2. Scapular stabilizer muscles
   1. Affected muscles
      1. Latissimus dorsi
      2. Trapezius
      3. Rhomboids
      4. Serratus anterior
   2. Clinical signs
      1. Sloping shoulder posture at rest
      2. Anterior axillary folds
      3. Straight (horizontally placed) clavicles
      4. Pectoral muscle atrophy
      5. Scapular winging, the most common initial finding
      6. Preferential weakness of the lower trapezius muscle, resulting in characteristic upward movement of the scapula when attempting to flex or abduct the arms
3. Proximal arm muscles
   1. Biceps and triceps selectively involved, resulting in atrophy of the upper arm
   2. Distal progression of wasting and weakness of upper arm muscles, leading to eventual weakness of wrist and finger extensors
   3. Deltoids minimally affected until late in the disease
   4. Sparing of the forearm muscles, resulting in so-called "popeye arms" appearance
4. Abdominal muscles
   1. Abdominal muscle weakness resulting in:
      1. Protuberance of the abdomen
      2. Exaggerated lumbar lordosis
   2. Selective involvement of the lower abdominal muscles, resulting in Beevor's sign (upward displacement or occasionally downward movement of the umbilicus upon flexion of the neck in a supine position)
      1. Present in 90% of patients.
      2. Helpful early sign in patients with equivocal findings, as it is rarely found in other muscle disorders.
      3. Positive Beevor's sign may be caused by spinal cord injury at or below the level of Th10 (Eger et al. 2010).
5. Lower extremity muscles
   1. Anterior compartment muscles of the distal leg (anterior tibial and peroneal muscles)
      1. Usually the first and most severely affected
      2. Resulting in the typical complaints of a foot slap while walking or frank foot drop
      3. Frequent tripping or unstable walking, particularly on uneven ground
   2. Pelvic girdle muscles
      1. Less common
      2. Involving hip flexors and hip abductors
      3. Resulting in early and relatively severe gait involvement

3. Degree of muscle involvement
   1. Extremely variable
   2. Wide range of muscle involvement
      1. Very mildly affected patients unaware of the disease symptoms
      2. Isolated facial weakness
      3. Severe generalized weakness
      4. Eventually requiring a wheelchair in approximately 20% of patients
   3. Sex difference in penetrance: males more severely affected than females
4. Clinical course of muscle involvement
   1. Early involvement of facial and scapular muscles with eventual spreading to pelvic and lower limb muscles
   2. A slowly progressive course
   3. A stepwise course with periods of rapid deterioration occurring against a background of stability
   4. Aggravation of muscle weakness during pregnancy but recover quickly in the puerperium

5. Bulbar and pharyngeal muscles, extraocular muscles, and respiratory muscles typically spared
5. Extra-muscular involvement (uncommon)
    1. Coats syndrome (Fitzsimons 1999)
        1. Neurosensory hearing loss (64%)
        2. Retinal vasculopathy (49–75%)
            1. Tortuosity of retinal arterioles (microaneurysms)
            2. Telangiectasia
    2. Mental impairment
    3. Cardiac involvement (5%)
        1. Conduction defects
        2. Supraventricular arrhythmia
    4. Neurologic manifestations
        1. Preserved sensation
        2. Often diminished reflexes
6. Diagnostic criteria include the following four main elements: The diagnosis of FSHD often remains a clinical diagnosis (Kissel 1999).
    1. Onset of disease in the facial or shoulder girdle muscles, sparing the eyes, pharynx, tongue, and heart
    2. Facial weakness in more than 50% of affected family members
    3. Autosomal dominant inheritance in familial cases
    4. Evidence of myopathic disease by electrodiagnostic studies and muscle biopsy in at least one affected family member
    5. In the absence of (Statland and Tawil 2014):
        1. Ptosis, weakness of extraocular muscles, or bulbar weakness
        2. Electromyography in a patient or affected family member showing myotonia or neurogenic changes

Diagnostic Investigations

1. Increase of seven serum biomarkers (no difference detected between FSHD types 1 and 2 for these markers (Statland et al. 2014))
    1. Creatine kinase
    2. Myoglobin
    3. Plasminogen pathway markers (tissue-type plasminogen activator)
    4. Vitronectin
    5. Inflammatory marker chemokine ligand 2
    6. Inflammatory marker CD40 ligand
    7. Epidermal growth factor
2. Serum creatine kinase (CK)
    1. Normal to elevated levels: raised level in only 80% of affected males under 40 years and 48% of affected women (Lunt and Harper 1991)
    2. Usually not exceeding three to five times the upper limit of the normal range
3. Audiogram for sensorineural hearing loss
4. Fluorescein angiography to demonstrate retinal vasculopathy
5. EMG: nonspecific myopathic features
    1. Fibrillations
    2. Positive waves in resting muscle
    3. Early recruitment of short-duration motor unit action potentials
6. Muscle biopsy: nonspecific features
    1. Underlying process: myopathic and help to exclude the following primary muscle diseases that can present with a FSHD-like phenotype (Kissel 1999)
        1. Congenital myopathies
            1. Nemaline (rod) myopathy
            2. Centronuclear myopathy
        2. Inflammatory myopathies
            1. Polymyositis
            2. Inclusion body myositis
        3. Other dystrophies
            1. Scapuloperoneal dystrophy
            2. Limb-girdle dystrophy
        4. Others: desmin storage myopathy
    2. Increased variation in fiber size
    3. Increased internalized nuclei
    4. Variable degrees of endomysial inflammatory cells
    5. Angulated “neuropathic-like” myofibers
    6. Mononuclear inflammatory reaction (75%)
7. Molecular genetic testing (Kissel 1999)
    1. Molecular confirmation of FSH may be sought (Fitzsimons 1999):
        1. To exclude another form of dystrophy

2. To exclude nonpenetrant carrier status in an adult
3. To diagnose the FSH status of a fetus
4. Useful in infants who present sporadically with deafness combined with facial immobility

2. Mutation analysis
   1. Combination of double digestion with *Eco*RI and *Bln*I followed by pulsed field gel electrophoresis: the most reliable molecular protocol for distinguishing patients with FSHD (Orrell et al. 1999).
   2. Detection of the short fragment in affected individuals.
      1. High sensitivity and specificity of the 4q35 deletion for FSHD.
      2. Using probe p13E-11 (D4F104S1), which hybridized to 4q35, to detect small *Eco*RI digestion fragments (Felice and Moore 2001).
      3. Deletion within the D4Z4 repeat region of chromosome 4q35 (demonstrable short fragment), observed in 95% of patients clinically affected with FSHD, whether familial or sporadic.
      4. Approximately 98% of patients with such a short fragment have clinically demonstrable FSHD.
      5. Confirms the diagnosis with a high degree of certainty.
   3. Large deletions in the 4q35 region (producing a smaller short fragment).
      1. Associated with more severe expression of the disease
      2. Manifest earlier onset of disease
      3. More severe degree of weakness
      4. Shorter fragment size generally associated with sporadic cases with an earlier age of onset than with familial cases
   4. Variability in fragment size: unable to explain the significant clinical variability sometimes seen within FSHD families, since the deletion size appears to remain stable from generation to generation.
   5. Findings of a short but less intensively hybridizing p13E-11/*Eco*RI/*Bln*I fragment strongly suggest germinal mosaicism. Minor clinical signs in parents may point toward germline mosaicism.
3. Genetic diagnosis (Tawil et al. 2010)
   1. The large majority (>95%) of patients with FSHD have a partially deleted D4Z4 repeat array on one of their chromosomes 4 (FSHD1).
   2. This repeat array is polymorphic in copy number, with alleles varying between 11 and 100 units in the general population.
   3. Patients with FSHD1 carry one allele with one to ten D4Z4 units (Tawil and van der Maarel 2006).
   4. In order to be pathogenic, this shortened D4Z4 repeat array needs to reside on the 4qA background of chromosome 4.
4. Absence of identifiable D4Z4 deletions in approximately 5% of individuals with FSHD

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Ten percent risk for a sib of a de novo case being a carrier. The figure of 10% is based on the observation that both somatic and germinal mosaics are detected, indicating that both types of mutations occur early in embryogenesis and therefore will give rise to a high percentage of mutated germ cells (Bakker et al. 1996).
      2. Fifty percent recurrence risk if a parent is affected.
   2. Patient's offspring: each offspring of an affected individual having a 50% chance of inheriting the deleted region within the D4Z4 repeat motif for FSHD
2. Prenatal diagnosis (Tawil et al. 2010)
   1. Available for fetuses at 50% risk for FSHD

2. Molecular genetic testing: follow a de novo mutation in a subsequent generation by analyzing DNA extracted from fetal cells obtained by (Bakker et al. 1996):
    1. CVS: preferred over amniocentesis since genetic diagnosis for FSHD can take several weeks to complete
    2. Amniocentesis
3. Conditions for inclusion for prenatal diagnosis
    1. Confirmed FSHD1 in the family
    2. Availability of DNA from parents and index case
4. Preimplantation genetic diagnosis (PGD)
    1. Southern blot genetic test: not applicable to single-cell PGD.
    2. Consequently, the disease-associated D4Z4 repeat can only be detected indirectly with the use of polymorphic markers, but the relatively high recombination frequency and the availability of few polymorphic markers specific for the region proximal to D4Z4 hamper PGD significantly.

3. Management (Kissel 1999; Lemmers and van der Maarel 2014)
    1. Lack of effective treatment
    2. Unpredictability of the clinical course
    3. Management of pain in the shoulders, back, abdomen, and leg
        1. Use of nonsteroidal anti-inflammatory drugs
        2. Range-of-motion exercise
        3. Gentle stretching through a physical therapy program
    4. Physiotherapy (Eggers et al. 1993)
    5. Supportive treatment of complications from progressive weakness
        1. Judicial use of bracing
        2. Ankle and foot orthoses to improve mobility and prevent falls in patients with foot drop
        3. Surgical fixation of the scapula to the chest wall (thoracoscapular fusion) or to the ribs (scapulocostal fusion)
            1. Often improving range of motion of the arms
            2. Short-lived effect in patients with rapidly progressive disease
    6. Pharmacologic treatment
        1. Limited to the use of corticosteroids in patients with evidence of inflammation on muscle biopsy
        2. Possible effect of albuterol, a β2-adrenergic agent (Sripathi 2014)
            1. Improvement of lean body mass
            2. Modest improvement in strength
    7. Treat respiratory dysfunction which occurs in <1% of patients with FSHD (Wohlgemuth et al. 2004)
    8. Treat cardiac dysfunction which is seen in about 5% of patients (Laforet et al. 1998)
    9. Pregnancy in FSHD
        1. Pregnancy outcomes in FSHD are generally good although two case series have conflicting reports about an increased incidence of operative deliveries and preterm births (Rudnik-Schoneborn et al. 1997; Ciafaloni et al. 2006).
        2. Pregnant women with FSHD be followed by high-risk obstetricians and that delivery occurs in a center that can provide comprehensive perinatal care.
        3. Additionally, it is recommended that pregnant women with FSHD and reduced lung function have serial monitoring of their FVC during the course of their pregnancy.
    10. Required assistance in caring the infants after delivery due to weakness in the shoulder girdle
    11. Evidence-based guideline for evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy (Tawil et al. 2015)
        1. Available genetic testing for FSHD type 1 is highly sensitive and specific.
        2. Although respiratory insufficiency occurs rarely in FSHD, patients with severe FSHD should have routine pulmonary function testing.
        3. Routine cardiac screening is not necessary in patients with FSHD without cardiac symptoms.

4. Symptomatic retinal vascular disease is very rare in FSHD. Exudative retinopathy, however, is potentially preventable, and patients with large deletions should be screened through dilated indirect ophthalmoscopy.
5. The prevalence of clinically relevant hearing loss is not clear. In clinical practice, patients with childhood-onset FSHD may have significant hearing loss. Because undetected hearing loss may impair language development, screening through audiometry is recommended for such patients.
6. Musculoskeletal pain is common in FSHD, and treating physicians should routinely inquire about pain.
7. There is at present no effective pharmacologic intervention in FSHD.
8. Available studies suggest that scapular fixation is safe and effective. Surgical scapular fixation might be cautiously offered to selected patients.
9. Aerobic exercise in FSHD appears to be safe and potentially beneficial. On the basis of the evidence, patients with FSHD might be encouraged to engage in low-intensity aerobic exercises.

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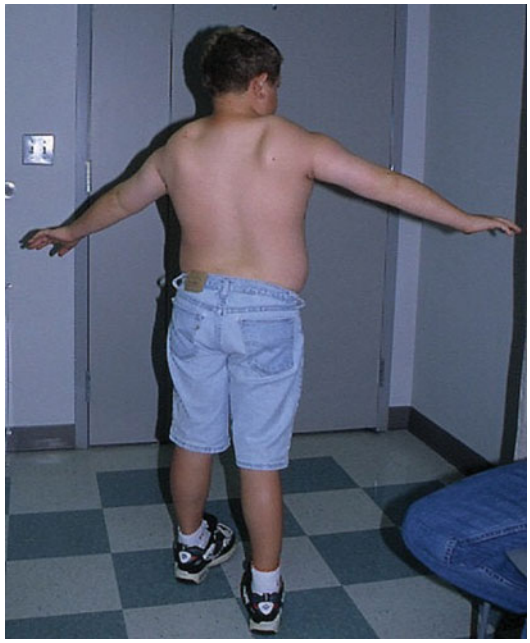

Fig. 1 A child with FSHD showing periscapular wasting and weakness resulting in scapular winging and inability to abduct the arm above the horizon

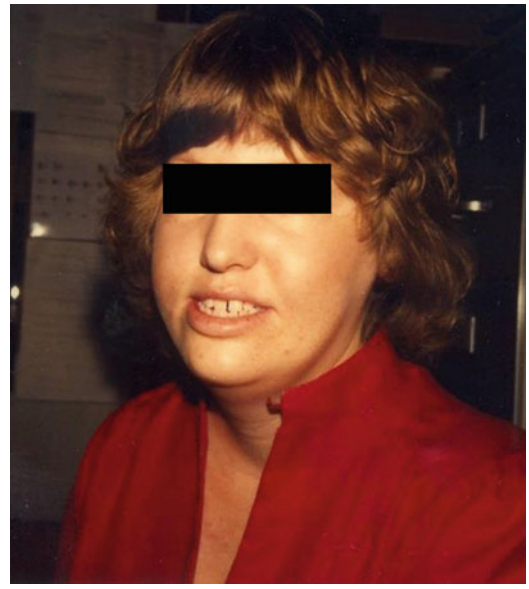

Fig. 3 An adult with FSHD showing facial weakness and inability to smile, purse the lips, and whistle

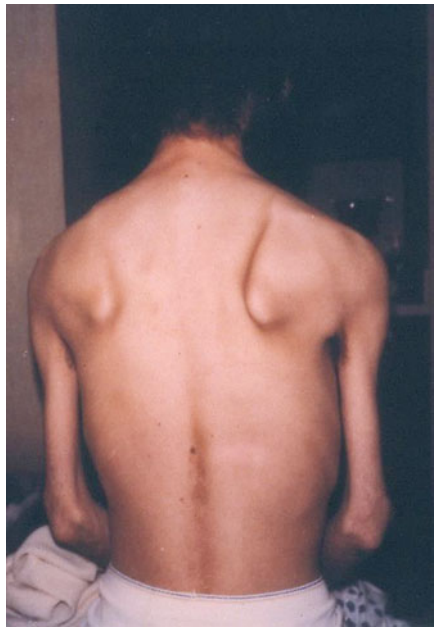

Fig. 2 An adult with FSHD showing scapular winging and wasting of proximal arm muscles

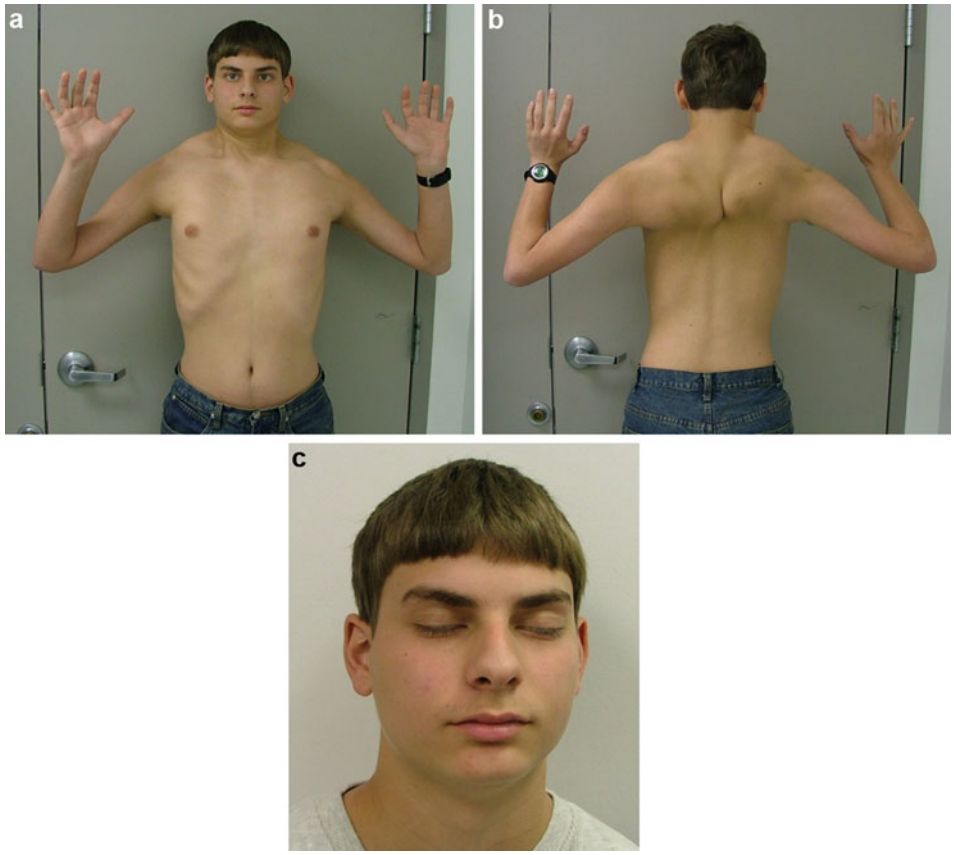

Fig. 4 (**a**–**c**) A 14-year-old boy with FSHD showing sloping shoulders, inability to raise arms above shoulders, and inability to close his eyelids completely. In addition, he had difficulty in pursing the lips and could not whistle (onset at about 2 years of age). His CPK was 1,295 (normal, 0–200 U/L). Molecular genetic analysis revealed FSHD allele 1 of 18 kb and FSHD allele 2 of >48 kb (FSHD deletion, 12–37; marginal, 38–41; no deletion, ≥42). The mother and several other family members are also affected

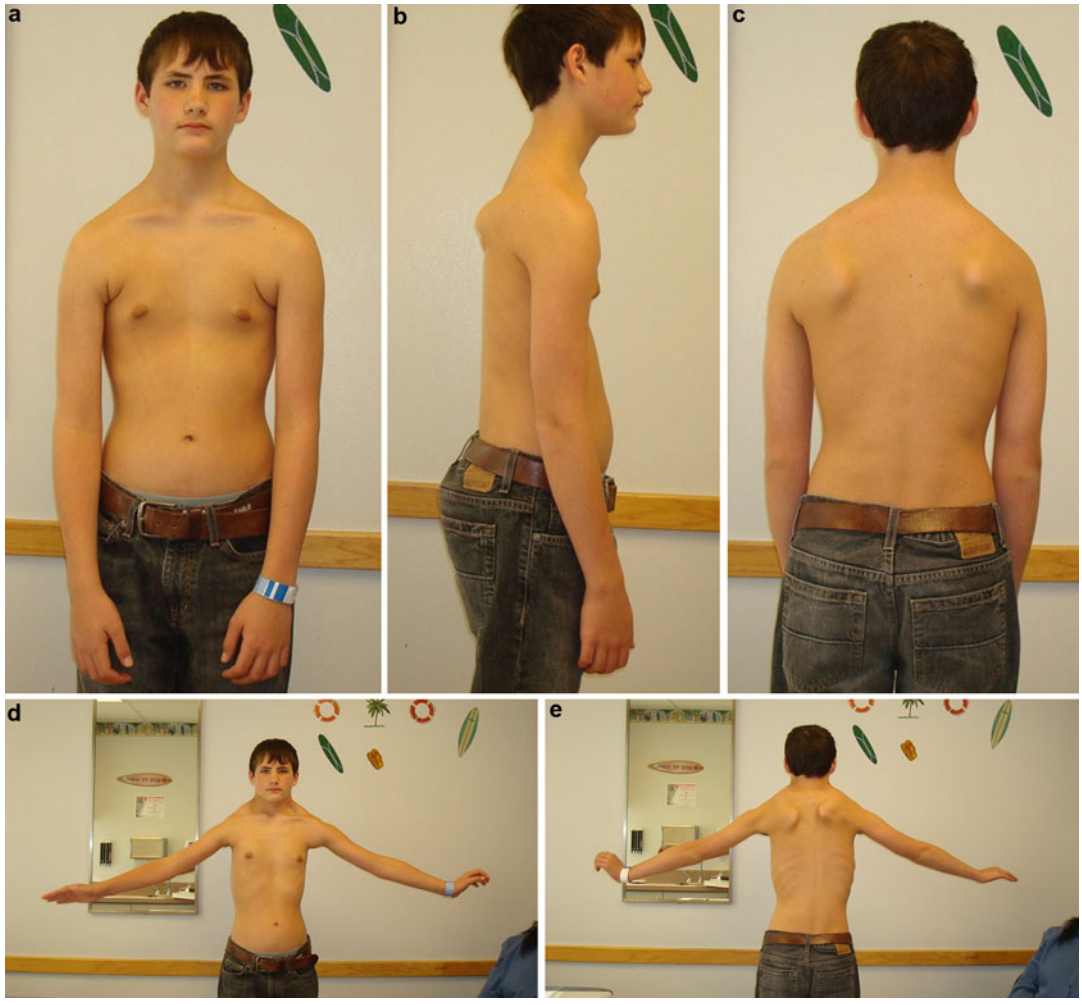

Fig. 5 (**a**–**e**) A 13-year-old boy was evaluated for his scapula deformities. He could not purse his lips, whistle, or smile. He could not raise his arms above his shoulders for the last 6 months. He had an elevated CK of 717 (normal, 35–232). On physical examination, he was noted to have sloping shoulder posture at rest, winging scapular, pectoral muscle atrophy, and mild atrophy of the upper arms. Molecular genetic testing revealed an FSHD gene mutation with allele 1 of 13 kb and allele 2 of >48 kb consistent with the diagnosis of facioscapulohumeral muscular dystrophy

Fig. 6 This 19-year-old female was evaluated for inability to raise arms above shoulders. Molecular genetic analysis revealed FSHD allele 1 of 22 kb (FSHD deletion mutation) and FSHD allele 2 of >48 kb (normal allele), confirming the clinical diagnosis of facioscapulohumeral muscular dystrophy

Familial Adenomatous Polyposis

Contents

Germline mutations in the adenomatous polyposis coli (*APC*) gene cause the most common form of hereditary polyposis syndromes termed "familial adenomatous polyposis (FAP)." The incidence is approximately 1 in 8,300 to 1 in 13,000 live births (Bisgaard et al. 1994).

Synonyms and Related Disorders

Adenomatous intestinal polyposis; Attenuated FAP; Familial colorectal cancer syndromes; Familial polyposis of the colon (familial polyposis coli); Gardner syndrome; Hereditary gastrointestinal cancer syndrome; Hereditary mixed polyposis; Hereditary polyposis syndrome; Juvenile polyposis; Lynch syndrome; MYH-associated polyposis; Peutz-Jeghers syndrome; Polymerase proofreading polyposis; PTEN hamartoma tumor (Cowden) syndrome; Serrated polyposis; Turcot syndrome

Genetics/Basic Defects

1. Inheritance
    1. Autosomal dominant (AD) with high penetrance (80–100%)
    2. Spontaneous mutations account for approximately 30% of cases
2. Caused by germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21 (Leppert et al. 1987; Lynch and Hoops 2002)
    1. More than 300 different disease-causing mutations of the *APC* gene are currently identified
    2. Nonsense or frameshift mutations that result in a truncated protein in nearly all of the germline mutations in APC
    3. Nearly 80% of FAP families have identifiable germline mutations in one allele of *APC* in affected individuals
    4. Similar high incidence of germline mutations is seen in the FAP variant, Gardner syndrome
3. *APC* gene
    1. A large gene consisting of approximately 6 kb in length
    2. A tumor suppressor gene encoding for a 2,843-amino acid protein with a putative role in:
        1. Cell adhesion
        2. Signal transduction
        3. Transcriptional activation

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3. The causative germline defect of *APC* gene predisposes to the following conditions (Gebert et al. 1999):
    1. FAP
    2. Nearly obligatory colorectal cancers
4. Loss of second *APC* allele either by somatic mutation or loss of heterozygosity in the earliest premalignant lesions:
    1. Dysplastic aberrant crypt foci
    2. Small adenomatous polyps
5. Adenoma formation (Robbins and Itzkowitz 2002)
    1. Beginning with loss of function of the APC tumor suppressor gene
    2. Followed by activation of the K-ras oncogene
    3. Subsequent loss of function of genes on chromosome 18q and inactivation of p53 ushers in malignant degeneration
6. The site of APC gene mutation is associated with pigmented ocular fundus lesions (codons 542–1309) and predisposition to multiplicity of extraintestinal manifestations (codons 1465, 1546, and 2621) (Giardiello et al. 1997)

4. Colorectal carcinogenesis: involves two principal pathways (Robbins and Itzkowitz 2002):
    1. Chromosomal instability
        1. Deletion of portions of a chromosome results in loss of specific genes and abnormal amounts of DNA per cell (aneuploidy). This pathway accounts for:
            1. All cases of colorectal cancers associated with FAP
            2. Nearly 85% of sporadic colorectal cancers
        2. The pathway of *c-myc* and *β-catenin* as downstream targets appears to impact on the kinetochore and microtubule attachment
        3. Mutations in *APC* interfere with the way that epithelial cells divide and distribute their nuclear DNA
        4. Mutations in the APC tumor suppressor gene cause chromosomal instability (Fodde et al. 2001)
    2. Microsatellite instability
        1. Produced by defects of the DNA base mismatch repair system
        2. This pathway accounts for:
            1. 15% of sporadic colorectal cancers
            2. Most cases of hereditary nonpolyposis colorectal cancer
5. Genotype-phenotype correlation
    1. FAP phenotype expressed in an individual depends in part on the site of the germline *APC* mutation
        1. Attenuated familial adenomatous polyposis coli occurs when there is a truncating mutation in the extreme ends of the *APC* coding sequence (Spirio et al. 1993; Soravia et al. 1998)
        2. Germline mutations in the 3′ part of APC exon 15 do not result in truncated proteins and are associated with attenuated adenomatous polyposis coli (Van der Luijt et al. 1996)
        3. Mutations between codons 169 and 1,393 resulting in classic FAP
        4. Mutations between codons 1,250 and 1,464, especially around codon 1,300, resulting in profuse colorectal polyposis and earlier onset of gastrointestinal polyps (Nagase et al. 1992)
        5. Retinal lesions (congenital hypertrophy of the retinal pigment epithelium, a condition present at any age in 60% of FAP families) occur only with mutations between codons 457 and 1,444 (Lynch and Hoops 2002; Cruz-Correa and Giardiello 2003)
        6. Up to 60% of patients with mutations between codons 1,445 and 1,580 result in desmoids (Leggett 2002)
    2. Limited clinical application of genotype-phenotype correlation: Considerable phenotypic variability exists even among individuals and families with identical genotypic mutations
6. Familial colorectal cancer syndromes (Novelli 2015; Syngal et al. 2015)
    1. FAP
    2. Attenuated FAP

3. Lynch syndrome (AD) (*MLH1*, 3p21.3; *PMS2*, 7p22.1; *MSH2*, 2p21; *MSH6*, 2p16.3)
    1. Polyp type(s): conventional adenomas
    2. Extraintestinal features: endometrial adenocarcinoma, transitional cell carcinoma of upper urogenital tract, ovarian carcinoma, pancreatobiliary carcinoma, brain tumors, skin tumors
4. MYH-associated polyposis (autosomal recessive) (*MUTYH*, 1p34.3)
    1. Polyp type(s): conventional adenomas, serrated polyps
    2. Extraintestinal features: Some FAP-type extraintestinal features but at low incidence
5. Serrated polyposis (unknown)
    1. Polyp type(s): serrated polyps (conventional adenomas)
    2. Extraintestinal features: none
6. Hereditary mixed polyposis (AD) (*GREM1*, 15q13.3)
    1. Polyp type(s): conventional adenomas, serrated polyps, hamartomas (juvenile polyps)
    2. Extraintestinal features: none
7. Polymerase proofreading polyposis (AD) (*POLE*, 12q24.3; *POLD1*, 19q13.33)
    1. Polyp type(s): conventional adenomas
    2. Extraintestinal features: endometrial carcinomas, ?brain tumors
8. Peutz-Jeghers syndrome (AD) (*STK11*, 19p13.3)
    1. Polyp type(s): hamartomas (polyps)
    2. Extraintestinal features: carcinomas in many organs
9. Juvenile polyposis (AD) (*SMAD4*, 18q21.1; *BMPR1A*, 10q23)
    1. Polyp type(s): hamartomas (juvenile polyps)
    2. Extraintestinal features: none
10. PTEN hamartoma tumor (Cowden) syndrome (AD) (*PTEN*, 10q23)
    1. Polyp type(s): conventional adenomas, hyperplastic polyps, hamartomas, ganglioneuromas, inflammatory polyps
    2. Extraintestinal features: breast carcinoma
11. Constitutional mismatch repair deficiency (autosomal recessive) (*MLH1*, 3p21.3; *PMS2*, 7p22.1; *MSH2*, 2p21; *MSH6*, 2p16.3)
    1. Polyp type(s): conventional adenomas
    2. Extraintestinal features: Cafe-au-lait spots, high-grade brain tumors, leukemias/lymphomas

Clinical Features

1. Spectrum of disease activity (Half et al. 2009)
    1. Attenuated FAP (AFAP): mild form of FAP
        1. Fewer number of adenomatous polyps: less than 100
        2. A later age of adenoma development and onset for colorectal cancers
    2. Fulminant FAP
        1. With hundreds to thousands of polyps at a young age
        2. A nearly 100% risk of developing colorectal cancers by the age of 40
2. Usually asymptomatic until puberty when colonic polyps begin to develop, the adenomas become large and numerous so as to cause rectal bleeding or even anemia
3. Average age of onset of polyps: 25 years
4. Presenting signs and symptoms
    1. Rectal bleeding: the most common symptom
    2. Anemia
    3. Abdominal pain
    4. Change in bowel habits, constipation, or diarrhea, occurring approximately 8 years later
    5. Palpable abdominal masses
    6. Weight loss
    7. Above signs and symptoms in young patients can lead to rectosigmoid examination and identification of polyps suggestive of FAP

5. Relative and approximate contributions of familial causes to the incidence of colorectal cancer (Half et al. 2009)
    1. About 85% of cases are sporadic
    2. Approximately 10% are familial cancer
    3. Three to five percent are hereditary nonpolyposis colorectal cancer (Lynch syndrome)
    4. Less than one percent are FAP, familial juvenile polyposis, and Peutz-Jeghers syndrome
6. Colonic manifestations of FAP
    1. Characterized by the presence of hundreds to thousands of colorectal adenomas of different sizes. Today, this is rarely seen in countries with well-developed public health services
    2. In the majority of patients, polyps begin to develop during childhood, mostly in the distal colon (rectosigmoid) as small intramucosal nodules
    3. By the time of adolescence, the polyps are usually identified throughout the colon and, thereafter, increase in size and numbers
    4. About half of FAP patients develop adenomas by 15 years of age and 95% by age 35 years (Petersen et al. 1991)
    5. Generally, cancers start to develop a decade after the appearance of the polyps. So, if the colon is left intact, the majority of patients with FAP eventually develop CRC by the ages 40–50 years
    6. Although uncommon, colorectal cancers can develop in children or in older adults
    7. Other gastrointestinal manifestations
        1. Gastric polyps (fundic gland polyps) develop in the stomach in 90% of patients with FAP
            1. Typically benign
            2. Adenomatous in rare cases
            3. An increased rate of gastric cancer in some kindreds
            4. Gastric cancer occur more frequently than duodenal cancer in Japanese FAP kindreds (Opposite is true for FAP kindreds with European Caucasian descent)
            5. Gastric adenomas occur in 50% of Japanese FAP kindreds
        2. Duodenal or periampullary (Bjork et al. 2001) adenomatous polyps (5–10% lifetime risk)
            1. May progress to cancer
            2. Five percent of these patients develop malignant transformation within 20 years after the onset of polyps
        3. Other small intestinal tract polyps: rare
    8. Adenomas of the ileal pouch may follow proctocolectomy
7. Extraintestinal (extracolonic) manifestations (Parks et al. 1970; Gebert et al. 1986)
    1. Pancreatic (2%) and biliary tract cancers: rare
    2. Adrenal adenomas: rare
    3. Papillary thyroid carcinomas
        1. Affect about 1–2% of patients with FAP
        2. A hundred-fold increased risk in the women with FAP
        3. Activation of *ret/ptc1* oncogene in FAP-associated thyroid papillary carcinomas (Cetta et al. 1998)
    4. Hepatoblastomas: a 1–3% risk of developing hepatoblastomas from birth until 6 years of age in infants and children who are at risk or known APC mutation carriers (Hughes and Michels 1992)
    5. Brain (medulloblastoma, glioblastoma) (<1%) (Cohen 1982)
    6. Osteomas (Jagelman 1987)
    7. Congenital hypertrophy of retinal pigment epithelium
        1. Multiple and bilateral lesions: a sensitive phenotypic marker that can direct clinical screening tests prior to or in lieu of genetic screening in an at-risk member of an FAP kindred
        2. Generally a benign condition but low-grade adenocarcinoma of the retina has been reported in several individuals with this condition

8. Dental abnormalities
    1. Unerupted teeth
    2. Congenital absence of one or more teeth
    3. Supernumerary teeth
    4. Dentigerous cysts
    5. Odontomas
9. Cutaneous lesions: rarely malignant
    1. Fibromas
    2. Lipomas
    3. Sebaceous and epidermoid cysts
    4. Nasopharyngeal angiofibromas

8. Desmoid tumors (Gebert et al. 1986; Jones et al. 1986; Clark et al. 1999)
    1. Also known as mesenteric fibromatosis
    2. A relatively common complication of FAP (Klemmer et al. 1987; Sturt and Clark 2006)
        1. A lifetime risk for men: 8%
        2. A lifetime risk for women: 13%
    3. No metastatic potential but can be both life threatening or problematic in treatment when the lesions slowly expand:
        1. To involve the intra-abdominal cavity
        2. To surround the nervous or vascular systems
    4. Conditions which may accelerate the growth:
        1. Surgery
        2. Estrogen receptor antagonists
        3. Radiation
        4. Chemotherapy
    5. Common recurrence
    6. Desmoids may follow a slow but unrelenting course with a lethal outcome (Herrera-Ornelas et al. 1987)
9. FAP variants (Lynch et al. 1979)
    1. Gardner syndrome
        1. Refers to FAP with additional extraintestinal phenotypic manifestations accompanying colonic polyposis
            1. Osteomas
            2. Sebaceous cysts
            3. Lipomas
            4. Desmoids
            5. Dental abnormalities
        2. Caused by mutations in the *APC* gene
    2. Attenuated FAP
        1. Characterized by the development of significantly fewer colonic adenomas (<100)
        2. Typically right-sided polyps
        3. Seventy percent of patients develop colorectal cancers by age 65 if polypectomy is not performed
        4. Presence of fundic gland polyps, a clue to the possible diagnosis of AFAP
    3. Turcot syndrome
        1. Characterized by medulloblastoma in association with colonic polyposis and colorectal cancers
        2. Caused by germline *APC* mutations
        3. Variable inter- and intrafamilial phenotypic expression

10. Differential diagnosis with two other main polyposis syndromes (Lynch et al. 1979) and one nonpolyposis syndrome, all of which are associated with an increased risk of GI cancer, especially colorectal cancer (Järvinen 2003)
    1. Juvenile polyposis
        1. An autosomal dominant disorder
        2. Caused by at least two separate genes
            1. *SMAD4*/*DPC4* in chromosome 18q21
            2. *BMPR1A*/*ALK3* in chromosome 10q21-22
        3. Characterized by multiple juvenile polyps of the colorectum
        4. Also involves the stomach and the small intestine
        5. Large polyps
            1. Commonly lobulated
            2. Adenomatous dysplasia in 50% of cases, giving rise to the increased risk of colorectal cancer (Järvinen and Franssila 1984)
        6. The APC gene mutation of familial juvenile polyposis suggests a genetic relationship with familial adenomatous polyposis (Kim et al. 1997)
    2. Peutz-Jeghers polyposis
        1. An autosomal dominant disorder
        2. Caused by mutations of the *LKB1* gene on 19p13.3

3. Characteristics
    1. Mucocutaneous melanin pigmentation
    2. Hamartomatous intestinal polyposis
4. Sites of polyps
    1. Affect small intestine preferentially
    2. Also affect stomach and large intestine

3. Hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome)
    1. An autosomal dominant disorder
    2. Caused by mutations of three DNA mismatch repair genes
        1. *MSH2* (2p21-23)
        2. *MLH1* (3p21)
        3. *MSH6* (2p16)
    3. More common than the polyposis syndromes
    4. Predominant tumors
        1. Colorectal cancer
        2. Endometrial cancer
    5. Other cancer types: cancers of the stomach, ovary, ureter and renal pelvis, bile ducts, kidney, small intestine, and brain tumors

Diagnostic Investigations

1. Basis of diagnosis of classic FAP (Eccles et al. 1997; Gebert et al. 1999)
    1. Suggestive family history
    2. Clinical findings
    3. Confirmed by genetic testing whenever possible
2. Screening in FAP (Boardman 2002)
    1. Colonoscopic examination for at risk and *APC* mutation carriers, initiate at 10–12 years of age
    2. Flexible sigmoidoscopy for at-risk individuals with unknown mutation status
        1. Annually from age 10 to 15
        2. Biennially from age 26 to 35
        3. Every third year from age 36 to 50
    3. Upper GI tract endoscopy for at-risk individuals with colorectal polyps and known gene carriers. Recent progress in endoscopic technology, including high-resolution endoscopy, capsule endoscopy, and double-balloon endoscopy, has made possible more detailed and wide-ranging investigation of the gastrointestinal tract (Aihara et al. 2014)
    4. Annual physical examination to assess thyroid nodules
    5. Hepatoblastoma screening in children with FAP (at risk or mutation-positive carriers until age 6)
        1. Annual screening by liver ultrasonography
        2. Annual serum α-fetoprotein levels
    6. Medulloblastoma screening: brain imaging for symptomatic or known Turcot syndrome kindreds
    7. Imagings (King et al. 2000)
        1. CT scan for desmoid tumors of the mesentery
        2. MRI to delineate vascular involvement and to predict desmoid growth
3. Screening in AFAP
    1. Colonoscopy required for individual at risk for AFAP
    2. Continued screening in the individual with AFAP because of the later age of onset of polyps
4. Detection of FAP in known kindreds
    1. Retinoscopy: Presence of more than three pigmented ocular fundic lesions confirms the diagnosis of FAP
    2. Flexible sigmoidoscopy
    3. Presymptomatic *APC* gene testing (Park et al. 1994)
        1. Indications (Leggett 2002)
            1. Children and siblings of affected individuals with FAP or AFAP: usually delayed until the early teenage years (10 years or older) when screening by flexible sigmoidoscopy would normally commence
            2. Patients with an unusually high number of colorectal adenomas for their age but not enough to be clinically diagnostic of classical FAP ($\geq$20 cumulative colorectal adenomas, suspected AFAP)
            3. $\geq$100 colorectal adenomas

2. Methods (Boardman 2002)
    1. Protein truncation testing of peripheral blood lymphocytes: detects *APC* mutation in more than 80–90% of affected families
    2. Conformation strand gel electrophoresis
    3. Single-strand conformation polymorphism
    4. Direct sequencing
    5. Linkage analysis to markers on chromosome 5q
3. Germline *APC* testing: the most efficient means for identifying gene carriers within an FAP kindred
4. Direct sequencing targeted at the known region of the *APC* gene if a mutation has already been detected within one member of a kindred
    1. Cost effective
    2. Nearly 90% accurate means of *APC* testing

5. Genetic tests for *MUTYH* (Half et al. 2009)
    1. A subset of patients that presents with clinical AFAP harbor a recessive disorder caused by the inheritance of mutations in the base-excision-repair gene *MUTYH* (Castellsagué et al. 2008)
    2. *MUTYH* mutation causes the polyposis condition known as *MUTYH* attenuated FAP (MAP)
    3. It is recessively inherited and patients have either a homozygous or compound heterozygous germline mutations of the *MUTYH* gene
    4. Recommended for all patients who have tens to hundreds of colorectal adenomas with no identified germline mutation in the *APC* gene and with a family history compatible with an autosomal recessive and rarely autosomal dominant modes of inheritance
    5. Therefore, DNA screening of the *MUTYH* gene should look for both heterozygous and homozygous mutations (Olschwang et al. 2007)
6. Despite technological advances, APC gene size, allelic and locus heterogeneity, and multiple mutational disease-causing mechanisms (truncations, deletions, duplications, splicing alterations, missense alterations, and others yet unknown) continue to make the detection of disease-causing mutations in patients with colorectal adenomatous polyposis challenging (Kerr et al. 2013)
7. Next-generation sequencing (NGS) technology can be included as an adequate diagnostic method for the identification of intragenic mutation testing of familial colorectal cancer syndromes, complemented in the mutation-negative cases with a reduced number of Sanger sequences to resolve the DNA regions not adequately assessed by NGS (Simbolo et al. 2015)

Genetic Counseling

1. Recurrence risk for autosomal dominant inheritance
    1. Patient's sib
        1. Not increased in a de novo case
        2. 50% if a parent is affected
    2. Patient's offspring: a 50% risk of inheriting the condition and virtually all children who inherit the condition will develop polyposis (Leggett 2002)
2. Prenatal diagnosis
    1. Molecular genetic testing of the *APC* gene on fetal DNA obtained from amniocentesis or CVS for fetuses at 50% risk for FAP if a clinically diagnosed relative has an identified disease-causing *APC* gene alteration
    2. Linkage analysis if the family is informative for linked markers
    3. Preimplantation genetic diagnosis (Ao et al. 1998)
3. Management (Boardman 2002)
    1. Surveillance: In patients with FAP and FAP variants including Gardner syndrome, Turcot syndrome, and attenuated FAP, the main goal of surveillance is to detect the colorectal cancer in early stages (Leoz et al. 2015), combining molecular and clinical approaches (Gebert et al. 1999)

2. Pre- and post-test genetic counseling
    1. A pretest counseling session covering:
        1. The nature of the disease itself
        2. The genetic aspects
        3. The implications of positive and negative test results on future screenings
        4. On insurability and family relationships
    2. A post-test counseling session
        1. Disclosure of the results
        2. Addressing psychological consequences
3. Potential consequences of genetic testing for hereditary colorectal cancer (Trimbath and Giardiello 2002)
    1. Positive consequences if the result is gene positive (the disease-causing mutation detected)
        1. Removal of uncertainty
        2. Early detection of polyps and prevention of cancer
        3. Greater ability to plan the future including family and career decisions
        4. Increased compliance with colonic screening/surveillance
        5. Greater choice of surgical and medical management
    2. Negative consequences if the result is gene positive (the disease-causing mutation detected)
        1. Psychological distress, including anxiety, depression, anger, or denial
        2. Changes in family psychosocial dynamics
        3. Stigmatization
        4. Increased fear about surgery or death
        5. Children at 50% risk of disease
        6. Guilt/worry about children
        7. Colon surgery and possible lifestyle changes
    3. Positive consequences if the result is gene negative (truly negative for gene mutation identified in family)
        1. Removal of uncertainty
        2. Children not at risk
        3. Fewer medical exams and costs
        4. Better insurability
    4. Negative consequences if the result is gene negative (truly negative for gene mutation identified in family)
        1. Survival guilt (guilt about being unaffected when other family members are affected)
        2. Changes in family psychosocial dynamics
    5. Negative consequences if the result is inconclusive (no pedigree mutation found or variant of unknown significance)
        1. False sense of security
        2. Does not rule out risk for disease
        3. Need for continued screening
        4. Confusion/anxiety
4. FAP (Forbes et al. 1987)
    1. Prophylactic surgery remains the best means to minimize the risk of developing colorectal cancers
    2. Laparoscopic prophylactic treatment for FAP can be performed safely and effectively with the advantage of minimal invasion by experienced surgeons (Huang et al. 2015)
    3. Consider colectomy (Giardiello et al. 2002)
        1. By late teen years for cancer prophylaxis for both gene carriers and at-risk individuals with polyposis
        2. Without colectomy, colorectal cancer is inevitable, appearing approximately 10–15 years after the onset of polyposis
    4. Total colectomy with ileorectal anastomosis remains the operation of choice for the majority of patients with FPC, but a total colectomy with ileal reservoir and ileo-anal anastomosis is appropriate in some cases (Aitken et al. 1986)
    5. Specific surgical recommendation (Heimann et al. 1986)
        1. Proctocolectomy with mucosectomy
        2. Ileal pouch anal anastomoses
        3. Ileorectal anastomosis
    6. Surgical removal of osteomas for cosmetic reasons

7. Treatments for desmoid tumors
    1. Surgical excision: associated with high rates of recurrence
    2. Nonsteroidal anti-inflammatory drugs (sulindac, celecoxib) (use before colectomy): remains experimental
    3. Antiestrogens
    4. Cytotoxic chemotherapy
    5. Radiation
    6. For intra-abdominal desmoid tumors: chemotherapy as a first choice treatment and reserve surgery when it is impossible or when desmoid tumors are life threatening (Desurmont et al. 2015)
8. Celecoxib (sulindac), a selective cyclooxygenase-2 (prostaglandin synthetase) inhibitor (Lipsky 1999; Corredor et al. 2001)
    1. Reduces by 28% the mean number of polyps in adult patients with FAP
    2. Potential use of this class of drugs as chemopreventive and therapeutic agents: subject of intense current investigation (Giardiello et al. 2002)

5. AFAP
    1. Endoscopy and polypectomy
    2. Surgery: ileorectostomy rather than ileal pouch anal anastomosis is recommended because the rectum is relatively spared by polyposis
        1. For recurrent, numerous polyposis
        2. For the presence of aggressive histologic features
    3. Continued need for annual endoscopic evaluation of the rectal remnant
6. Prognosis (Half et al. 2009)
    1. Most patients with clinical FAP can be identified and have their diagnosis confirmed by genetic testing
    2. Individuals with FAP carry a 100% risk of colorectal cancer that is reduced almost absolutely when patients enter a screening and treatment program
    3. Once proctocolectomy has been performed, the risk of ampullary and duodenal cancer is significant and requires lifelong upper gastrointestinal surveillance that has been shown to save lives of FAP patients
    4. Desmoids need to be identified early while small and not causing local perturbations
    5. Duodenal cancer and desmoids are the two main causes of mortality after total colectomy has removed the risk for CRC
    6. The sociological, psychological, and physiological issues related to the diagnosis and treatment of FAP need to be addressed
    7. The colectomy and ensuing change in bowel habits frequently lead to dietary changes that can be unbalanced and lead to vitamin-mineral deficiencies

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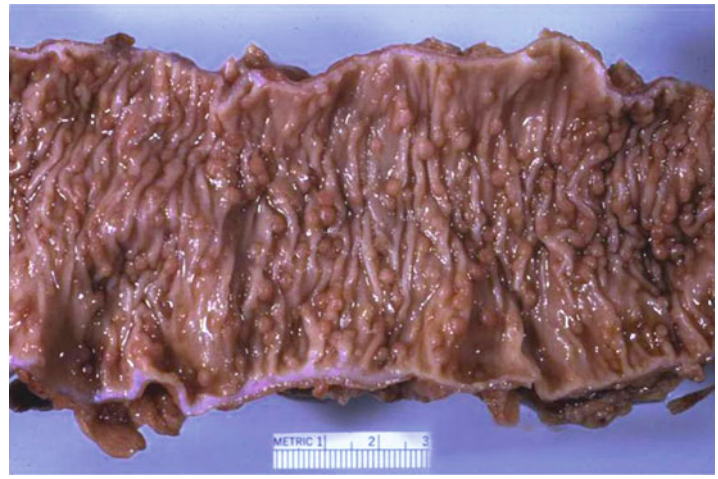

Fig. 1 Colon of an 8-year-old girl with familial adenomatous polyposis. Numerous small polyps were present on the mucosal surface of the entire colon. The polyps measured up to 3 mm in size. Occasional polyps had a slender stalk, up to 2 mm in length. Histologically, the polyps were of tubular (adenomatous) type

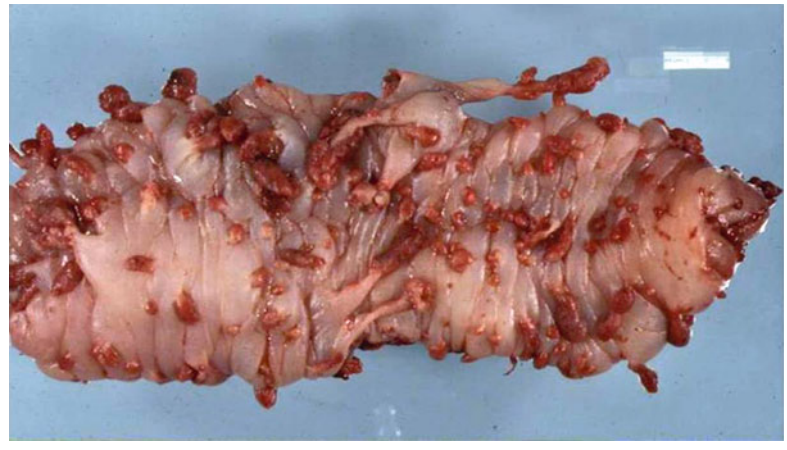

Fig. 2 A segment of colon showing juvenile polyposis. The polyps are large and lobulated. Stalks are present in some of them. The number of polyps is not as numerous as seen in Fig. 1 (AFP)

Fig. 3 A 50-year-old female had a history of multiple removals of numerous pedunculated and sessile polyps (adenomatous) during past 12 years. Her mother was diagnosed with colon cancers and had most colon surgically removed. Molecular testing of the patient showed intron 3 alteration [IVS3(−3)T > A]. Aberrations within the intron can affect normal splicing of RNA. Whether this is a disease-causing mutation or a normal variant cannot be determined without determination of the mother's DNA status

Familial Hyperlysinemia

Contents

Familial hyperlysinemia is an inborn error of metabolism caused by a defect in the bifunctional protein α-aminoadipic semialdehyde synthase (Woody 1964; Markovitz et al. 1984; Sacksteder et al. 2000; Cox 2001).

Synonyms and Related Disorders

Alpha-aminoadipic semialdehyde synthase deficiency; L-lysine NAD-oxido-reductase deficiency; Lysine alpha-ketoglutarate reductase deficiency

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. A heterogeneous group of at least four disorders
    1. Caused by mutations in the gene (mapped to 7q31.3) encoding α-aminoadipic semialdehyde synthase (AASS), the bifunctional protein that contains both lysine-ketoglutarate reductase (LKR) and saccharopine dehydrogenase (SDH) activity.
    2. Deficiency in lysine-ketoglutarate reductase (LKR) and/or saccharopine dehydrogenase (SDH) activities leads to a clinical phenotype characterized by hyperlysinemia, lysinuria, and variable saccharopinuria.
    3. Deficiency in saccharopine oxidoreductase activity, along with deficient LKR and SDH activities, is also observed in children with familial hyperlysinemia (Dancis et al. 1969, 1976, 1979).
    4. Mitochondrial NADP(H) deficiency due to a mutation in NADK2 causes dienoyl-CoA reductase deficiency with hyperlysinemia (Houten et al. 2014).

Clinical Features

1. Generally considered a benign metabolic variant
2. The more severe neurological disease course in two patients with a contiguous deletion syndrome may be explained by the additional loss of *PTPRZ1* (Houten et al. 2013)
3. Mental retardation of varying degree (Woody 1964; Ghadimi et al. 1965, 1967; Armstrong and Robinow 1967)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_86

4. Other neuromuscular manifestations
    1. Poor muscle tone (hypotonia)
    2. Muscle weakness
    3. Clumsy hand movements
    4. Cross adductor reflexes
    5. Ankles clonus
    6. High-arched feet
    7. Awkward gait
    8. Hyperactive deep tendon reflexes
    9. Seizures
    10. Progressive spastic paraparesis/diplegia (Yiannikas and Cordato 1996)
5. Developmental delay, especially speech delay
6. Hyperactive behavior
7. Ligamentous laxity
8. Ocular manifestations (Smith et al. 1971)
    1. Bilateral subluxated lenses (ectopia lentis)
    2. Lateral rectus muscle paresis
    3. Bilateral spherophakia
9. Hyperlysinemia alone may not be associated with a clinical phenotype (Woody et al. 1966; Van Gelderen and Teijema 1973; Özalp et al. 1981; Dancis et al. 1983)
10. Differential diagnosis
    1. Hyperlysinemia: periodic hyperlysinemia with ammonia intoxication
    2. Ectopia lentis
        1. Marfan syndrome
        2. Homocystinuria
        3. Weill-Marchesani syndrome
        4. Ehlers-Danlos syndromes
        5. Dominant and recessive forms of inherited subluxation of the lens

Diagnostic Investigations

1. Plasma amino acid quantitative analysis: hyperlysinemia (Simell et al. 1972)
2. Urinary amino acid quantitative analysis: hyperlysinuria (Armstrong and Robinow 1967; Woody and Ong 1967)
3. Urinary organic acid analysis: variable saccharopinuria (Carson et al. 1968)
4. Excretion of pipecolic acid by infants and by patients with hyperlysinemia (Woody and Pupene 1970)
5. Excretion of hypusine by children and by patients with familial hyperlysinemia (Woody and Pupene 1973)
6. Cultured skin fibroblasts: absent lysine-ketoglutarate reductase and saccharopine dehydrogenase activities (Cederbaum et al. 1979)
7. Molecular genetic study: homozygous deletion in *AASS* gene
8. EEG for seizures

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25%
    2. Patient's offspring: not increased unless the spouse is a carrier in which case 50% of the offspring will be affected
2. Prenatal diagnosis has not been reported
3. Management
    1. Dietary control with reduction in lysine intake (Tondo et al. 2013): two children with hyperlysinemia type I and neurological impairment in which implementation of lysine-restricted diet achieved a mild improvement of some signs but did not reverse cognitive impairment. The moderate decrease of plasma lysine concentrations after dietary treatment supports the need of increase in lysine restriction.
    2. Other supportive therapies

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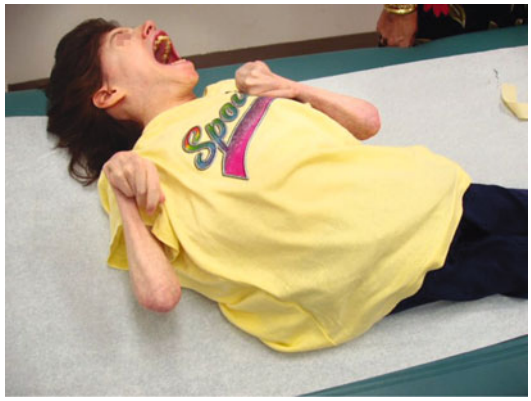

Fig. 1 A 27-year-old female with hyperlysinemia showing global delay, spasticity, rigidity, and multiple joint contractures. She was diagnosed to have hyperlysinemia since about 1 1/2 years of age with markedly elevated serum lysine of 1,618 μM (45–144). As a neonate, she had frequent emesis and noted to be stiff and irritable with progressive developmental delay. She began to walk with a ramp and rails until approximately 4 years of age when she started to develop increased spasticity and significant scissoring, necessitating adductor release. On the recent plasma amino acid analysis, lysine was markedly elevated at 1,252 μM (41–225)

Familial Mediterranean Fever

Contents

Familial Mediterranean fever (FMF), also known as an autoinflammatory syndrome, is the most frequent periodic fever syndrome, affecting not only eastern Mediterranean people such as non-Ashkenazi Jews, Armenians, Arabs, and Turks but also reported throughout the world's populations (Papadopoulos et al. 2008; Guz et al. 2009).

Synonyms and Related Disorders

Autoinflammatory diseases (Hausmann and Dedeoglu 2013); Hereditary periodic fever syndromes; Recurrent hereditary polyserositis

Genetics/Basic Defects

1. An autosomal recessive disorder caused by missense mutations in the *MEFV* gene, located on the short arm of chromosome 16 (16p13.3). The *MEFV* gene is responsible for encoding a protein called pyrin or marenostrin
2. Pathogenesis
    1. Partially elucidated only after the identification of pyrin or marenostrin
    2. A new macromolecular complex, called inflammasome, seems to play a major role in the control of inflammation and it might be involved in the pathogenesis of FMF
3. Role of pyrin in innate immunity (Manukyan and Aminov 2016)
    1. Formation of several supramolecular structures and inflammasome assembly
    2. Sensing various intracellular danger signals
    3. Mounting the innate immune responses
    4. Resolution of inflammation
4. Phenotype expression of the FMF should depend on the presence of a homozygote or heterozygote genotype for the *MEFV* gene mutations
5. Genotype-phenotype correlation, however, is complex due to influence of genotype and the ethnic and environmental factors, playing a role in the clinical outcome with a very wide clinical spectrum

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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6. Etiology of the periodicity and the self-limited nature remains largely unexplained
7. These rare conditions are collectively named
8. "Hereditary periodic fever syndromes" (HPFS) and protean pathogenetic mechanisms combined with several clinical phenotypes characterize at least four distinct conditions (Rigante et al. 2016):
    1. Familial Mediterranean fever: the prototype and the most widely recognized among HPFS, inherited as an autosomal recessive disorder showing recurrent dysregulated inflammatory processes, caused by an abnormal interaction between cytoskeleton and inflammasome, a key-signaling platform that releases interleukin-1β (IL-1β)
    2. The group of cryopyrin-associated periodic syndrome: upsets directly the production of IL-1β, with a dominant pattern of inheritance
    3. Tumor necrosis factor receptor-associated periodic syndrome: an autosomal dominant disorder subverting the functions and traffic of a cell membrane protein
    4. Mevalonate kinase deficiency: an autosomal recessive metabolic disorder halting the biosynthesis of cholesterol
    5. *MEFV*, *NLRP3*, *TNFRSF1A*, and *MVK* are respectively the four causing genes of these conditions, all resulting in excessive IL-1β signaling, though the encoded proteins act at different levels in cytoskeletal filament organization, apoptosis, and activation of the IL-1β-structured inflammasome

Clinical Features

1. Clinical manifestations (Fonnesu et al. 2009; Ozel et al. 2000)
    1. Onset of the disease: occurs before the age of 30 in almost all patients
    2. Recurrent attacks
        1. Last 1–4 days on average
        2. Resolve spontaneously with a frequency varying from once a week to once every 3–4 months or, sometimes, years
        3. Severity and frequency of attacks have an inter- and intra-individual variations
    3. Presence of fever: absent in rare cases
    4. Gastrointestinal symptoms
        1. Abdominal pain: localized or diffuse
        2. Stypsis/diarrhea
        3. Associated disease
    5. Musculoskeletal symptoms
        1. Arthralgia: transient or abortive
        2. Arthritis
            1. Acute asymmetric nondegenerative mono/oligoarthritis
            2. Protracted arthritis
            3. Chronic degenerative arthritis
            4. Migrating polyarthritis: usually induced by exertion
        3. Myalgias
        4. HLA-B27 negative sacroiliitis during the prodromes or the attack
        5. Seronegative spondyloarthropathy (Borman et al. 2009)
    6. Cardiopulmonary symptoms
        1. Pleuritis
        2. Pericarditis
    7. Cutaneous symptoms: erysipelas-like erythema
    8. Vasculitis
        1. Henoch-Schoenlein purpura
        2. Polyarteritis nodosa
        3. Behcet disease
    9. Other manifestations
        1. Acute orchitis
        2. Mollaret's meningitis
        3. Splenomegaly
        4. Retinopathy
2. Known trigger factors
    1. Physical and emotional stress
    2. Exposure to cold
    3. Fat-rich meals
    4. Banal infections
    5. Drugs such as cisplatin
    6. Menstrual cycle

7. Presence of *Helicobacter pylori*

3. Secondary amyloidosis: the most devastating and important long-term complication
   1. Predominantly renal
   2. Genetic risk factors
      1. Genetic factors linked to *MEFV* gene
      2. Genetic factors linked to modifier genes (Seroamyloid A gene – SAA – and major histocompatibility complex class 1 chain-related A gene – MICA)
   3. Nongenetic factors
      1. Male gender: males four times higher than in females
      2. Environmental factors: country identified as the primary risk factor for renal amyloidosis (e.g., Armenians residing in Armenia have higher incidence than those who reside in the USA)
4. Two phenotypes of FMF (Shohat et al. 2014)
   1. FMF type I
      1. Characterized by recurrent short episodes of inflammation and serositis including:
         1. Fever
         2. Peritonitis
         3. Synovitis
         4. Pleuritis
         5. Rarely pericarditis and meningitis
      2. Inter-individual and intra-familial variation of symptoms
      3. Amyloidosis which can lead to renal failure is the most severe complication of FMF type I
   2. FMF type II: characterized by amyloidosis as the first clinical manifestation of disease in an otherwise asymptomatic individual (Pras 1998; Langevitz et al. 1999; Shohat et al. 1999; Koné Paut et al. 2000)
5. Differential diagnosis (Lidar and Livneh 2007; Portincasa et al. 2013)
   1. Abdominal attacks (recurrent peritonitis)
      1. Appendicitis
      2. Diverticulitis
      3. Cholecystitis
      4. Pyelonephritis
      5. Pelvic inflammatory disease
      6. Pancreatitis
   2. Recurrent abdominal attacks (without peritonitis)
      1. Peptic disease
      2. Renal colic
      3. Endometriosis
      4. Menstruation pain
      5. Irritable bowel syndrome
   3. Chest attacks (recurrent pleuritic chest pain)
      1. Pulmonary embolism
      2. Pleuritis (idiopathic, infectious, autoimmune)
      3. Pericarditis (idiopathic, infectious, autoimmune)
   4. Joint attacks (recurrent synovitis)
      1. Gout
      2. Pseudogout
      3. Spondyloarthropathy
      4. Juvenile idiopathic arthritis
   5. Febrile attacks (recurrent)
      1. Lymphoma
      2. Infections (malaria, relapsing fever)
      3. PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenopathy) (Thomas et al. 1999)
   6. Non-FMF inflammatory disorders (Ozen 2003)
      1. Inflammatory bowel disease
      2. Hyper IgD syndrome
      3. Tumor necrosis factor receptor-associated periodic fever syndrome
      4. Acute intermittent porphyria
      5. Familial cold urticaria or familial cold autoinflammatory syndrome
   7. Systemic lupus erythematosus

8. Adult Still's disease
9. Muckle-Wells syndrome
10. Chronic infantile neurological cutaneous arthropathy
11. Neonatal onset multisystem inflammatory disease syndrome
12. Clinical criteria of periodic fever-aphthous stomatitis, pharyngitis, cervical adenitis (Ahmadinejad et al. 2014)
    1. Regulatory recurring fevers with an early age of onset (<5 years of age)
    2. Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
       1. Aphthous stomatitis
       2. Cervical lymphadenitis
       3. Pharyngitis
    3. Exclusion of cyclic neutropenia, completely asymptomatic interval between episodes, normal growth, and development

Diagnostic Investigations

1. Tel Hashomer diagnostic criteria (Sohar et al. 1967; Livneh et al. 1997; Sohar and Gafni 1997; Portincasa et al. 2013; Giancane et al. 2015; Sönmez et al. 2016)
   1. Major criteria
      1. Recurrent febrile episodes accompanied by peritonitis, synovitis, or pleuritis serositis
      2. Amyloidosis of AA type without predisposing disease
      3. Favorable response to continuous colchicine treatment
   2. Minor criteria
      1. Recurrent febrile episodes
      2. Erysipela-like erythema
      3. First-degree relatives affected by FMF
   3. Definitive diagnosis: two major criteria or one major criterion and two minor criteria
   4. Probable diagnosis: one major criterion and one minor criterion
2. Tel Hashomer revised diagnostic criteria (Fonnesu et al. 2009)
   1. Presence of typical attacks
      1. Fever
      2. Serositis
   2. Positive response to colchicine
3. Livneh criteria for the diagnosis of FMF (Lidar and Livneh 2007; Livneh et al. 1997; Portincasa et al. 2013; Giancane et al. 2015; Sönmez et al. 2016)
   1. Major criteria: typical attacks (recurrent, febrile, and short)
      1. Peritonitis (generalized)
      2. Pleuritis (unilateral) or pericarditis
      3. Monoarthritis (hip, knee, ankle)
      4. Fever alone
   2. Minor criteria
      1. Incomplete (painful and recurrent) attacks involving one or more of the following sites:
         1. Abdomen
         2. Chest
         3. Joint
      2. Exertional leg pain
      3. Favorable response to colchicine
   3. Supportive criteria
      1. Family history of familial Mediterranean fever
      2. Appropriate ethnic origin
      3. Age <20 years at disease onset
      4. Features of attacks
         1. Severe, requiring bed rest
         2. Spontaneous remission
         3. Symptom-free interval
         4. Transient inflammatory response with one or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
      5. Episodic proteinuria/hematuria
      6. Unproductive laparotomy or removal of "white" appendix
      7. Consanguinity of parents
   4. Requirements for diagnosis of FMF
      1. Greater than or equal to one major criteria, or
      2. Greater than or equal to two minor criteria, or

3. One minor plus >5 supportive criteria
4. Modified diagnostic criteria for PFAPA (Thomas et al. 1999)
   1. Regularly recurring fevers with an early age of onset (<5 years)
   2. Constitutional symptoms in the absence of upper respiratory infection with at least one of the following clinical signs:
      1. Aphthous stomatitis
      2. Cervical lymphadenitis
      3. Pharyngitis
   3. Exclusion of cyclic neutropenia
   4. Completely asymptomatic intervals between episodes
   5. Normal growth and development
5. General clinical laboratory findings: No common biomarker or imaging study is specific for FMF (Portincasa et al. 2013)
   1. Leukocytosis
   2. Leukopenia: associated with colchicine treatment
   3. Elevated acute-phase reactant proteins such as erythrocyte sedimentation rate, C-reactive protein, fibrinogen, haptoglobin, C3, C4, and serum amyloid A (SAA) protein, interleukin-6, and tumor necrosis factor-alpha during attack (Guz et al. 2009)
   4. Urinalysis for the presence of proteinuria which may be present in between attacks when renal amyloidosis has developed
   5. Synovial fluid leucocyte count can be elevated during febrile attacks (up to 1,000,000/μL) and consists mainly of neutrophils
6. Diagnostic algorithm (Lidar and Livneh 2007)
   1. Clinical criteria
   2. Results of MEFV mutation analysis
   3. Therapeutic trial, monitored by clinical response and SAA levels
7. Renal biopsy: indicated in all FMF patients who develop proteinuria or nephrotic syndrome
8. Molecular genetic study of the MEFV gene to confirm the diagnosis
9. Recommendations for familial Mediterranean fever (FMF) genetic diagnosis (Giancane et al. 2015)
   1. FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing
   2. Consider patients homozygous for M694V at risk of developing, with very high probability, a severe phenotype
   3. FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutations at position 680–694 on exon 10, must be considered at risk of having a more severe disease
   4. The E148Q variant is common of unknown pathogenic significance and, as the only *MEFV* variant, does not support the diagnosis of FMF
   5. Patients homozygous for M694V mutation are at risk of early onset disease
   6. Individuals homozygous for M694V who are not reporting symptoms should be evaluated and followed closely in order to consider therapy
   7. For individuals with two pathogenic mutations for FMF who do not report symptoms, if there are risk factors for AA amyloidosis (such as the country, family history, and persistently elevated inflammatory markers, particularly serum amyloid A protein), close follow-up should be started and treatment considered
   8. Consultation with an autoinflammatory disease specialist may be helpful in order to aid in the indication and interpretation of the genetic testing and diagnosis

Genetic Counseling

1. Recurrence risk
   1. Both parents carrying at least one *MEFV* gene mutation
   2. Patient's sib
      1. Twenty-five percent with MFM
      2. Fifty percent with MFM carrier
   3. Patient's offspring
      1. All offspring inherit one *MEFV* gene mutation from the proband

   2. Low recurrence risk unless the spouse is affected or a carrier of *MEFV* gene mutation
2. Prenatal diagnosis (Shohat et al. 2014)
   1. Possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling, giving that both disease-causing alleles of an affected family member must be identified or linkage established in the family before prenatal testing can be performed
   2. Prenatal diagnosis of FMF, a treatable condition associated with a good prognosis with early treatment, may be controversial if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis
3. Management (Guz et al. 2009; Portincasa et al. 2013)
   1. Colchicine (lifelong therapy): currently the only effective treatment of familial Mediterranean fever (Fonnesu et al. 2009)
      1. Should be introduced as soon as the diagnosis is made and continued for life
      2. Reduces the attack frequency, severity, and duration in most FMF patients
      3. Can prevent, arrest, and even reverse renal amyloidosis, even if it fails to stop the attacks (Lidar et al. 2004; Kallinich et al. 2007)
      4. Also recommended for treatment of amyloidosis
      5. Higher colchicines dosage, up to 2 mg/day, may be needed in high-risk patients such as after kidney transplantation or patients with amyloidosis
   2. Anakinra can be an effective and safe adjunctive drug to colchicine for prevention of FMF attacks in colchicine-refractory patients, even after kidney transplantation (Celebi et al. 2014)
   3. Anti-interleukin-1 (IL-1) targeting drugs seem safe and effective therapies in colchicine-resistant FMF (Cetin et al. 2015)
   4. No effective mean to treat acute attacks of FMF
      1. Methylprednisolone may relieve abdominal pain and tenderness (Erken et al. 2008), although steroids in general play no role
      2. Interferon (IFN)-α injection at the earliest signs of an attack may provide some benefit (Tunca et al. 2004; Tweezer-Zaks et al. 2008)
   5. Controversy in treating asymptomatic individuals with mutations in the *MEFV* gene who may or may not develop FMF in the future
   6. Prognosis of FMF: normal if AA amyloidosis is prevented (Portincasa et al. 2013)

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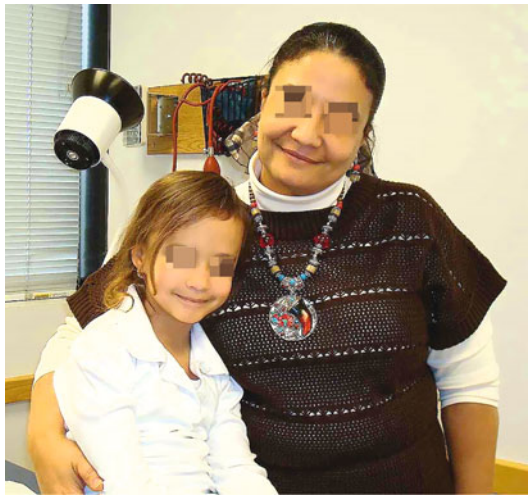

Fig. 1 A 40-year-old female was diagnosed to have familial Mediterranean fever. She had a history of low grade fever, abdominal pain, joint pain, and peritonitis. She responded well to colchicine treatment. She is a compound heterozygote for two different mutations: MM680I and V726A, in exon 10 of the *MEFV* gene which confirms the clinical diagnosis. Her brother and sister are similarly affected. Her 5-year-old daughter was found to be heterozygous for the V726A FMF mutation. The parents are from Egypt

Fanconi Anemia

Contents

In 1927, Fanconi (1927) described a familial form of aplastic anemia in three brothers with short stature, hypogonadism, and skin pigmentation. It is the most common inherited form of aplastic anemia, affecting 1 in 100,000 to 1 in 200,000 live births (Ahmad et al. 2002; Rosenberg et al. 2011). The carrier frequency is estimated as 1 in 300 (Erdmann 2003) in Europe and the United States. Founder mutations have been described in Ashkenazi Jews, who have carrier frequency of 1 in 89 (Tischkowitz and Hodgson 2003).

Synonyms and Related Disorders

Chromosome breakup syndrome; Constitutional aplastic anemia; DNA repair disorder; Fanconi pancytopenia; Inherited aplastic anemia; Inherited bone marrow failure syndrome; Inherited pancytopenia; Premalignant disorder

Genetics/Basic Defects

1. Inheritance: genetically and phenotypically heterogeneous
    1. Autosomal recessive
    2. X-linked recessive (*FANCB* mutation)
2. Presence of at least 16 complementation groups delineated by cell fusion studies (Dokal 2000; Blom et al. 2004; Alter and Kupfer 2013; Schneider et al. 2015)
    1. FA-A (65–70%)
    2. FA-B (<2%)
    3. FA-C (10–15%)
    4. FA-D1 (*BRCA2*)
    5. FA-D2
    6. FA-E (2–5%)
    7. FA-F (<2%)
    8. FA-G (10%)
    9. FA-I
    10. FA-J (*BRIP1/BACH1*)
    11. FA-L
    12. FA-M
    13. FA-N (*PALB2*)
    14. FA-O (*RAD51C*)
    15. FA-P (*SLX4*)
    16. FA-Q (*XPF*)
3. The FA pathway is composed of at least 16 genes. Each of these genes, when biallelically mutated, causes FA (Green and Kupfer 2009; Alter and Kupfer 2013; Schneider et al. 2015):

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_88

1. *FANCA*, mapped to 16q24.3
2. *FANCB*, mapped to Xp22.31
3. *FANCC*, mapped to 9q22.3
4. *FANCD1*, mapped to 13q12.13
5. *FANCD2*, mapped to 3p25.3
6. *FANCE*, mapped to 6p21.22
7. *FANCF*, mapped to 11p15
8. *FANCG*, mapped to 9p13
9. *FANCI*, mapped to 15q25-26
10. *FANCJ*, mapped to 17q22-24
11. *FANCL*, mapped to 2p16.1
12. *FANCM*, mapped to 14q21.3
13. *FANCN*, mapped to 16p12
14. *FANCO*, mapped to 17q22
15. *FANCP*, mapped to 16p13
16. *FANCQ*, mapped to 16p13.12

4. A candidate gene approach leads to the breast cancer susceptibility gene BRCA2 as the gene defective in FA-D1 patients. The Fanconi-BRCA pathway is activated in response to certain kinds of DNA damage, particularly DNA agents that cause double-strand breaks in DNA such as ultraviolet light, ionizing radiation, and cisplatin.
5. FA cells are hypersensitive to cross-linking agents such as diepoxybutane (DEB) (increased chromosome breakage and rearrangement) (Esmer et al. 2004), nitrogen mustard (NTM) (Deviren et al. 2003), and mitomycin C (MMC) (radial figures) (Cervenka et al. 1981): induction of chromosomal aberrations (breaks and rearrangements) (Blom et al. 2004)
6. Mosaicism (Lo Ten Foe et al. 1997)
   1. Not infrequent in Fanconi anemia
   2. Presence of two populations of lymphocytes in mosaic Fanconi anemia patients
      1. One being hypersensitive to the clastogen
      2. The other normal
   3. Phenotypic reversion to normal
      1. Correlated with intragenic homologous recombination in compound heterozygous patients giving rise to the segregation of a wild-type allele at the disease locus.
      2. The resulting cells are thus essentially cured from the disease.
      3. Progeny from a reverted stem cell expected to have a proliferative advantage over affected cells and thus may gradually expand and take over hematopoiesis.
   4. Patients with a high proportion of reverted cells may be falsely diagnosed as negatives.
7. Defective FA functional pathway
   1. Defective DNA repair
   2. Prolonged G2/M transition in the cell cycle
   3. Increased oxygen sensitivity
   4. Abnormally regulated apoptosis and accelerated telomere shortening
   5. Defective hemopoiesis

Clinical Features

1. Variable clinical expression and severity (Fanconi 1967; Schroeder et al. 1976; Alter 1993; Giampietro et al. 1993; 1997)
2. Hematological abnormalities secondary to bone marrow failure (>90%)
   1. Clinical hallmark of Fanconi anemia
   2. Usually starting in childhood
   3. Increased incidence of aplastic anemia, myelodysplastic syndrome, and acute myeloid leukemia
   4. Initial presentation
      1. Pallor
      2. Bleeding
      3. Recurrent infections
   5. Thrombocytopenia or leukopenia typically preceding anemia
   6. Severe progressive pancytopenia due to loss of hematopoietic stem cells: the cardinal clinical feature
   7. Increased risk of infections due to neutropenia
   8. Sweet syndrome (neutrophilic skin infiltration) reported in a few patients with Fanconi anemia and myelodysplastic syndrome
3. Diverse congenital abnormalities (Zierhut et al. 2014)

1. Endocrine (79%)
    1. Intrauterine growth retardation/short stature
    2. Hypothyroidism
    3. Diabetes
    4. Growth hormone deficiency
    5. Decreased fertility
2. Upper limb anomalies (70% of all skeletal defects)
    1. Mainly radius and thumb abnormalities
        1. Absent, hypoplastic, or supernumerary thumbs with hypoplastic thenar eminence
        2. Absent, hypoplastic radii, and ulnae associated with abnormal thumbs
        3. Absent first metacarpal
    2. Hypoplastic thenar eminence
    3. Dysplastic ulnar
    4. Clinodactyly
    5. Polydactyly
    6. Short fingers
    7. Transverse palmar crease
3. Other skeletal abnormalities
    1. Microcephaly
    2. Micrognathia
    3. Triangular face
    4. Short webbed neck with low hairline
    5. Sprengel deformity/Klippel-Feil anomaly
    6. Spine anomalies
        1. Spina bifida
        2. Scoliosis
        3. Abnormal ribs
        4. Sacrococcygeal sinus
        5. Other vertebral anomalies
    7. Lower limb anomalies
        1. Toe syndactyly
        2. Pes planus
        3. Abnormal toes
        4. Congenital hip dislocation
4. Skin pigmentary changes (40%)
    1. Generalized hyperpigmentation
    2. Café au lait spots
    3. Hypopigmentation
5. Eye anomalies (20%)
    1. Microphthalmia
    2. Strabismus
    3. Epicanthal folds
    4. Hypertelorism/hypotelorism
    5. Ptosis
    6. Cataracts
    7. Epiphora
    8. Nystagmus
    9. Astigmatism
6. Ear anomalies (15%)
    1. Deafness (11%), usually conductive secondary to middle ear abnormalities
    2. Abnormal pinna
    3. Stenosis or atresia of the external auditory meatus
    4. Low-set ears
7. Heart disease (6%)
    1. Congenital heart disease
        1. Patent ductus arteriosus
        2. Ventricular septal defect
        3. Pulmonary stenosis
        4. Aortic coarctation
    2. Cardiomyopathy
8. Renal anomalies (20%)
    1. Kidney
        1. Ectopic kidney
        2. Pelvic kidneys
        3. Horseshoe kidneys
        4. Hypoplastic/aplastic/dysplastic kidneys
    2. Collecting system (hydronephrosis, hydroureter, reflux)
    3. Abnormal artery
9. Gastrointestinal problems (5–7%)
    1. Atresia
        1. Esophagus (7%)
        2. Duodenum
        3. Jejunum
    2. Tracheoesophageal fistula
    3. Anteriorly placed anus
    4. Imperforate anus
    5. Persistent cloaca
    6. Meckel diverticulum
    7. Umbilical hernia
    8. Abnormal biliary ducts
    9. Megacolon
    10. Abdominal diastasis
    11. Budd-Chiari syndrome
    12. Annular pancreas

10. CNS abnormalities
    1. Microcephaly
    2. Hydrocephalus
    3. Absent septum pellucidum
    4. Neural tube defects
11. Hypogonadism in males (25%).
    1. Underdeveloped gonads.
    2. Cryptorchidism.
    3. Hypospadias.
    4. Micropenis.
    5. Defective spermatogenesis (infertility).
    6. A few males with Fanconi anemia fathered children.
12. Hypogonadism in females (2%)
    1. Hypogenitalia
    2. Bicornuate uterus
    3. Absent uterus or vagina
    4. Ovarian atresia
    5. Delayed menarche
    6. Irregular menses
    7. Early menopause
    8. Successful pregnancies with live-born children observed
13. Absence of obvious congenital abnormalities in approximately 33% of patients with Fanconi anemia

4. Predisposition to malignancy (Alter 1996, 2003; Rosenberg et al. 2003)
    1. Hematologic tumors (60%)
        1. Acute myelogenous leukemia (30%)
        2. Myelodysplastic syndrome (26%)
        3. Acute lymphocytic leukemia
        4. Chronic myelomonocytic leukemia
        5. Burkitt lymphoma
    2. Non-hematologic tumors (40%)
        1. Liver tumors (9%)
            1. Adenoma
            2. Hepatocellular carcinoma
            3. Adenocarcinoma
        2. Brain tumor (2%)
            1. Medulloblastoma
            2. Astrocytomas
        3. Renal tumors (3%)
            1. Wilms tumor
            2. Renal cell carcinoma
            3. Nephroblastoma
        4. Squamous cell carcinoma (20%)
            1. Head and neck
            2. Vulvar
            3. Cervix
            4. Cutaneous
            5. Anus
            6. Esophagus
        5. Miscellaneous tumors (6%)
            1. Breast carcinoma
            2. Basal cell carcinoma
            3. Neuroblastoma
            4. Desmoid tumor
            5. Gonadoblastoma
            6. Melanoma
            7. Neurilemmomas
            8. Osteogenic sarcoma
5. Cumulative probability of developing leukemia, liver tumors, and solid tumors in FA patients
    1. Close to 40% by age 30
    2. About 50% by age 45
    3. An astounding 76% by age 45
6. Prognosis (Kutler et al. 2002)
    1. Mean survival: 16 years
    2. Main causes of death
        1. Pancytopenia which develops in the first decade of life
        2. Associated progressive microcytosis
        3. Extremely high probability of developing bone marrow failure
        4. A predisposition to malignancy, particularly acute myeloid leukemia and aplastic anemia
7. A guideline of the indications for testing for FA (Wu 2013)
    1. Definite.
        1. Sibling with FA with following:
        2. Aplastic anemia
        3. Characteristic birth defects, particularly one or more of abnormal radii and/or thumbs; renal structural anomalies; microphthalmia, microcephaly, café au lait spots, and features of VACTERL-H such as tracheoesophageal fistula, imperforate anus, and others
        4. Spontaneous chromosome breaks
        5. Primary MDS (at a young age)
        6. Primary AML (at a young age)

7. Unusual sensitivity to chemo- or radiotherapy
8. Cancer typical of FA at an atypical age
9. Family history consistent with FA or with cancer (e.g., breast cancer)

2. Consider.
   1. Single cytopenias with following:
   2. Macrocytosis unexplained by B12 or folate deficiency
   3. Liver tumors without alcohol or hepatitis
   4. Premature ovarian failure <30 years old
   5. Diminished ovarian reserve <30 years old
   6. Brain tumor <5 years old
   7. Wilms tumor <4 years old
   8. Increased Hb F not otherwise explained
   9. Male (or female) infertility
   10. Liver adenomas or hepatomas without alcohol or hepatitis

8. Differential diagnosis (Tischkowitz and Hodgson 2003; Alter 2014)
   1. VATER/VACTERL association overlap with FA (Giampietro et al. 1993)
      1. Vertebral defects
      2. Tracheoesophageal atresia
      3. Renal defects
      4. Radial ray defects
   2. Dyskeratosis congenita
      1. Aplastic anemia
      2. AML
      3. Squamous cell carcinomas
   3. Diamond-Blackfan anemia (Aase syndrome)
      1. Defective erythroid progenitor maturation
      2. Normochromic or macrocytic anemia
      3. AML
      4. Osteosarcomas
      5. Congenital malformations in over one third of patients
         1. Head (micrognathia, cleft lip)
         2. Upper limb defects
         3. Genitourinary anomalies
      6. A heterogeneous disorder
         1. Sporadic in most cases
         2. Autosomal dominant in some cases
         3. Rarely autosomal recessive inheritance
   4. Shwachman-Diamond syndrome
      1. Neutropenia
      2. AML
   5. Nijmegen breakage syndrome
      1. A rare autosomal recessive disorder
      2. Resulting from mutations in *NBS1*, which codes for the nibrin protein
      3. Clinical characteristics
         1. Immune deficiency
         2. Microcephaly
         3. Hypersensitivity to ionizing radiation
   6. Other chromosomal breakage syndromes (Bloom syndrome, ataxia-telangiectasia)
      1. Also exhibit high rates of spontaneous chromosomal breakage.
      2. Only FA cells exhibit increased chromosomal breakage in response to DEB.
   7. Severe congenital neutropenia
      1. Neutropenia
      2. AML
   8. Amegakaryocytic thrombocytopenia
      1. Thrombocytopenia
      2. AML
   9. Thrombocytopenia-absent radii (TAR) syndrome
      1. Thrombocytopenia
      2. AML
   10. Holt-Oram syndrome

Diagnostic Investigations

1. Difficult to diagnose FA because of phenotypic diversity.
2. Hematologic investigation.
   1. Progressive decrease in peripheral blood counts, often present by 7–8 years of age:
      1. Thrombocytopenia
      2. Leukopenia
      3. Anemia

2. Macrocytic red blood cells, often with increased fetal hemoglobin.
3. Generally increased serum erythropoietin concentration.
4. Hypocellular or dysplastic bone marrow.
5. Bone marrow failure with pancytopenia.
6. Bone marrow cytogenetic testing: Cytogenetic abnormalities may progress to leukemia or myelodysplastic syndrome (MDS) (Alter et al. 2000).
7. Clonal amplifications of chromosome 3q26-q29 were reported in association with an increased risk of progression to MDS or acute myelogenous leukemia (AML) (Tonnies et al 2003, Cioc et al 2010).

3. Individuals with FA should be routinely screened for endocrine abnormalities, including evaluation of growth; glucose, insulin, and lipid metabolism; thyroid function; puberty; gonadal function; and bone mineral metabolism (Petryk et al. 2015).
4. DEB testing: (Auerbach et al. 1986, 1989)
   1. Tenfold to 100-fold increased chromosomal breakage (breaks, rearrangements, radials, exchanges) of Fanconi anemia cells after incubation of the patient's cells with chemical clastogen, DEB, a bifunctional DNA interstrand cross-linking agent (Auerbach 1993)
   2. Highly sensitive and specific test for Fanconi anemia
   3. Allowing diagnosis of Fanconi anemia in persons with diverse clinical features including those without clinically detectable congenital abnormalities
   4. Used successfully in prenatal diagnosis of Fanconi anemia
   5. Remains underutilized mainly because there are some clinical conditions in which FA is not usually suspected
   6. Disadvantage
      1. Requires a high degree of cytogenetic expertise and meticulous attention to cell culture and safety conditions
      2. Fails to distinguish among Fanconi anemia patients in different complementation groups
      3. Fails to identify heterozygote carriers of mutant Fanconi anemia genes
5. Immunoblot assay of FANCD2 protein monoubiquitination (Shimamura et al. 2002).
6. Cell cycle arrest in G2 phase induced by MMC (Seyschab et al. 1995; Pulsipher et al. 1998).
   1. Alternative to cytogenetic testing
   2. Diagnostic potential of the cell cycle test for Fanconi anemia
   3. Based on the observation that Fanconi anemia cells experience difficulties in traversing the S and G2 compartments of the cell cycle
   4. Limitation of cell cycle test
      1. Applicable only to nonleukemic cells
      2. Confirmatory DEB studies required in cases with evidence for G2-phase arrest
7. Molecular genetic testing (Alter and Kupter 2013; Zierhut et al. 2014):
   1. Used primarily for carrier detection and prenatal diagnosis
   2. Complicated by the presence of 13 genes, which are responsible for the 13 FA complementation groups [A, B, C, D1 (BRCA2), D2, E, F, G, I, J, L, M, and N]
   3. Complementation testing
      1. Traditionally, complementation group testing was the first tier of testing following a positive chromosome breakage assay.
      2. Complementation testing assesses each FA protein individually to identify the dysfunctional protein in an individual with FA; however, this testing cannot provide information about the location or type of mutation (Chandra et al. 2005).
      3. If a dysfunctional protein is identified, single-gene sequencing and, if necessary, deletion/duplication analysis of the corresponding gene are completed (Ameziane et al. 2008). This process can be both expensive and time consuming (Ameziane et al. 2012) and has been replaced by newer genetic testing technologies.
   4. Linkage analysis once a family has been assigned to a complementation group by a

functional assay or by the detection of a specific mutant allele using highly polymorphic microsatellite markers located in close proximity to both FAA and FAAC genes
    1. Used for carrier detection
    2. Used for prenatal diagnosis
5. Sequence analysis for *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, and *FANCI*
6. Mutation analysis for the common Ashkenazi Jewish *FANCC* mutation (IVS4 + 4A > T)
7. Targeted mutation analysis
    1. Helpful in testing patients with an ethnic background that has well-established founder mutation(s)
    2. Further, if the mutations are known for an individual affected with FA, targeted mutation analysis can help facilitate in other relatives for diagnostic testing, carrier testing, prenatal testing, and preimplantation genetic diagnosis
8. Single-gene sequencing: likely used mostly for testing partners of individuals with FA or carriers of an FA mutation.
9. Deletion/duplication analysis (Wu 2013):
    1. To detect deletions of one or more exons or of an entire gene of any suspected case of FA.
    2. The next-generation sequencing technology has enabled an effective and faster molecular diagnostic approach for FA gene studies in which it is able to perform the mutation analysis for FA genes without the requirement of complementation group testing step in which the living cells are required.
    3. Recently, Ameziane et al. (2012) applied the next-generation sequencing approach to identify *BRCA2*, *FANCD2*, *FANCI*, and *FANCL* mutations in novel unclassified FA patients.
10. Fanconi anemia panel testing:
    1. Testing of all FA genes simultaneously can now be accomplished through panel testing using next-generation sequencing technologies.
    2. It has many benefits over other testing methods, including reduced cost and turnaround times and, for some platforms, the ability to identify mutations in the deep intronic regions that are not typically detected in Sanger sequencing (Ameziane et al. 2012).
    3. It is recommended that families be offered panel testing for the known FA genes following a positive chromosome breakage study.
    4. If the panel does not include FANCD1/BRCA2 or if the phenotype is consistent with the more severe features typically seen in patients with mutations in FANCD1/BRCA2, testing should be ordered through a separate lab that can perform single-gene sequencing.
11. Comparative genomic hybridization and multiplex ligation-dependent probe amplification:
    1. While next-generation sequencing for FA significantly improves the testing process, it typically cannot detect all large deletions, duplications, and insertions that can account for up to one third of all FA mutations.
    2. Comparative genomic hybridization or multiplex ligation-dependent probe amplification may be an important part of the testing process (Knies et al. 2012).
    3. This testing can precede or follow next-generation sequencing if the panel testing does not include this analysis.

8. Cancer surveillance
    1. Annual bone marrow examination provides early evidence for myelodysplastic syndrome or leukemia:
        1. Aspirate for cell types.
        2. Biopsies for cellularity
        3. Cytogenetics

2. Liver function tests and ultrasound examinations to identify adenomas or hepatomas before becoming symptomatic.
3. Screening for solid tumors: more complex because of multiplicity of cancer types:
    1. Direct visualization of the oropharynx and fiber-optic endoscopy for screening for aerodigestive cancers and precancerous lesions
    2. Gynecologic examinations for vulvar and cervical tumors beginning with menarche

Genetic Counseling

1. Recurrence risk (Alter and Kupfer 2013)
    1. Patient's sib:
        1. Autosomal recessive inheritance in all but one of the FA complementation groups
            1. Twenty-five percent chance of inheriting both mutation alleles and being affected
            2. Two third chance of being carriers in unaffected sibs who have a normal DEB test
        2. X-linked recessive inheritance (FANCB mutation)
            1. Risk to sibs depends upon the carrier status of the mother.
            2. Fifty percent of male sibs who inherit the mutation will be affected.
            3. Female sibs who inherit the mutation will be carriers and will usually not be affected.
            4. Risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism if the disease-causing mutation cannot be detected in the DNA extracted from leukocytes of the mother of the only affected male in the family.
    2. Patient's offspring: recurrence risk not increased unless the spouse is a carrier, in which case 50% of offspring will be affected; otherwise all offspring of the affected parent will be carriers who will be asymptomatic.
2. Prenatal diagnosis
    1. Prenatal ultrasonography to evaluate fetal anomalies consistent with FA
    2. Prenatal diagnosis available to at-risk families by CVS, amniocentesis, or cordocentesis
        1. Demonstration of chromosome instability by DEB test (Auerbach et al. 1986)
        2. The fetus at risk is shown to suffer from FA on the grounds of excessive chromosome breakage, both spontaneous and MMC induced, in fetal blood culture (Shipley et al. 1984)
        3. Molecular genetic testing of FA gene (*FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, and *FANCI*) mutations if the disease-causing mutations are previously characterized in a given family
        4. Preimplantation genetic diagnosis possible for families in which the disease-causing mutations have been identified by using molecular methods, resulting in implantation of an embryo without FA mutations (Verlinsky et al. 2001; Bielorai et al. 2004; Grewal et al. 2004)
3. Management
    1. Supportive care:
        1. Developmental assessment
        2. HLA typing of the patient, sibs, and parents in anticipation of possible bone marrow transplantation
        3. Full blood typing
        4. Packed red blood cell transfusions for symptomatic anemia
        5. Platelet transfusions for symptomatic thrombocytopenia
        6. Antimicrobials for secondary infections
    2. Surgical care:
        1. Splinting and hand surgery indicated for thumb and radial anomalies
        2. Surgery for congenital heart defects and gastrointestinal anomalies such as TE fistula

3. Transient response:
    1. Androgens (oxymetholone) shown to improve the blood counts in approximately 50% of patients
    2. Corticosteroids
    3. Cytokines
    4. Granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor (shown to improve the neutrophil count in some patients) for symptomatic neutropenia
4. Hematopoietic stem cell transplantation may cure sibling's aplastic anemia and prevent myelodysplastic syndrome or leukemia (Lipton 2016):
    1. Peripheral blood stem cells
    2. Allogenic bone marrow transplant with a histocompatible sibling donor: treatment of choice
    3. Umbilical cord blood offers a potential source of hematopoiesis stem cells for Fanconi anemia patients without sibling matches
5. FA patients are uniquely hypersensitive to hematopoietic stem cell transplantation (HSCT) conditioning agents due to the underlying chromosomal instability. HSCT has shown important progress in the last years, especially after the introduction of fludarabine and the reduction of cyclophosphamide in the preparative regimen. For patients with HLA-identical related donors, HSCT should be performed as first-line therapy; for patients with alternative donors, HSCT remains a therapy with increased morbidity and mortality (Schifferli and Kühne 2015).
6. Successful transplantation obtained by using in vitro fertilization and preimplantation genetic diagnosis of hematopoietic stem cells from a donor selected on the basis of specific, desirable disease and HLA characteristics (Grewal et al. 2004):
    1. Select embryos which are HLA identical to the patient and unaffected by FA for intrauterine transfer and let the pregnancy continue to term.
    2. Obtain the umbilical cord blood from the healthy newborn infant and use it as the source of HLA-identical hematopoietic stem cells to reconstitute normal hematopoiesis in the affected sibling.
7. Follow-up surveillance for solid malignancies.
8. The genetic characterization of patients with FA is essential for developing therapies, including hematopoietic stem cell transplantation from a savior sibling donor after embryo selection, gene therapy, or genome editing using genetic recombination or engineered nucleases (Bogliolo and Surrallés 2015).
8. The genetic characterization of patients with FA is essential for developing therapies, including hematopoietic stem cell transplantation from a savior sibling donor after embryo selection, gene therapy, or genome editing using genetic recombination or engineered nucleases (Bogliolo and Surrallés 2015).
9. Gene therapy not currently available (Liu et al. 1994)

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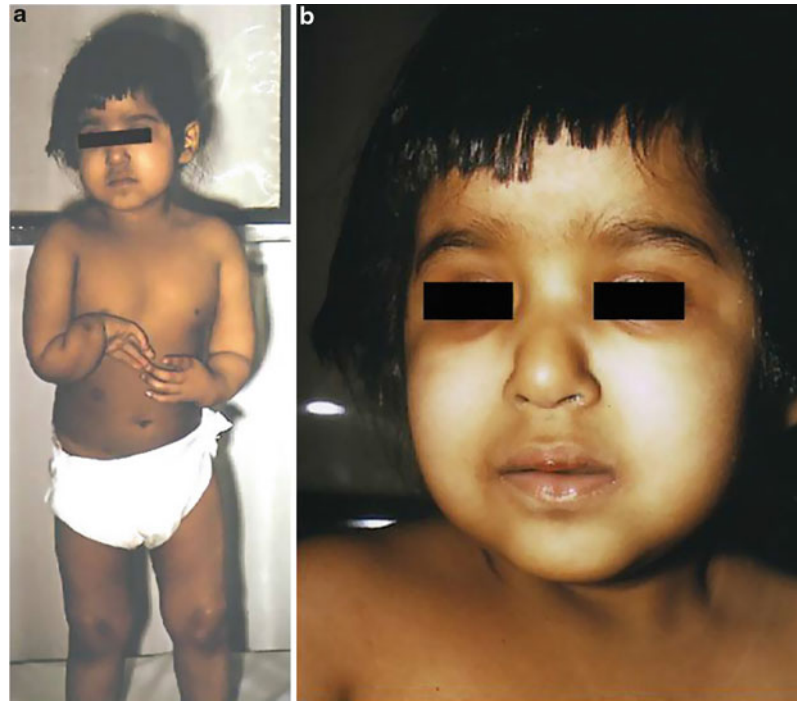

Fig. 1 (**a**, **b**) A young boy with Fanconi anemia showing pallor and radial ray defects of the upper extremities

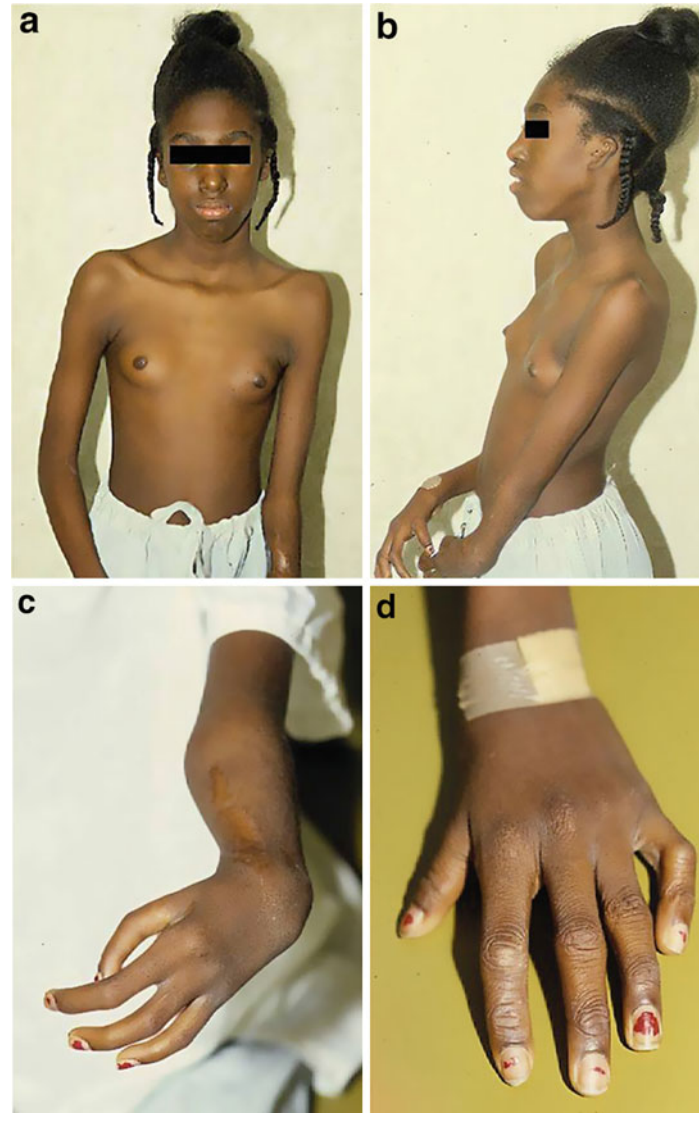

Fig. 2 (**a**–**d**) An adolescent girl with Fanconi anemia showing similar phenotype

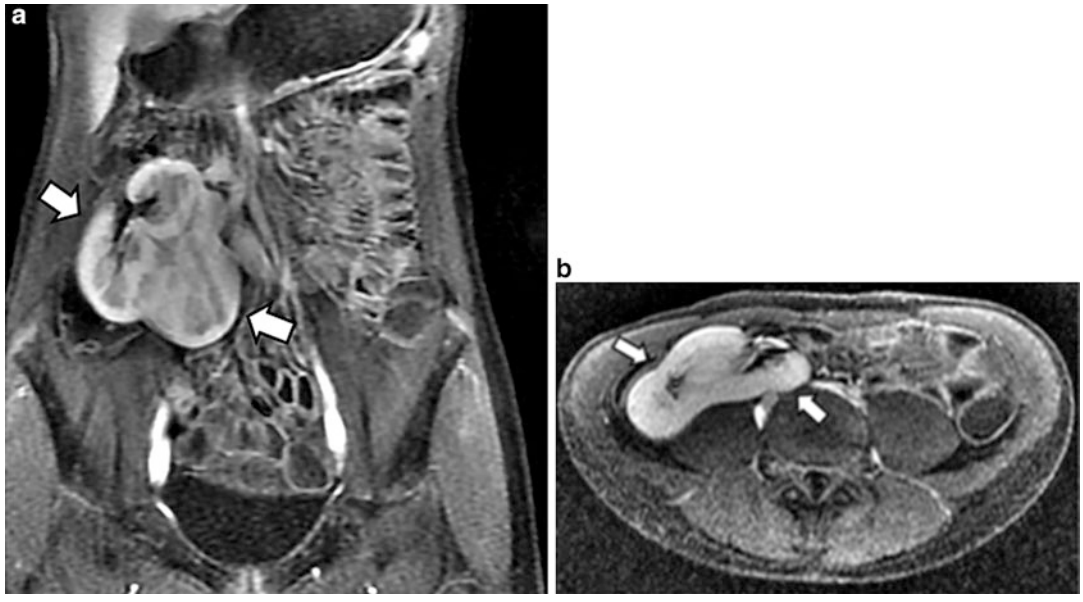

Fig. 3 (**a, b**) A 14-year-old boy has a history of short stature, undescended testis, and hematologic abnormalities and chromosome breakage. DEB stress studies showed findings consistent with fanconi anemia. C1MR1 (**a**) and C1MR4 (**b**) demonstrated crossed fused renal ectopia in the right mid-abdomen (*arrows*). Bilateral renal fossae are empty (Courtesy of Dr. Grace Guo)

Feingold Syndrome

Contents

Feingold in 1975 originally described a father, son, and grandmother with microcephaly, hand abnormalities, tracheoesophageal fistula, duodenal atresia, and normal intelligence. Later in 1978, Feingold reported a mother and daughter with similar findings except for the absence of tracheoesophageal fistula and duodenal atresia.

Synonyms and Related Disorders

Feingold syndrome 1 (oculodigitoesophagoduodenal (ODED) syndrome); Feingold syndrome 2 (brachydactyly with short stature and microcephaly due to hemizygous deletion of the *MIR17HG* gene on chromosome 13q31.3); Microcephaly mesobrachyphalangy-tracheoesophageal fistula syndrome; Microcephaly-digital anomalies-normal intelligence syndrome; Microcephaly-oculo-digito-esophageal-duodenal (MODED) syndrome

Genetics/Basic Defects

1. Feingold syndrome 1
   1. Autosomal dominant inheritance with full penetrance and variable expressivity.
   2. Caused by mutations in the neuroblastoma-derived V-myc avian myelocytomatosis viral-related oncogene (*MYCN*) maps to 2p24.3 (Teszas et al. 2006; Blaumeiser et al. 2008).
   3. MYCN haploinsufficiency is associated with reduced brain size and intestinal atresias in Feingold syndrome (van Bokhoven et al. 2005).
2. Feingold syndrome 2
   1. Identification of germline hemizygous deletion of the microRNA 17 host gene (*MIR17HG*), maps in 13q31.3, has been described in two individuals with microcephaly, short stature, and digital anomalies (Feingold syndrome 2) (de Pontual et al. 2011).
   2. *MIR17HG* locus is considered as the best candidate to explain the skeletal abnormalities and digital malformations observed in

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_258

patients with Feingold syndrome 2 (Tassano et al. 2013).

Clinical Features

1. Feingold syndrome 1
   1. Clinical features (Fig. 1) (Celli et al. 2003; Marcelis et al. 2008)
      1. Digital anomalies: the most constant findings
         1. Brachymesophalangy (shortening of the 2nd and 5th middle phalanges of the hand with clinodactyly of the 5th finger) (100%)
         2. Toe syndactyly (2–3 and/or 4–5) (97%)
         3. Thumb hypoplasia (17%)
      2. Microcephaly (89%)
      3. Facial dysmorphism
         1. Short palpebral fissures (73%)
         2. Micrognathia (32%)
      4. Mild learning deficit (51%)
      5. Atresia
         1. Gastrointestinal (55%)
         2. Esophageal atresia (32%)
         3. Duodenal atresia (31%)
         4. Jejunal (3%)
         5. Anal (2%)
         6. Multiple (12%)
      6. Short stature (<10th centile) (60%)
      7. Renal abnormalities (18%)
      8. Cardiac abnormalities (15%)
      9. Deafness (10%)
      10. Asplenial/polysplenia (0.25%)
   2. Differential diagnosis
      1. "▶ VATER (VACTERL) Association": please see the chapter.
      2. "▶ CHARGE Syndrome": please see the chapter.
      3. "▶ Fanconi Anemia" (thumb hypoplasia and other congenital anomalies): please see the chapter.
      4. Brachydactyly type A4: please see the chapter "▶ Brachydactyly."
2. Feingold syndrome 2 (De Pontual et al. 2011; Tassano et al. 2013)
   1. Growth and psychomotor retardation
   2. Short stature
   3. Microcephaly
   4. Mild generalized hypotonia
   5. Mild facial dysmorphisms
      1. Epicanthus
      2. Short palpebral fissures
   6. Digital abnormalities (brachymesophalangy)
      1. Brachydactyly or brachymesophalangy of the second and fifth fingers
      2. Hypoplastic thumbs of variable severity
      3. Clinodactyly of 5th fingers
      4. Cutaneous syndactyly of the toes
      5. Clinodactyly of 3rd toes
   7. Lack of gastrointestinal abnormalities and short palpebral fissures

Diagnostic Investigations

1. Radiology for microcephaly and digital abnormalities
2. Echocardiogram for cardiac evaluation
3. Renal ultrasound for renal abnormalities
4. Audiometry for hearing loss
5. Cytogenetics/CGH microarray analysis
   1. Feingold syndrome 1: microdeletion of 2p23-p24
   2. Feingold syndrome 2: del(13)(q31.1q32.1)
6. *MYCN* analysis: presence of brachymesophalangy and toe syndactyly in combination with microcephaly sufficient to justify MYCN analysis to confirm mutation or deletion (Marcelis et al. 2008)

Genetic Counseling

1. Recurrence risk: autosomal dominant inheritance
   1. Patient's sib: not increased unless a parent is affected or having gonadal mosaicism
   2. Patient's offspring: 50%
2. Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

3. Management
    1. Surgery for gastrointestinal atresia
    2. Management of cardiac and renal anomalies

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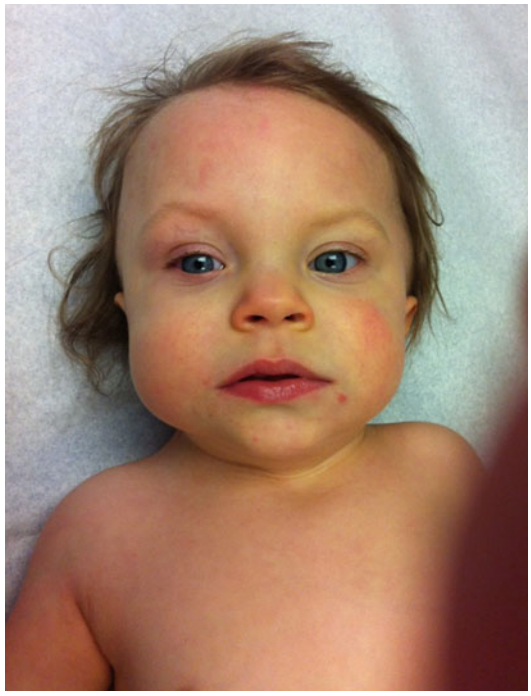

Fig. 1 A 10-month-old Caucasian male was evaluated for microcephaly with a head size of 41.8 cm. Other craniofacial features include prominent nasal bridge with retrognathia and slightly prominent ears. There was partial syndactyly on the 2nd and the 3rd toes on both feet and the fourth and the fifth toes on the right foot. He also has pyelectasis on his renal ultrasound. Chromosomal microarray analysis showed a microdeletion of 2p24.3-p24.2 which includes six genes, one of which is MYCN. Heterozygous mutations or deletions of that gene are associated with Feingold syndrome type I. (Courtesy of Dr. Susonne Ursin)

Femoral Hypoplasia: Unusual Facies Syndrome

Contents

In 1973, Daentl et al. (1973) delineate a distinctive pattern of malformation which includes femoral hypoplasia and unusual facies in four unrelated individuals. The syndrome is also known as femoral facial syndrome.

Synonyms and Related Disorders

Femoral facial syndrome

Genetics/Basic Defects

1. Inheritance/etiology (Burn et al. 1984)
    1. Sporadic in most cases
    2. Familial cases with autosomal dominant inheritance reported (Lampert 1980; Robinow et al. 1995)
    3. Multifactorial trait in some families (Lord and Beighton 1981)
    4. Maternal/gestational diabetes causative in more than 20% of the reported cases (Johnson et al. 1983; Burn et al. 1984; Giacoia and Tunnessen 1996; Hinson et al. 1996)
    5. Genetic contribution suspected in affected children born to non-diabetic mothers
    6. A report of a girl with femoral facial syndrome and a de novo complex chromosome rearrangement: The duplication 2q37.2 could be causative for the femoral hypoplasia phenotype (Spielmann et al. 2016).
2. Possible causes
    1. Fetal constraint (deformation) due to severe oligohydramnios
    2. Maternal diabetes (disruption)
    3. Undetermined etiology

Clinical Features

1. Characteristic facial features (Daentl et al. 1973)
    1. Up-slanting eyes
    2. A short nose with broad tip
    3. Elongated philtrum
    4. Thin upper lip
    5. Micrognathia
    6. Cleft palate
    7. Low-set ears
2. Hypoplasia/aplasia of the femurs
    1. Usually asymmetric

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Presence of some degree of shortened lower extremities in most cases
3. Variable shortening of the lower extremities depending on the absence or degree of hypoplasia of the femurs, with or without absent fibulas
4. Complete absence of the femur: very rare in femoral facies syndrome (Johnson et al. 1983; Bum et al. 1984; Ahmed et al. 2015)

3. Short stature due to reduced length of the lower extremities
4. Normal intelligence
5. Other anomalies
    1. Club foot in most cases
    2. Occasional preaxial polydactyly (Baraitser et al. 1994)/syndactyly
    3. Sprengel's deformity
    4. Upper extremity hypoplasia
    5. Restricted motion of the elbows
    6. Stiff shoulders
    7. Pelvic and spinal abnormalities
    8. Inguinal hernia
    9. Genitourinary anomalies
        1. Hypoplastic/dysplastic kidneys
        2. Polycystic kidneys
        3. Cryptorchidism
        4. Genital hypoplasia
            1. Hypoplastic penis
            2. Hypoplastic labia majora
        5. Inferiorly placed kidneys
        6. Septated urinary bladder
    10. Rare cardiovascular anomalies
        1. Ventricular septal defect
        2. Pulmonary stenosis
        3. Truncus arteriosus
    11. Caudal dysplasia (Riedel and Froster-Iskenius 1985)
6. Differential diagnosis (Pryde et al. 2003)
    1. Kyphomelic dysplasia (Pitt 1986)
        1. Femur
            1. Symmetrically short
            2. Severe bowing
        2. Other long bones
            1. Mild shortening
            2. Minimal bowing
        3. Genitourinary: no abnormalities
        4. Face: micrognathia
        5. Scapulae: normal
        6. Others
            1. Mild small thorax
            2. Male sex predilection
        7. Prognosis
            1. Good developmental prognosis
            2. Ambulatory
        8. Genetics: autosomal recessive
    2. Campomelic dysplasia
        1. Femur
            1. Symmetric mild shortening
            2. Moderate-to-severe bowing/amputation
        2. Other long bones
            1. Tibial bowing more marked than femora bowing
            2. Hypoplastic fibulae
        3. Genitourinary
            1. Ambiguous genitalia
            2. Sex reversal in XY
        4. Face
            1. Micrognathia
            2. Cleft palate
        5. Scapulae: hypoplastic
        6. Others
            1. Occasional lateral ventriculomegaly
            2. Cardiac anomalies
            3. Talipes
        7. Prognosis
            1. Often lethal in early infancy
            2. Survivors often severely disabled
        8. Genetics
            1. Autosomal dominant
            2. *SOX*-9 mutations
    3. Antley-Bixler syndrome
        1. Femur; symmetric short, severely bowing
        2. Other long bones
            1. Radiohumeral synostosis
            2. Joint contractures
        3. Genitourinary: occasional abnormalities
        4. Face
            1. Frontal bossing
            2. Depressed nasal bridge
        5. Scapulae: severely hypoplastic

6. Others
   1. Craniosynostosis
   2. Arachnodactyly
7. Prognosis
   1. Occasional death
   2. Normal neurodevelopment
   3. Severe orthopedic disability
8. Genetics: autosomal recessive

Diagnostic Investigations

1. Radiography
   1. Mandibular hypoplasia
   2. Femoral hypoplasia including proximal femoral focal deficiency and hypoplastic fibulae (Sorge et al. 1995)
   3. Less frequent thoracocostovertebral anomalies
      1. Thorax: congenital elevation of the scapula (Sprengel's deformity)
      2. Ribs
         1. Absent
         2. Hypoplastic
         3. Fused
      3. Spine
         1. Dysplastic vertebrae
         2. Scoliosis
         3. Hemivertebrae
         4. Spina bifida occulta
         5. Lumbar scoliosis
         6. Sacral dysgenesis
      4. Pelvis
         1. Small iliac wings
         2. Wide obturator foramen
         3. Hypoplasia/aplasia of the acetabula with dislocation of the hips
   4. Less frequent upper extremity anomalies
      1. Hypoplasia of the humerus
      2. Radiohumeral/radioulnar synostosis
      3. Ulnar deviation of the hands
2. Histopathology
   1. Femur from one infant showed hyaline cartilage with foci of fibrous dysplasia.
   2. A disorganized growth plate and relative decrease in the resting cartilage matrix in another patient (Urban et al. 1997).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Sporadic cases: not increased.
      2. Autosomal dominant inheritance: not increased unless one of the parents is affected.
      3. Maternal diabetes: Risk is significantly increased.
   2. Patient's offspring: 50% if the patient has the autosomal dominant form of the syndrome
2. Prenatal diagnosis possible by ultrasonography (Tadmor et al. 1993; Robinow et al. 1995; Gonçalves et al. 1996; Hinson et al. 1996; Campbell and Vujanic 1997; Gillerot et al. 1997; Urban et al. 1997; Filly et al. 2004; Paladini et al. 2007; Ho et al. 2008; Figureoa et al. 2009; Nowaczyk et al. 2010; Castro et al. 2014)
   1. Micrognathia
   2. Cleft palate
   3. Other facial features
   4. Short, bowed femora
3. Management
   1. Cleft palate repair
   2. Care for cardiovascular and genitourinary complications
   3. Orthopedic management of limb deformity and hip dysplasia

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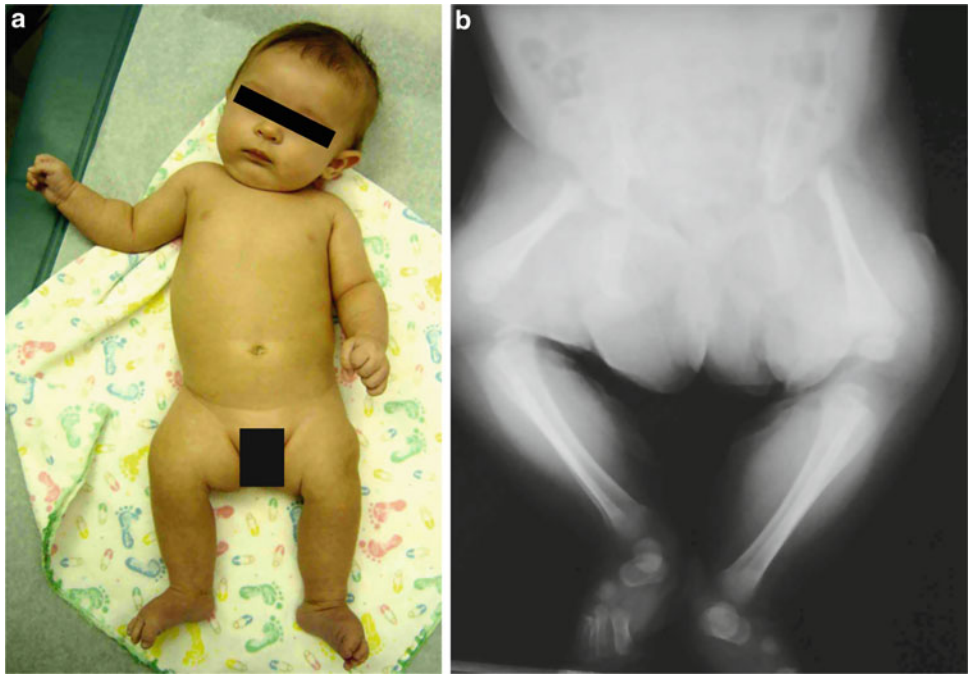

Fig. 1 (**a**, **b**) A 3-month-old infant with femoral hypoplasia – unusual facies syndrome showing short nose, long philtrum, thin upper lip, micrognathia, low-set ears, and marked bilateral rhizomelic shortening of the lower extremities. The radiograph showed hip dysplasia and bilateral proximal femoral hypoplasia

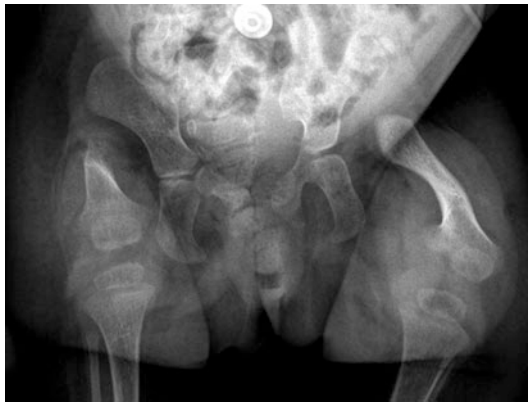

Fig. 2 This 8-month-old girl was diagnosed with femoral hypoplasia-unusual facies syndrome. The pelvic radiography demonstrates type D right proximal focal femoral deficiency. The left femur is also diffusely hypoplastic, particularly the proximal end. Marked acetabular dysplasia was present bilaterally (Courtesy of Dr. Grace Guo)

Fetal Akinesia Deformation Sequence

Contents

Fetal akinesia deformation sequence (FADS) refers to the condition of decreased intrauterine fetal movement and its consequent manifestations of multiple joint contractures, pulmonary hypoplasia, and abnormal face present at birth. It is also known as Pena-Shokeir phenotype (Hall 2009). The incidence is estimated to be 1 in 12,000, reflecting causal heterogeneity.

Synonyms and Related Disorders

Arthrogryposis multiplex congenita with pulmonary hypoplasia; Fetal akinesia sequence; Pena-Shokeir phenotype

Genetics/Basic Defects

1. Genetics:
    1. Sporadic in majority of cases
    2. Familial cases:
        1. Autosomal recessive inheritance (Bacino et al. 1993; Bisceglia et al. 1987; Vuopala et al. 1995b)
        2. Possible X-linked recessive inheritance
2. Heterogeneous causes (Beemer 1990):
    1. Inadequacy of the intrauterine fetal environment:
        1. Etiologic factors:
            1. Ovarian cyst
            2. Bicornuate uterus
            3. Umbilical cord wrapping
            4. Twins
            5. Extrauterine pregnancy
            6. Insufficient placental circulation
            7. Maternal tetanus, drug treatment
            8. Amniotic bands
        2. Oligohydramnios sequence (Rodriguez and Palacios 1991):
            1. Facial deformities (Potter's facies)
            2. Arthrogryposis
            3. Lung hypoplasia
        3. Types of defects determined by the timing of constraint:
            1. Early in pregnancy leading to limb reduction defects, syndactyly, and polydactyly.
            2. Later in pregnancy (third trimester) leading to genu recurvatum, dislocated hips, and deviated wrists.
            3. Various developmental defects occurring earlier in the upper than in the lower limbs.

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4. Embryonic onset of immobility interferes with limb development and results in joint fixation and pterygium formation, in contrast to fetal-onset immobility, which causes joint contractures alone (Davis and Kalousek 1988).

2. Pena-Shokeir phenotype or sequence (Hall 1986, 2009):
   1. Pena-Shokeir syndrome:
      1. Originally described by Pena and Shokeir in 1974 (Pena and Shokeir 1974a).
      2. Syndrome consisting of camptodactyly, multiple ankyloses, facial anomalies, pulmonary hypoplasia, and lethal outcome.
      3. Currently the term "Pena-Shokeir phenotype or sequence" is recommended instead of Pena-Shokeir syndrome.
      4. This form clearly exists as an autosomal recessive trait with frequent consanguinity and even incest reported.
   2. Curarization of fetal rats during pregnancy (study by Moessinger 1983) resulted in better understanding of fetal akinesia deformation sequence with the following features almost identical with those described in the Pena-Shokeir syndrome:
      1. Multiple contractures or arthrogryposis
      2. Pulmonary hypoplasia
      3. Craniofacial anomalies
      4. Polyhydramnios
      5. Intrauterine growth retardation
      6. Short umbilical cord
   3. Currently the term "Pena-Shokeir phenotype or sequence" is recommended instead of "Pena-Shokeir syndrome."

3. Fetal akinesia not associated with primary malformations (Grubben et al. 1990; Porter 1995):
   1. Mechanical causes:
      1. Oligohydramnios
      2. Polyhydramnios
      3. Premature rupture of the membrane
      4. Chorioamnionitis
   2. Congenital infections:
      1. Rubella
      2. CMV
      3. Toxoplasmosis
   3. Physical or chemical agents:
      1. Toxic agents
      2. Drugs
      3. X-rays
      4. Hyperthermia
   4. Fetal hypoxia:
      1. Fetal anemia:
         1. Blood loss
         2. Hemolysis
      2. Compression of umbilical cord
      3. Placental insufficiency
      4. Severe toxemia
   5. Maternal myasthenia gravis

4. Role of fetal akinesia in heterogeneous syndromes and conditions (Grubben et al. 1990):
   1. Cerebro-oculo-facio-skeletal (COFS) syndrome (Pena and Shokeir 1974b)
   2. Potter sequence
   3. Neu-Laxova syndrome
   4. Syndrome described by Herva et al. (1985)
   5. Osteochondrodysplasias:
      1. Thanatophoric dysplasia
      2. Achondrogenesis
      3. Diastrophic dysplasia
   6. Lethal multiple pterygium syndrome (LMPS) (Chen et al. 1984; Hall 1984; Moerman and Fryns 1990)
   7. CNS anomalies:
      1. Hydranencephaly
      2. Dandy-Walker malformation with hydrocephalus
      3. Schizencephaly
      4. Olivopontocerebellar degeneration
   8. Skin/connective tissue disorders:
      1. Restrictive dermopathy
      2. Epidermolysis bullosa
      3. Congenital ichthyosis
   9. Metabolic disorders:
      1. Lysosomal storage disorders
      2. Generalized gangliosidosis syndrome type I
      3. Glycogenosis type VII (Moerman et al. 1995)
   10. Known single-gene disorders affecting the spinal cord, peripheral nerves,

neuromuscular junction, or skeletal muscles that result in fetal akinesia (Ravenscroft et al. 2011):

1. Fetal akinesia due to mutations in genes involved in motor neuron development and survival:
    1. Survival motor neuron 1 (*SMN1*)
    2. Epidermal growth factor receptor 3 (*ERBB3*)
    3. mRNA export mediator GLE1 (*GLE1*)
    4. Phosphatidylinositol-4-phosphate 5-kinase, type I, gamma (*PIP5K1C*)
    5. Trisomy 1q
    6. Ubiquitin-activating enzyme 1 (*UBE1*)
2. Fetal akinesia due to mutations in genes affecting the peripheral nerves
3. Fetal akinesia due to mutations in genes encoding components of the neuromuscular junction:
    1. The acetylcholine receptor (AChR): a and d subunits (*CHRNA1* and *CHRND*), γ subunit (*CHRNG*), and antibodies to the γ subunit of the AChR
    2. Contactin-1 (*CNTN1*)
    3. Downstream of kinase-7/muscle intrinsic activator of MUSK (*DOK7*) (Wilbe et al. 2015)
    4. Nesprin-1/synaptic nuclear envelope protein-1 (*SYNE1*)
    5. Rapsyn (*RAPSN*)
4. Fetal akinesia due to mutations in genes encoding adult skeletal muscle proteins:
    1. Actin, skeletal muscle alpha (*ACTA1*)
    2. Amphiphysin 2 (*BIN1*)
    3. Dystrophia myotonica protein kinase (*DMPK*)
    4. Fukutin-related protein (*FKRP*)
    5. Lamin A/C (*LMNA*)
    6. Myotubularin (*MTM1*)
    7. Nebulin (*NEB*)
    8. Ryanodine receptor 1 (*RYR1*)
    9. Tropomyosin, slow beta (*TPM2*)
    10. Troponin I, fast skeletal muscle (*TNNI2*)
    11. Troponin T, fast skeletal muscle (*TNNT3*)
5. Fetal akinesia due to mutations in genes encoding fetally expressed myostructural proteins:
    1. Myosin heavy chain, embryonic (*MYH3*)
    2. Myosin heavy chain, perinatal (*MYH8*)
    3. Myosin-binding protein C1, skeletal muscle slow type (*MYBPC1*)
    4. Utrophin (*UTRN*)
6. Fetal akinesia associated with other genes:
    1. Fibroblast growth factor receptor 2 (*FGFR2*)
    2. Glycogen branching enzyme (*GBE1*)
7. Examples of neuromuscular disorders:
    1. Congenital muscular dystrophy
    2. Congenital myotonic dystrophy
    3. Congenital spinal muscular atrophy
    4. Central core disease
    5. Nemaline myopathy
    6. Others

11. Other disorders causing restrictive fetal akinesia:
    1. Loss of anterior horn cells
    2. Radical disease
    3. Peripheral neuropathy
    4. Congenital myasthenia gravis
    5. Amyoplasia congenita
    6. Prader-Willi syndrome
    7. Cohen syndrome
    8. Angelman syndrome
    9. Neurofibromatosis I
    10. Moebius syndrome
    11. Bilateral dislocation of the hips
    12. Exstrophy of the cloaca and bladder
    13. Chromosome abnormalities:
        1. Fetal triploidy
        2. Trisomies 4p, 9, 9q, 9p, 10q, 11q, proximal 14, proximal 15, and 18
        3. Monosomies 4p and 13q

14. Miscellaneous:
    1. Cornelia de Lange syndrome
    2. Catel-Manzke syndrome
    3. Opitz-Frias syndrome
    4. Bowen-Conradi syndrome
    5. Marden-Walker syndrome
5. Pathogenesis of fetal akinesia sequence (Hageman et al. 1987; Witters et al. 2002):
    1. Spinal cord lesions observed most often (28%)
    2. Brain lesions (19%)
    3. Miscellaneous or connective tissue disorders (11%)
    4. Combined brain and spinal cord lesions (9%)
    5. Mechanical restriction (7%)
    6. Muscle disorders (5%)
    7. Peripheral neuropathy and myasthenia gravis (1%)
    8. No underlying defect observed in 14% of cases
6. Molecular basis of lethal fetal akinesia phenotype (Vogt et al. 2008, 2009):
    1. Mutations in the acetylcholine receptor (AChR) subunits *CHRNA1*, *CHRNB1*, *CHRND*, and rapsyn (*RAPSN*) can also result in a multiple pterygium syndrome (MPS)/FADS phenotype.
    2. Whereas incomplete loss of *DOK7* function may cause congenital myasthenia, more severe loss of function can result in a lethal fetal akinesia phenotype.
7. Mutations in the fetally expressed g subunit (CHRNG) of AChR were found in two FADS disorders, lethal multiple pterygium syndrome (LMPS) and Escobar syndrome. Other AChR subunits α1, β1, and δ (CHRNA1, CHRNB1, CHRND) as well as receptor-associated protein of the synapse (RAPSN) previously revealed missense or compound nonsense-missense mutations in viable congenital myasthenic syndrome (Michalk et al. 2008).
8. Fetal akinesia deformation sequence due to a congenital disorder of glycosylation: characteristic features of the fetal akinesia sequence with other unique features, including joint contractures, cataracts, hypotonia, vermian hypoplasia, and consanguinity, which was found to have CDG-DPAGT1 (Ganetzky et al. 2015).

Clinical Features

1. Pregnancy history (Grubben et al. 1990):
    1. Feeble fetal movement (limitation of fetal movement) (Hammond and Donnenfeld 1995)
    2. Polyhydramnios
    3. Oligohydramnios
    4. Craniofacial abnormalities:
        1. Ocular hypertelorism
        2. Micrognathia
        3. Low-set ears
        4. Depressed nasal tip
        5. Short neck
    5. Limb anomalies:
        1. Lack of normal growth
        2. Limitation of joint movement
        3. Abnormal shape
        4. Abnormal position
        5. Decreased bone calcification
        6. Multiple perinatal fractures (Chen et al. 1995)
2. Phenotype present at birth (Mease et al. 1976):
    1. Multiple joint contractures
    2. Limb pterygia
    3. Craniofacial abnormalities
    4. Pulmonary hypoplasia
    5. Short umbilical cord
    6. Growth retardation
3. Lethal outcome with pulmonary hypoplasia
4. Identifiable familial forms of Pena-Shokeir phenotype/fetal akinesia deformation sequence:
    1. Classic Pena-Shokeir syndrome (type I):
        1. Classic signs of fetal akinesia deformation sequence (lack of normal fetal movement in utero):
            1. Intrauterine growth retardation
            2. Joint contractures
            3. Short gait
            4. Short umbilical cord
            5. Pulmonary hypoplasia

6. Characteristic facial features: hypertelorism, prominent nasal bridge, posteriorly rotated low-set ears, depressed tip of the nose, micrognathia, and cleft palate (probably related to micrognathia and lack of in utero tongue movement)
2. Sticklike limbs with flexion or extension contractures
3. Feet usually in severe equinovarus position but rocker bottom feet may be present
4. Elbows usually flexed
5. Hypoplastic dermatoglyphics
6. Normal CNS and most skeletal muscle, although muscle biopsies often show disuse atrophy, no myopathy changes, and rarely fatty, fibrous replacement
7. Other often reported features:
    1. Disproportionately large head
    2. Short limbs
    3. Thin ribs and long bones
    4. Clenched hands
    5. Ankylosis of large joints
    6. Thoracic kyphosis

2. Lower motor neuron disorder with generalized decrease in anterior horn cells (Chen type) (Chen et al. 1983):
    1. Intrauterine growth retardation.
    2. Polyhydramnios.
    3. Lack of fetal movement in the early second trimester.
    4. Pulmonary hypoplasia.
    5. Characteristic facial appearance:
        1. Nasal bridge: depressed or high
        2. Long philtrum
        3. Small mouth
    6. Limb abnormalities:
        1. Flexion contractures
        2. Hyperextended and overlapping distal phalanges
        3. Ulnar deviation of fingers
        4. Radioulnar synostosis
        5. Clubfeet
    7. Other findings:
        1. Mild kyphosis
        2. Hypoplastic adrenals
    8. Small muscles with disuse atrophy.
    9. Cases reported by Abe et al. (1989), Moerman et al. (1983), Moerman and Fryns (1990), and possibly Imamura et al. (1981) and Gullino et al. (1993) appear to have this subtype.
3. Lethal congenital contracture syndrome type I (LCCS-1) (GLE mRNA export mediator gene mapped at 9q34) (Herva et al. 1985, 1988; Vuopala et al. 1994):
    1. An autosomal recessive disorder frequently seen in Finland
    2. Intrauterine growth retardation
    3. Pulmonary hypoplasia
    4. Micrognathia
    5. Short neck
    6. Thin ribs
    7. Thin, sticklike limbs which may fracture, associated with decreased muscle mass
    8. Extended legs, often with flexed arms
    9. Dislocated hips always present
    10. Striking and characteristic feature: decrease of anterior horn cells in the ventral part of the spinal cord with normal cerebellum
    11. Prenatal diagnosis possible by molecular testing of mutations in the messenger RNA export mediator GLE (*GLE1*) (Nousiainen et al. 2008)
4. Lethal congenital contracture syndrome type II (LCCS-2) (Landau et al. 2003):
    1. Described in two Israeli Bedouin consanguineous kindreds
    2. Clinical features:
        1. Extended elbows
        2. Flexed knees
        3. Mild IGUR
        4. Micrognathia
        5. Hydronephrosis
        6. Distended bladders
    3. Generally decreased anterior horn cells in the spinal cord and muscle wasting suggesting a neuropathic etiology
    4. *ERBB3* gene mapped at 12q13

5. Lethal congenital contracture syndrome type III (LCCS-3):
    1. Represented by a large consanguineous Israeli Bedouin kindred
    2. Clinical features identical to LCCS-2 without bladder involvement
    3. *PIP5K1C* gene mapped at 19p13
6. Lethal lower motor neuron deficiency (Vuopala et al. 1995a):
    1. Described in 11 families.
    2. Considered to be a disorder of the degeneration of anterior horn cells leading to lethality.
    3. Clinical features:
        1. Legs and arm: hyperextended or flexed
        2. Mild IUGR
        3. Usually born near the term
        4. Craniofacial: micrognathia, high nasal bridge, underdeveloped nasal tip, posteriorly rotated ears, and short neck
        5. Early death due to respiratory failure
    4. This disorder mapped to 5q.
7. Families with apparent increase in monozygotic (MZ) twinning (Chen et al. 1983; Lindhout et al. 1985; Ho 2000):
    1. Affected twins and affected singletons occur in the same families.
    2. Clinical features:
        1. Polyhydramnios
        2. Increased fetal movement signal problems
        3. Severe pulmonary hypoplasia
        4. IUGR
        5. Mildly webbed necks
        6. Multiple flexion contractures including camptodactyly and clubfeet
        7. Relatively large head compared to short trunk
        8. Triangular face
        9. Ocular hypertelorism
        10. Clenched jaw
        11. Posteriorly angulated ears
    3. Other features in some affected infants
    4. Relationship between MZ twinning and this type of PSP/FADS:
        1. Unclear.
        2. Potentially they are cases of classic Pena-Shokeir syndrome.
8. Normal in utero growth, macrocephaly, and Pena-Shokeir phenotype (Lammer type):
    1. Affected brothers described by Lammer et al. (1989)
    2. Clinical features:
        1. Normal intrauterine growth
        2. Died with severe pulmonary hypoplasia
        3. Trismus
        4. Micrognathia
        5. Hydronephrosis
        6. Macrocephaly
        7. Choanal atresia in one brother
9. Absence of pyramidal cells, immature CNS development, adducted thumbs, kyphoscoliosis, and severe pulmonary hypoplasia (Biscegli type):
    1. Described in a consanguineous family
    2. Clinical features:
        1. Polyhydramnios
        2. IUGR
        3. Immaturity or delayed development of the CNS
        4. Marked ocular hypertelorism
        5. Hypoplasia and atrophy of skeletal muscles
        6. Extension contractures of arms and legs
        7. Camptodactyly with abducted thumbs
        8. Clubfeet
        9. Marked congenital kyphoscoliosis
10. CNS dysgenesis and degeneration, seizures, trismus, and abdominal wall herniation (Erdl type):
    1. Sibs described by Erdl et al. (1989)
    2. Clinical features:
        1. IUGR
        2. Extended knees
        3. Trismus
        4. Seizures (intrauterine and after birth)
        5. Generalized edema at birth

6. Severe lung hypoplasia
7. Died shortly after birth
8. Abdominal herniation (muscle defect) in the first sib
9. A short and extremely thin umbilical cord
10. Left lung trilobation and large thyroid and adrenal glands
11. Polyhydramnios
12. Fetal hydrops at 30–34 weeks of gestation
13. CNS abnormalities: internal hydrocephalus, hypoplasia of basal ganglia, reduced or degenerating anterior horn cells, and other dystrophic brainstem and cerebellar changes

11. Skeletal muscle maturation defect:
    1. Finnish female siblings described by Vuopala et al. (1994)
    2. Clinical features:
        1. Polyhydramnios
        2. Severe pulmonary hypoplasia
        3. Congenital scoliosis
        4. Normal birth weight for gestation
        5. Edema
        6. One sib stillborn and other lived only 7 weeks
        7. Normal CNS
        8. Skeletal muscle immature with small muscle fibers and prominent atypical spindles
12. Pyramidal tract degeneration:
    1. Two female sibs described by Vuopala et al. (1994)
    2. Pena-Shokeir phenotype
    3. Presence of pyramidal tract degeneration
    4. Normal brain in one sib
    5. Holoprosencephaly in other sibs
    6. May represent an upper motor neuron disorder or a variation on holoprosencephaly
13. In utero seizures and scoliosis, together with cerebral and cerebellar hypoplasia in males (Persutte type):
    1. Two male sibs in a consanguineous family described by Persutte et al. (1988).
    2. Clinical features:
        1. Congenital scoliosis apparent at 18 weeks of gestation
        2. Decreased fetal movement
        3. Polyhydramnios
        4. IUGR
        5. Severe pulmonary hypoplasia leading to death within a few minutes after birth
        6. Flexion contractures
        7. Relatively large head
        8. Short neck
        9. Small low-placed ears
        10. CNS anomalies: agenesis of the corpus callosum and septum pellucida, hydrocephaly, hypoplastic cerebellum, and brain stem
    3. A family of male sibs with similar structural anomalies was described by Skrupski et al. (1996).
    4. This disorder could be X-linked recessive.
14. Microphthalmia, microtia, and normal birth size (Thomas type):
    1. Two male sibs described by Thomas et al. (1993)
    2. Clinical features:
        1. Polyhydramnios.
        2. Normal size at birth.
        3. Multiple congenital contractures.
        4. Died of respiratory insufficiency.
        5. Persistent truncus arteriosus.
        6. Microphthalmia.
        7. Microtia.
        8. One had duodenal atresia, hydronephrosis, and dilated bladder.
15. Olivopontocerebellar hypoplasia:
    1. A family of three siblings reported by Goutieres et al. (1977)
    2. Clinical features:
        1. Contractures
        2. Anterior horn disease
        3. Olivopontocerebellar hypoplasia

4. Death shortly after birth due to pulmonary hypoplasia

16. Failure to myelinate peripheral nerve:
    1. Affected male and female siblings reported by Pena et al. (1968)
    2. Clinical features:
        1. Multiple congenital contractures
        2. Lack of myelination of the peripheral nerve
17. Holoprosencephaly with hypokinesia and congenital contractures in an X-linked recessive pattern of inheritance:
    1. First reported by Morse et al. (1987) and then by Hockey et al. (1988)
    2. Other clinical findings with typical features of FADS
18. Hydranencephaly, calcification of the basal ganglion, and proliferative vasculopathy (Fowler type):
    1. Families reported by Fowler et al. (1972), Harper and Hockey (1983), and Harding et al. (1995)
    2. Clinical findings:
        1. Polyhydramnios
        2. Lack of fetal movements
        3. Generalized edema
        4. Cleft palate
        5. Pterygia of large joints
19. Calcification of leptomeninges, the surface of cerebral convolutions, neurons, muscles, and vessels (Illum type):
    1. A family of male and female siblings reported by Illum et al. (1988)
    2. Other clinical findings:
        1. Multiple congenital contractures
        2. Camptodactyly with ulnar flare and clubfeet
        3. Round face, depressed nasal bridge, long philtrum, short nose, puckered mouth, a deep horizontal crease below the lower lip, and trismus
        4. Early lethality
20. Familial intrauterine anoxia and/or ischemia and PSP/FADS can be associated with the following situations:
    1. Maternal cocaine
    2. Monozygotic twins at increased risk for this type of change because of their vascular connection
    3. Polymicrogyri
    4. Oligogyri
    5. Atrophy of the cerebellum and cerebrum
    6. Cerebral neuronal loss and gliosis
    7. Cyst of the brain
    8. Heterotopia
    9. Decreased number of anterior horn cells with ferrigination
    10. Dilated ventricles with calcification
21. A newly recognizable subtype of FADS with bulbous digital tips, prominent digit pads, and cerebellar anomalies and that highlights the phenotypic diversity of syndromes with multiple congenital contractures manifesting in utero (Nayak et al. 2014)

Diagnostic Investigations

1. Radiography:
    1. Thin tubular bones
    2. Gracile ribs
    3. Multiple fractures possible at mid-diaphyses of humeri, distal diaphyses of femora, proximal diaphyses of tibiae and fibulae
    4. Camptodactyly
2. Histopathologic and other laboratory studies:
    1. Trophoblastic inclusions in the chorionic villi of the placenta:
        1. Triploidy
        2. Lethal multiple pterygium syndrome
    2. Lung hypoplasia
    3. Bones:
        1. Unremarkable resting cartilage
        2. Normal cartilage cell columns at the chondro-osseous junctions
        3. Marrow bony spicules often unusually thin and underossified
        4. Irregular and focal areas of extreme diaphyseal thinning: a consistent finding

4. CNS, muscles, and other organ systems
5. Biochemical studies for lysosomal storage disease
6. Analysis for chromosome abnormality

3. Molecular genetic diagnosis:
   1. *DOK7*- and *RAPSN*-related fetal akinesia deformation sequence available clinically.
   2. The potential of the whole exome sequencing will be crucial to identifying the unknown genetic bases of fetal akinesia (Ravenscroft et al. 2011).

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib:
      1. Autosomal recessive inheritance, 25%
      2. A recurrence risk of 10–15% suggested in the nonfamilial sporadic cases
   2. Patient's offspring: a lethal entity not surviving to reproductive age
2. Prenatal diagnosis by ultrasonography (Ohlsson et al. 1988; Yfantis et al. 2002; Ruano et al. 2003; Hellmund et al. 2016) in high-risk pregnancies after the birth of a previous child with a heritable (mostly autosomal recessive) form of fetal akinesia sequence:
   1. Marked decreased fetal activity:
      1. Restricted limb movements
      2. Decreased fetal chest movements
   2. Hydramnios/oligohydramnios.
   3. Intrauterine growth retardation.
   4. Hydrops noted in some affected babies late in pregnancy.
   5. Nuchal edema.
   6. Abnormal profile:
      1. Micro-/retrognathia
      2. Flat profile
      3. Edema of the forehead
      4. Permanently open mouth
      5. Not visualized because of hydrops
   7. Absent/minimal filling of the stomach.
   8. Thorax hypoplasia/narrow thorax.
   9. Scoliosis.
   10. Permanent opisthotonus.
   11. Fixation of the elbow joint, wrist, fingers, knee joint, and ankle joint.
   12. Pterygia.
   13. Some affected babies often die in utero if not shortly following birth.
   14. Other echographic abnormalities associated with fetal akinesia:
      1. Brain:
         1. Microcephaly
         2. Holoprosencephaly
         3. Hydranencephaly
         4. Meningomyelocele
         5. Lissencephaly
         6. Dilated ventricles
         7. Absence of septum pellucidum
      2. Spinal cord: sacrococcygeal agenesis
      3. Gastrointestinal tract:
         1. Omphalocele
         2. Gastroschisis
      4. Renal:
         1. Bilateral renal agenesis
         2. Renal malformations
      5. Craniofacial:
         1. Hypertelorism
         2. Hypotelorism
         3. Micrognathia
         4. Cleft palate
      6. Limbs:
         1. Contractures (arthrogryposis)
         2. Camptodactyly
         3. Webbing
         4. Syndactyly
         5. Polydactyly
         6. Overlapping fingers and toes
         7. Abnormal position
         8. Clubfoot
         9. Partial absence or shortness
      7. Cardiopulmonary:
         1. Pulmonary hypoplasia
         2. Cardiac defects
   15. Prenatal MR imaging in Pena-Shokeir syndrome: to look for associated neurological malformation (Persutte et al. 1988; Senocak et al. 2009; Gupta et al. 2011; Nemec et al. 2011).
3. Management: no effective treatment for pulmonary hypoplasia

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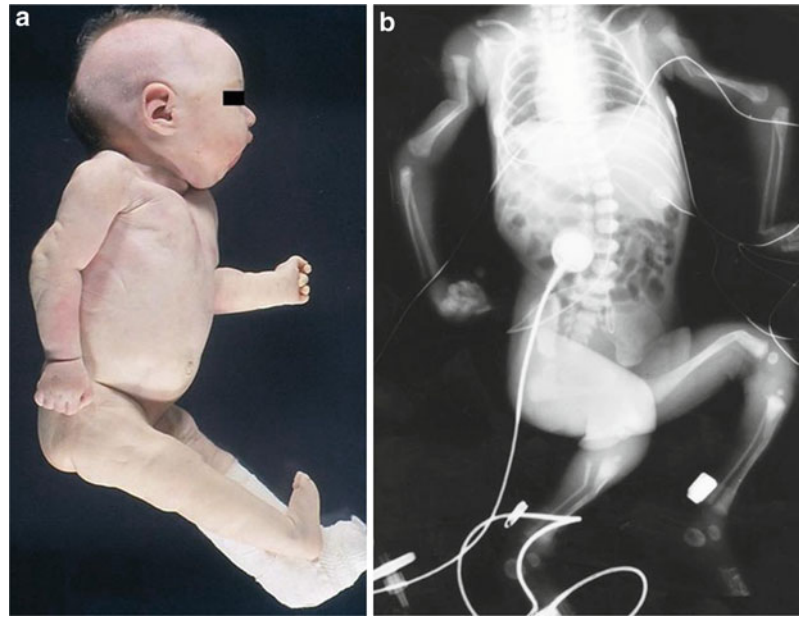

Fig. 1 (**a**, **b**) A neonate with fetal akinesia sequence showing micro-/retrognathia, short neck, narrow thorax, flexion contractures of hips, fixed extension of the right knee, and inverted and rotated feet. The radiograph showed gracile ribs; thin long bones with multiple fractures at mid-diaphyses of humeri, distal diaphysis of femora, and proximal diaphyses of both tibiae and the left fibula; and clubhands

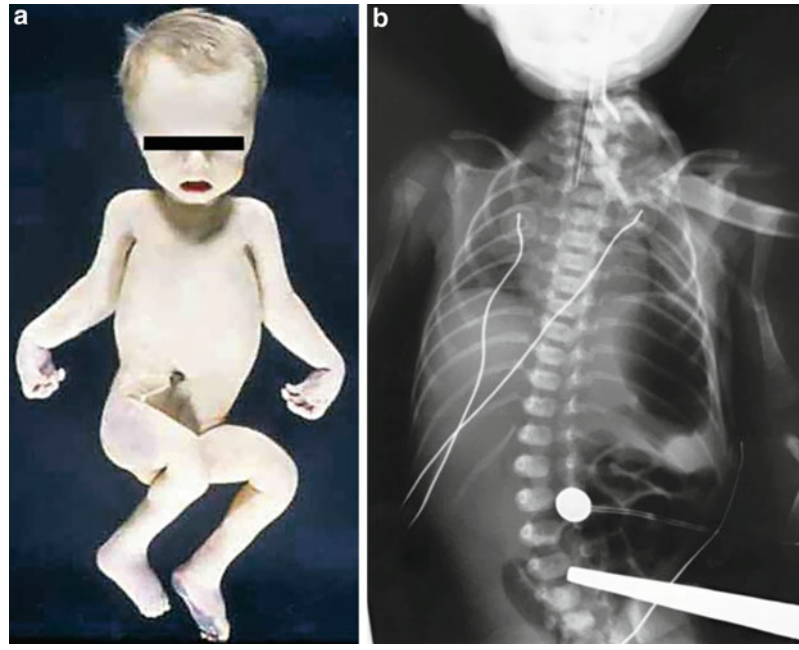

Fig. 2 (**a**, **b**) A neonate with fetal akinesia sequence showing micrognathia and multiple contractures. The radiograph showed gracile ribs and fractures at mid-diaphyses of humeri

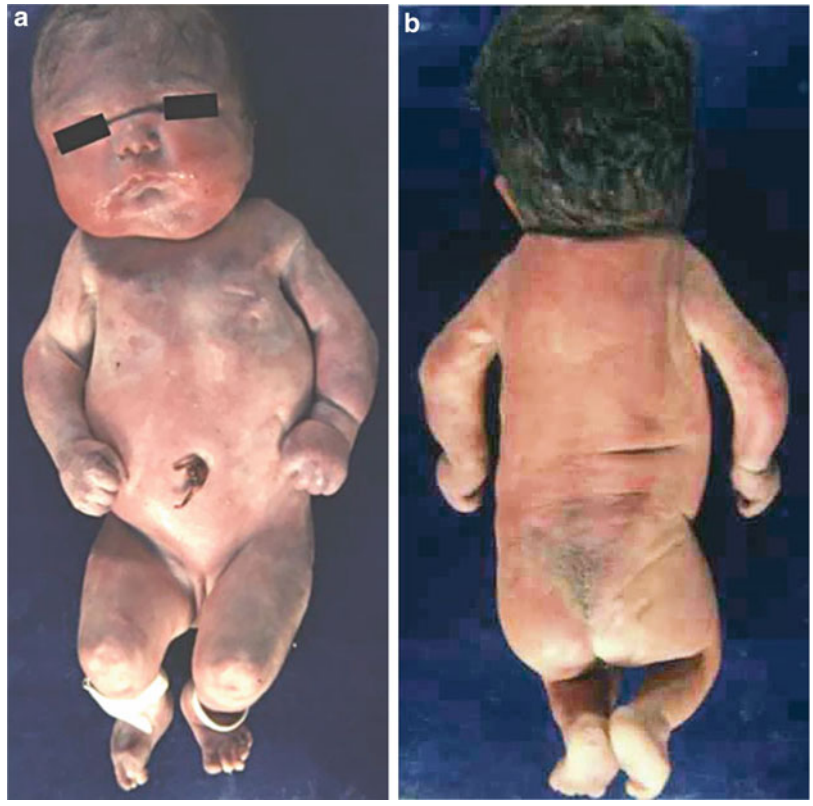

Fig. 3 (**a**, **b**) A neonate with Pena-Shokeir sequence (Chen type) showing hypertelorism; a short nose with depressed nasal bridge; long philtrum; a small and recessed jaw; low-set malformed ears; a short neck; clenched hands; multiple contractures at the hip, elbows, knees, and ankles; and clubfeet. The infant had scalp edema and pulmonary hypoplasia. Neuromuscular histology showed lower motor neuron disorder with generalized decrease in anterior horn cells

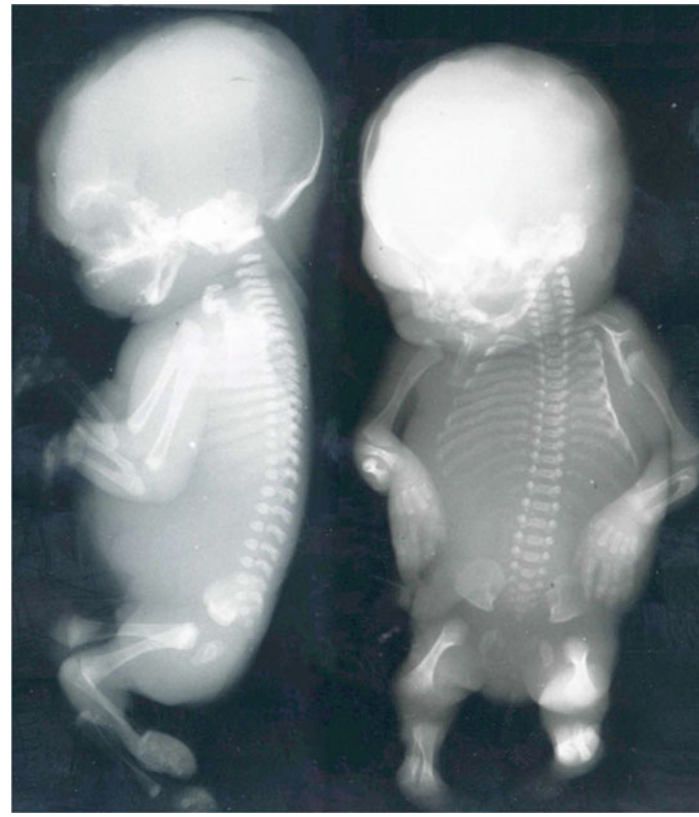

Fig. 4 Radiographic study of the infant showed gracile ribs; thin long bones; and multiple contractures at the hip, elbows, knees, and ankles; and clubfeet

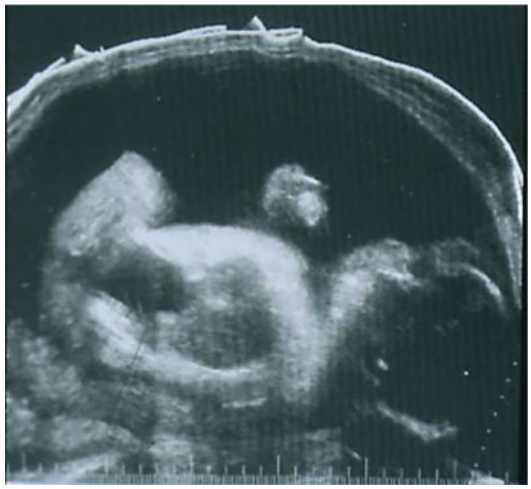

Fig. 5 Prenatal ultrasonography showed hydramnios, retrognathia, low-set ears, scalp edema, and flexion contractures at the elbows and knees

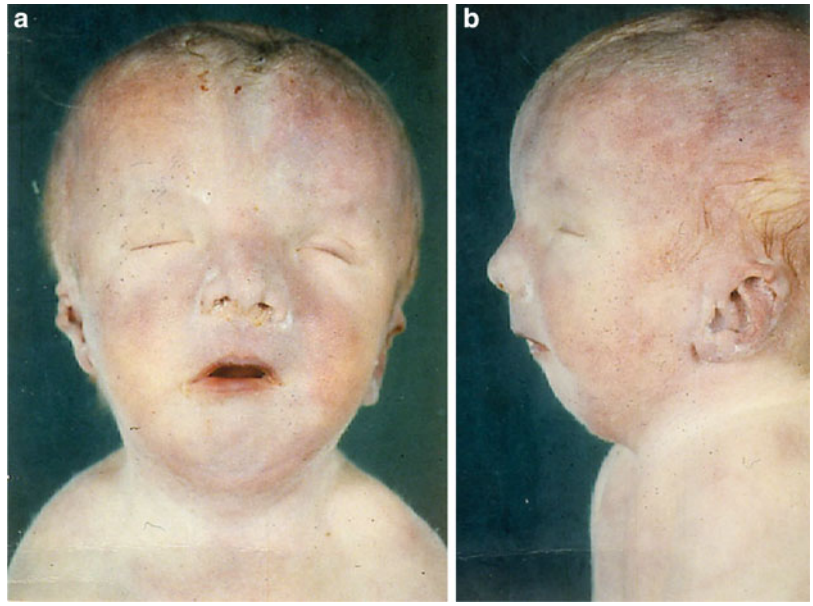

Fig. 6 (**a**, **b**) An infant in a family with MZ twinning. Note small jaw, ocular hypertelorism, antimongoloid slant of the palpebral fissures, high bridge of the nose, posteriorly rotated large ears, triangular-shaped face, and short-appearing mildly webbed neck

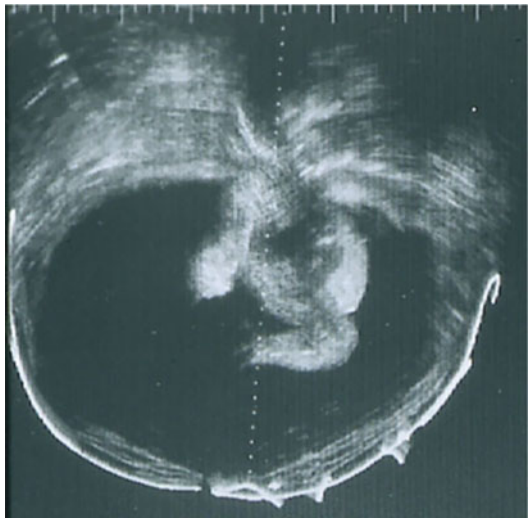

Fig. 7 Prenatal ultrasound of this fetus showed polyhydramnios, IUGR, and flexion contractures of the knees

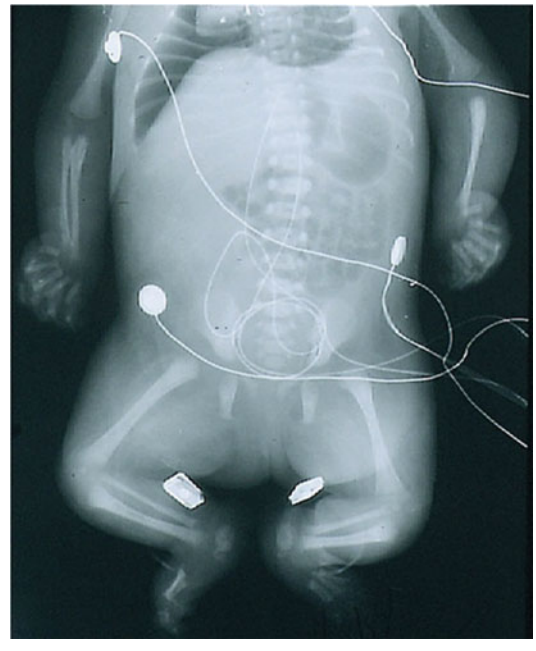

Fig. 8 Radiograph showed gracile ribs, thin long bones, flexion contractures at the elbows and knees, and clenched hands

Fetal Alcohol Spectrum Disorders

Contents

In 1973, Jones et al. described, in the American medical literature, a constellation of features in children born to alcoholic mothers, now known as fetal alcohol syndrome (FAS). In 1996, the Institute of Medicine further defined criteria of FAS and proposed two new terms, alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBDs), to include structural CNS and cognitive abnormalities in children in whom fetal exposure to alcohol has been confirmed.

It is established that prenatal exposure to alcohol produces a range of morphological and cognitive-behavioral outcomes in the offspring, commonly referred to as fetal alcohol spectrum disorder (FASD) (Kodituwakku 2007). Fetal alcohol syndrome refers to severely affected children on the spectrum displaying a pattern of altered growth and morphogenesis, characterized by prenatal and postnatal growth retardation, craniofacial anomalies, abnormal brain function reflected by cognitive deficits, and developmental delays. The majority of children (about three times as many children as those with FAS) with substantial prenatal alcohol exposure show only some of the abovementioned features (Sampson et al. 1997), commonly referred to having fetal alcohol effects (FAEs). The term FAE, however, has been replaced by two new terms: ARND and ARBD.

The incidence of FAS in the United States is estimated to be about 1–3 per 1,000 live births. The incidence is higher in certain population, such as Native Americans (Gleason 2001).

Synonyms and Related Disorders

Alcohol-related birth defects (ARBDs); Alcohol-related neurodevelopmental disorder (ARND); Fetal alcohol effect; Fetal alcohol syndrome; Partial fetal alcohol syndrome

Genetics/Basic Defects

1. Genetics (Thackray and Tifft 2001):
    1. Genetic susceptibility:
        1. Observation of differences in the severity and spectrum of FAS based on genetic background.
        2. Higher concordance of FAS in monozygotic twins than in dizygotic twins supports the concept of genetic factors in the fetal effects of alcohol.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_91

2. Possible mechanism of heritable susceptibility to FAS – genetically encoded differences in alcohol dehydrogenase, the enzyme responsible for metabolizing alcohol in the liver:
    1. The mother of children with FAS: possibly with less functional enzyme resulting in higher peak blood alcohol concentration after the ingestion of alcohol.
    2. Fetuses with FAS: possibly with deficient alcohol dehydrogenase activity and thus less tolerance to elevated maternal alcohol levels.
2. Pathogenesis (Erb and Andresen 1978; Thackray and Tifft 2001):
    1. Clinical features of FAS: result from exposure of the developing fetus to toxic levels of alcohol and its metabolites at critical periods in development.
    2. Specific pathophysiology unknown: may involve free radical formation that causes cellular damage in the developing tissues of the fetus.
    3. Exposure in the first trimester:
        1. Affects organogenesis and craniofacial development, leading to minor and major malformations such as the characteristic facial features and ARBD.
        2. Excessive cell death in the midline of the developing embryo may account for the development of these facial features.
    4. Continuous use of alcohol by the mother later in pregnancy resulting in low birth weight and affecting postnatal growth.
    5. Alcohol exposure at varying times in pregnancy may result in similar CNS neurodevelopmental effects.
    6. Detrimental defects on the fetus when there is concomitant maternal use of other drugs (marijuana, nicotine, caffeine).
3. Key risk factors for alcohol-induced brain damage:
    1. Peak blood alcohol concentration rather than the length of alcohol exposure: the critical variable in determining the risk for adverse effects on brain development.
    2. Cessation of drinking alcohol at any time during pregnancy likely to be beneficial on the developing brain.
    3. The cerebellum particularly vulnerable to alcohol-induced growth restriction as well as neuronal loss following alcohol exposure during the brain growth spurt (third trimester in humans).
    4. Heavy alcohol consumption during the first trimester associated strongly with craniofacial abnormalities in humans.
4. A potential molecular target for morphological defects of fetal alcohol syndrome: Kir2.1 (Bates 2013).
5. Potential role of endocannabinoid signaling (Basavarajappa 2015):
    1. Several molecular mechanisms are expected to contribute to the damaging effects of prenatal alcohol exposure on the developing fetus.
    2. These events including endocannabinoid mechanisms contribute to impaired development and function of neuronal communication and circuit formation.
    3. These alcohol-induced deficits result in long-lasting abnormalities in neuronal plasticity and learning and memory and can explain many of the neurobehavioral abnormalities found in FASD.
6. Epigenetic mechanisms in developmental alcohol-induced neurobehavioral deficits (Mead and Sarkar 2014; Basavarajappa and Subbanna 2016):
    1. Several epigenetic mechanisms are suggested to contribute to the harmful consequences of alcohol abuse during pregnancy in the developing fetus.
    2. Epigenetic modifications, such as altered DNA methylation, specific histone protein modification, and dysregulation of miRNA, in response to developmental alcohol exposure, can contribute to impaired neurogenesis, neuronal communication, and neural circuit assembly.
    3. These alcohol-induced neuronal deficits can be long-lasting and could result in

abnormalities in synaptic plasticity and cognitive function and can provide bases for many of the neurobehavioral abnormalities found in FASD.

Clinical Features

1. Characteristic craniofacial features in the young child (Jones and Smith 1973, 1975; Clarren and Smith 1978; Clarren 1981; Colangelo and Jones 1982; Gleason 2001; Moore et al. 2002; Jones 2003):
    1. Discriminating features:
        1. Short palpebral fissures (Miller et al. 1981)
        2. Flat midface
        3. Indistinct (smooth, flat) philtrum
        4. Thin upper lip
    2. Associated features:
        1. Epicanthal folds
        2. Low nasal bridge
        3. Minor ear anomalies
        4. Short nose
        5. Micrognathia
2. Growth retardation (Hanson et al. 1976; Jones et al. 1976; Jones 1986):
    1. Low birth weight for gestational age (prenatal growth deficiency) (97%)
    2. Decelerating weight over time not due to nutrition (postnatal growth deficiency) (97%)
    3. Disproportionate low weight to height
3. Alcohol-related birth defects (ARBDs) – birth defects associated with in utero alcohol exposure:
    1. Ocular abnormalities (Strömland 1987; Strömland and Hellström 1996):
        1. Strabismus
        2. Retinal vascular anomalies
        3. Optical nerve hypoplasia
        4. Refractive problems secondary to small globes
        5. Coloboma
    2. Cardiovascular abnormalities:
        1. Atrial septal defect
        2. Ventricular septal defect
        3. Aberrant great vessels
        4. Tetralogy of Fallot
    3. Hepatic abnormality: extrahepatic biliary atresia
    4. Skeletal abnormalities (Gonzalez 1979; Spiegel et al. 1979):
        1. Hypoplastic nails
        2. Shortened fifth digits
        3. Radioulnar synostosis
        4. Flexion contractures
        5. Camptodactyly
        6. Clinodactyly
        7. Pectus excavatum/carinatum
        8. Klippel-Feil syndrome
        9. Hemivertebrae
        10. Scoliosis
    5. Muscular abnormalities:
        1. Hernias:
            1. Diaphragm
            2. Umbilicus
            3. Inguinal
        2. Diastasis recti
    6. Renal abnormalities:
        1. Aplastic/dysplastic/hypoplastic kidneys
        2. Horseshoe kidneys
        3. Ureteral duplications
        4. Megaureter
        5. Hydronephrosis
        6. Cystic diverticula
        7. Vesicovaginal fistula
    7. Genital abnormalities:
        1. Hypospadias
        2. Labial hypoplasia
    8. Cutaneous abnormalities:
        1. Hemangiomas
        2. Hirsutism
    9. Auditory abnormalities (Church and Abel 1998):
        1. Conductive hearing loss
        2. Neurosensory hearing loss
    10. Neuroendocrine abnormalities:
        1. Altered hypothalamic-pituitary-adrenocortical axis-heightened stress response
        2. Abnormal thyroid function
    11. Other abnormalities: include virtually any malformation

4. Alcohol-related neurodevelopmental disorder (ARND):
    1. Structural CNS abnormalities associated with in utero alcohol exposure:
        1. Microcephaly
        2. Microencephaly
        3. Decreased size of the cerebrum, cerebellum, basal ganglia, and diencephalons
        4. Partial or complete agenesis of the corpus callosum
        5. Neuroglial heterotopia
        6. Dendritic neuronal abnormalities
        7. Holoprosencephaly sequence
        8. Anencephaly
        9. Porencephaly
        10. Ventricular enlargement
        11. Dandy-Walker malformation
    2. Neurologic abnormalities associated with in utero alcohol exposure:
        1. Impaired fine motor skills
        2. Deficits in balance
        3. Poor tandem gait
        4. Neurosensory hearing loss
        5. Poor hand-eye coordination
        6. Hypotonia
    3. Neurobehavioral abnormalities associated with in utero alcohol exposure (Streissguth et al. 1991; Olson et al. 1997; Abel 1980):
        1. Learning disabilities
        2. Decreased IQ scores (Streissguth et al. 1978)
        3. Mental retardation
        4. Attention deficit/hyperactivity disorder (Spohr and Steinhausen 1984)
        5. Poor impulse control
        6. Problems in memory, attention, or judgment
        7. Problems in social perception
        8. Deficits in higher-level receptive or expressive language: speech and language abnormalities (Iosub et al. 1981)
        9. Poor capacity for abstraction or metacognition
        10. Autism
        11. Adult mental illness:
            1. Alcohol or drug dependence
            2. Psychotic disorders
            3. Avoidant, antisocial, or dependent personality disorder
            4. Depression
            5. Suicide
        12. Alcohol or drug dependence
        13. Psychotic disorders
        14. Avoidant, antisocial, or dependent personality disorder
        15. Depression
        16. Suicide
5. Neuropsychological abnormalities found in individuals with fetal alcohol spectrum disorders (FASDs) when compared to typically developing children (Basavarajappa 2015):
    1. General intelligence: lower IQ (~70)
    2. Executive function: impaired executive functions such as planning, fluency, and working memory
    3. Learning and memory:
        1. Verbal: impaired initial learning without affecting retention of information already learned due to implicit learning strategies
        2. Nonverbal: impaired nonverbal learning and memory but impairment of retention of information is inconsistent
    4. Motor function: deficits in motor abilities and visual-motor tasks
    5. Attention and hyperactivity: deficits in attention and exhibit hyperactivity
6. Neonatal alcohol withdrawal signs:
    1. Hypoglycemia
    2. Irritability
    3. Tremors
    4. Seizures
    5. Autonomic dysregulation, including temperature instability
    6. Blood pressure abnormalities:
        1. Hypotension
        2. Hypertension
    7. Excessive glucocorticoid release
    8. Altered behavioral state organization
7. Medical risks for women who drink alcohol (Bradley et al. 1998):
    1. Increased mortality and breast cancer in women who drink more than two drinks daily

2. Increased menstrual symptoms, hypertension, and stroke in women with higher levels of alcohol consumption
3. Increased infertility and spontaneous abortion in women who drink heavily
4. Adverse fetal effects after variable amounts of alcohol consumption, making any alcohol use during pregnancy potentially harmful

Diagnostic Investigations

1. Diagnosis of FAS based on clinical features in the setting of maternal alcohol use
2. Radiography for skeletal abnormalities
3. Neuroimaging in FASD (Norman et al. 2009):
    1. MRI imagings for CNS abnormalities:
        1. Overall reduction in brain volume
        2. CNS disorganization
        3. Wide range of structural abnormalities (Johnson et al. 1996):
            1. Corpus callosum agenesis/hypoplasia
            2. Cavum septi pellucidi and cavum vergae
            3. Ventriculomegaly
            4. Hypoplasia of inferior olivary eminences
            5. Small brain stem
            6. Micrencephaly
    2. Neuroimaging techniques:
        1. Regional increases in cortical thickness and gray matter volume
        2. Decreased volume and disorganization of white matter in individuals
    3. Functional imaging studies: functional and neurochemical differences in those prenatally exposed to alcohol
4. Echocardiography for cardiovascular anomalies
5. Ultrasound for renal abnormalities
6. Neurologic and neurobehavioral evaluations

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: high if the mother abuses alcohol during the pregnancy
    2. Patient's offspring: high if the affected woman abuses alcohol during her pregnancy
2. Prenatal diagnosis:
    1. Low maternal serum alpha-fetoprotein and low pregnancy-specific β_1-glycoprotein observed in one report possibly reflecting primary or secondary effects of ethanol abuse in pregnancy and possibly useful in predicting fetal alcohol syndrome (Halmesmäki et al. 1986)
    2. Prenatal ultrasound examination recommended for pregnant women who drink to detect fetal growth retardation and various birth defects associated with in utero alcohol exposure
3. Management (Thackray and Tifft 2001):
    1. Beneficial effects of early diagnosis of FAS on medical intervention of affected infants and children
    2. Management of issues (medical and surgical interventions) regarding specific birth defects.
    3. Implementation of resource programs for developmental delay, functional abilities, speech abilities, and social/behavioral interactions
    4. Appropriate interventions with educational evaluation and support and community resources such as the National Organization on Fetal Alcohol Syndrome (NOFAS)
    5. Evaluation and management of the siblings who also have FAS
    6. Prevention of alcohol-induced fetal brain damage (American Academy of Pediatrics Committee on Substance Abuse and Committee on Children with Disabilities 2000):
        1. Abstinence recommended for pregnant women and for those planning pregnancy since there is no known safe amount of alcohol consumption during pregnancy
        2. High-quality educational programs regarding the deleterious effects of alcohol on the unborn child
        3. High awareness of FAS and ARND and their prevention by health-care professionals

4. Appropriate support services including prevention of recurrence for parents and children diagnosed as having FAS or ARND

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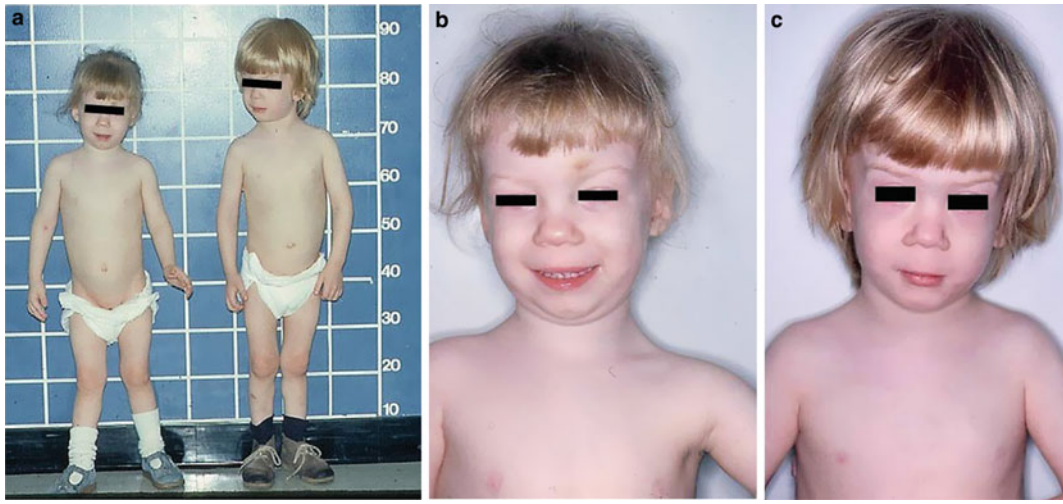

Fig. 1 (**a**–**c**) Two brothers (**a**) with fetal alcohol syndrome showing prenatal and postnatal growth deficiency and characteristic facial features (short palpebral fissures, flat nasal bridge, flat midface, smooth philtrum, and thin upper lip) (**b**, **c**)

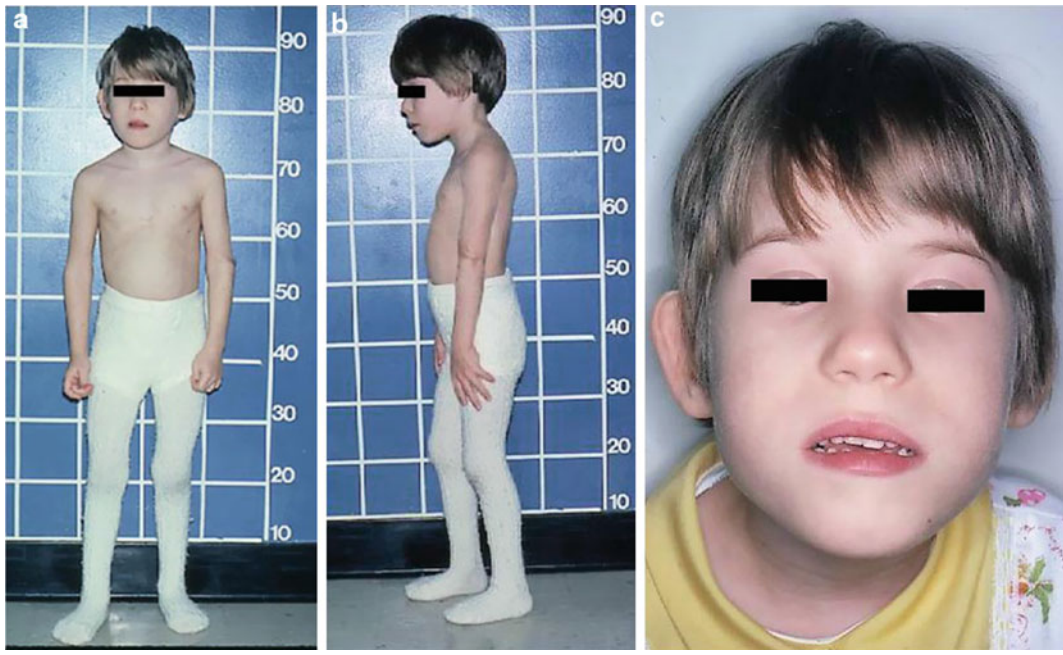

Fig. 2 (**a**–**c**) Another boy with fetal alcohol syndrome showing short stature (**a**, **b**) and similar characteristic facial appearance (**c**)

Fetal Hydantoin Syndrome

Contents

Fetal hydantoin syndrome is by far the best-characterized malformation complexes induced by anticonvulsant drugs used to treat maternal epilepsy.

Genetics/Basic Defects

1. Cause: maternal exposure to hydantoin anticonvulsant
2. Effect of prenatal exposure to hydantoin (Hanson et al. 1976; Buehler et al. 1994):
   1. Fetal hydantoin syndrome in 11% of cases
   2. Fetal hydantoin effect in an additional 31% of cases
3. Teratogenicity of hydantoin:
   1. Mediated not by the parent compound but by toxic intermediary metabolites that are produced during the biotransformation of the parent compound
   2. Epoxide (oxidative intermediates) – the primary teratogenic agent of phenytoin:
      1. Thought to occur before the formation of the dihydrodiol metabolite in a reaction catalyzed by the enzyme epoxide hydrolase
      2. Highly reactive and capable of covalently binding to embryonic or fetal nucleic acids, which at critical periods of embryogenesis are theoretically capable of disrupting normal development

Clinical Features

1. Eleven percent of infants exposed prenatally to hydantoin classified as having the fetal hydantoin syndrome
2. The presence of variable patterns of malformations (Bustamante and Stumpff 1978; Robinow 1984)
3. Classic features (Hanson 1986):
   1. Growth and development:
      1. Developmental delay
      2. Mild to moderate mental retardation
      3. Prenatal and postnatal growth deficiencies
      4. Microcephaly
   2. Craniofacial anomalies (Hanson and Smith 1975; Kousseff et al. 1981):
      1. Ridging of the metopic suture
      2. Broad and low nasal bridge
      3. Ocular defects (Hampton and Krepostman 1981):

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_92

1. Hypertelorism
2. Ptosis
3. Strabismus
4. Wide epicanthal folds
5. Congenital glaucoma
6. Retinoschisis
7. Nasolacrimal duct deformity and agenesis
8. Coloboma of the iris and choroid

4. Short upturned nose
5. Low-set abnormal ears
6. Wide mouth with prominent lips
7. Long philtrum
8. Wide alveolar ridges
9. Cleft lip and/or palate

3. Limb defects (Smith 1977; Sabry and Farag 1996):
   1. Hypoplasia of distal phalanges and nails (most characteristic feature) (Nagy 1981; Verdeguer et al. 1988)
   2. A finger-like thumb
   3. Hyperphalangism
   4. Adactyly/absent nails
   5. Acheiria (congenital absence of one or two hands)
   6. Positional limb defects:
      1. Calcaneovalgus deformity
      2. Pes cavus
   7. Abnormal palmar creases
4. Less frequently observed abnormalities:
   1. Neck webbing
   2. Low hairline
   3. Cardiovascular anomalies:
      1. Aortic coarctation
      2. Patent ductus arteriosus
      3. Septal defects
   4. Gastrointestinal abnormalities:
      1. Pyloric stenosis
      2. Duodenal atresia
   5. Renal defects
   6. Genital abnormalities in males:
      1. Hypospadias
      2. Bifid or shawl scrotum
   7. Hernias:
      1. Diaphragmatic hernia
      2. Umbilical hernia
      3. Inguinal hernias
   8. Other skeletal anomalies (Kogutt and Young 1984):
      1. Spinal anomalies:
         1. Scoliosis
         2. Segmentation defects of vertebral bodies
      2. Rib and sternal anomalies
      3. Hip dislocation
   9. Occasional tumor association:
      1. Neuroblastoma
      2. Melanotic neuroectodermal tumor of infancy
   10. Single umbilical artery

Diagnostic Investigations

1. Radiography for skeletal defects
2. Echocardiography for associated congenital heart defect
3. Renal ultrasound for renal defects
4. Developmental evaluation

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib: minimal in the absence of maternal exposure to hydantoin during pregnancy
   2. Patient's offspring: minimal in the absence of maternal exposure to hydantoin during pregnancy
2. Prenatal diagnosis: prenatal ultrasound examination recommended for pregnant women who take hydantoin anticonvulsant to detect fetal growth retardation and various birth defects associated with in utero hydantoin exposure
3. Prenatal risk prediction of fetal hydantoin syndrome (Buehler et al. 1993):
   1. Not recommending chorionic-villus sampling
   2. Not recommending the use of placental cultures

4. Management:
    1. Management of issues (medical and surgical interventions) regarding specific birth defects
    2. Implementation of resource programs for developmental delay, functional abilities, speech abilities, and social/behavioral interactions
    3. Appropriate interventions with educational evaluation and support
    4. Avoid hydantoin anticonvulsant during pregnancy

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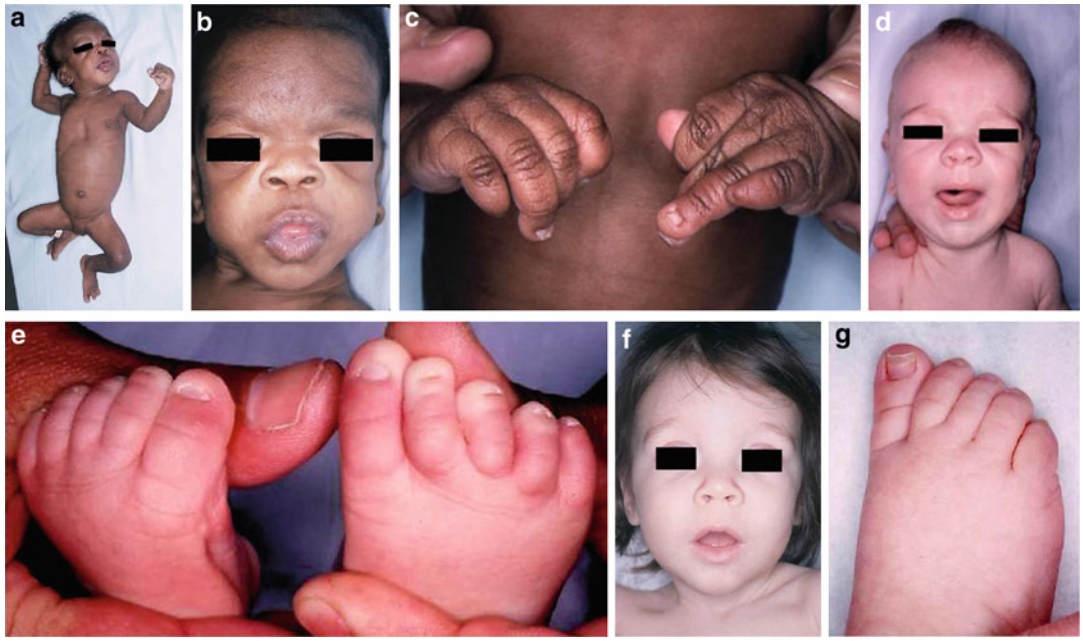

Fig. 1 (**a**–**g**) Three patients (**a**, **d**, **f**) with fetal hydantoin syndrome showing typical craniofacial features (ocular hypertelorism, flat nasal bridge, epicanthal folds, small upturned nose, wide mouth with prominent lips) (**b**, **d**, **f**) and nail hypoplasia (**c**, **e**, **g**)

Fibrodysplasia Ossificans Progressiva

Contents

Fibrodysplasia ossificans progressiva (FOP), an extremely rare and catastrophic genetic disorder of progressive heterotopic ossification, is the most disabling condition of extraskeletal ossification known to mankind. It is also known as myositis ossificans progressiva. The incidence of FOP was estimated to be approximately 1 in 1.64 million (Connor and Evans 1982b).

Synonyms and Related Disorders

Myositis ossificans progressiva

Genetics/Basic Defects

1. Inheritance
   1. Usually sporadic in occurrence: very few affected individuals have children because of the devastating nature of the disease
   2. Autosomal dominant inheritance (Connor et al. 1993; Kaplan et al. 1993; Pachajoa and Botero 2015; Pawar et al. 2015)
      1. Complete penetrance
      2. Variable expression
      3. FOP in two half sisters: evidence of maternal mosaicism (Janoff et al. 1996)
      4. Phenotypic and molecular heterogeneity in FOP (Virdi et al. 1999)
2. Cause (Shore et al. 2006)
   1. FOP is caused by a recurrent heterozygous mutation (c.617G>A; p.R206H) of codon 206 in the glycine-serine (GS) activation domain of activin receptor 1A (ACVR1)/activin-like kinase 2 (ALK2) (Herrera-Esparza et al. 2013), a highly conserved BMP (bone morphogenetic protein) type I receptor, in all sporadic and familial cases of classically affected individuals worldwide, making this one of the most highly specific disease-causing mutations in the human genome (Kaplan et al. 2007).
   2. Not all FOP cases are caused by the common mutation, as there are several FOP variants with varying phenotypes (Faruqi et al. 2014).
   3. Overexpression of a potent bone-inducing morphogen, bone morphogenetic protein 4 (BMP4), in lymphocytes is associated with the disabling ectopic osteogenesis of FOP (Shafritz et al. 1996).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Noggin gene (*NOG*) mutations in FOP (Lucotte et al. 1999; Sémonin et al. 2001).
5. Chromosomal locus for the *FOP* gene:
    1. 2q23-24 by genome-wide linkage analysis
    2. 4q27-31 (Feldman et al. 2000)
    3. 17q21-22 (Lucotte et al. 2000)

3. The presence of two skeletons in patients with FOP (Mahboubi et al. 2001)
    1. A normotopic bone formation during embryogenesis
        1. Grossly normal normotopic skeleton
        2. Exceptions
            1. Segmentation defects in the cervical spine
            2. Malformation of the great toes at birth due to shortening of the first metatarsal and proximal phalanx
            3. Monophalangic great toes due to synostosis: the earliest phenotypic feature of fibrodysplasia ossificans progressiva
    2. A heterotopic bone formation following birth
        1. Usually beginning in the first decade of life
        2. Progressing in characteristic anatomic patterns
        3. Typically involving the upper back and neck
        4. Heralded by large painful swellings of the highly vascular fibroproliferative tissue involving ligaments, tendons, and skeletal muscle, often following minor trauma
        5. Early swelling regresses spontaneously but often matures to true heterotopic bone
4. Pathogenesis
    1. p.R206H mutation in the *ACVR1* gene enhances ACVR1 activation and disrupts the highly conserved BMP signaling pathway (Groppe et al. 2007).
    2. When triggered by an inflammatory stimulus, some normal-functioning connective tissue may metamorphose into heterotopic bone (Kaplan et al. 2008).
5. Genotype-phenotype correlation (Hüning and Gillessen-Kaesbach 2014)
    1. Individuals with the "classical" p.R206H mutation have an early onset of ossifications (during childhood) that can be triggered by trauma. The course of the disease is usually severe and leads to immobility at early age.
    2. Also patients with the mutations p.G328W and p.G328E show early disease onset and severe progression, but the ossifications seem not to be influenced by trauma.
    3. Individuals with the mutation p.G356D seem to have later onset of the disease, which could, however, progress quickly.
    4. Also the mutations p.G328W and p.G328E are probably associated with early onset and severe disease course but do not seem to be triggered by trauma.
    5. Interestingly, the amino acid change p.G328R in the same codon seems to be associated with a mild disease course and late onset, but ossifications show a high correlation with injury or surgical intervention.
    6. The amino acid changes p.R258S, p.R375P, and p.L196P seem to be associated with a milder phenotype with less influence on life quality than in patients with other mutations.
6. Precipitating factors for ectopic ossification (Connor and Evans 1982c; Kocyigit et al. 2001)
    1. Biopsies of lumps
    2. Intramuscular injections
    3. Dental therapy
    4. Prolonged pressure on the body, such as tight clothing
    5. Aggressive physical therapy
    6. Falls
    7. Injuries to muscle
    8. Exacerbation of bone formation common in response to surgery and other tissue trauma

9. Operation to excise ectopic bone
10. Careless venipuncture

Clinical Features

1. Appears to be normal at birth except for telltale malformations of the great toes (Kaplan et al. 2005)
2. Extraskeletal abnormalities (100%) (Connor and Evans 1982c)
   1. Progressive widespread heterotopic ossification of muscles, tendons, ligaments, aponeurosis, and fascia. The heterotopic bony masses lead to progressive immobility/disability (100%).
   2. Onset: about 4 years of age in majority of patients (Rogers and Geho 1979).
   3. Typical course of lesional progression at any site (Mahboubi et al. 2001)
      1. Early lesions during the first few weeks: characterized by pain, erythema, swelling, warmth, and tenderness
      2. Intermediate lesions after several weeks
         1. Swelling beginning to subside
         2. Decrease in pain, tenderness, and erythema
      3. Late lesions after approximately 12 weeks
         1. Disappearance of swelling.
         2. A hard, non-tender lesion remains. It is roentgenographically a new area of heterotopic ossification.
   4. Characteristic anatomical progression of heterotopic bone formation (Cohen et al. 1993; Mahboubi et al. 2001)
      1. Typical earliest involvement: dorsal, axial, cranial, and proximal regions of the body.
      2. Later involvement: ventral, appendicular, caudal, and distal regions of the body.
      3. Painful swelling of muscle (myositis) leading to ossification began at mean age of 4.6 years (0–16 years) initially in the neck and upper spine and later around the hips, other major joints, and jaw (Smith 1998).
5. Proximal medial tibial osteochondromas (>90%)
6. Variation in size of soft tissue nodules involving the neck and back: often the first indication of heterotopic ossification in a child
7. Progressive ankylosis:
   1. Shoulder joints
   2. Elbow joints
   3. Hip joints
   4. Knee joints
   5. Neck (>90%): painful swelling or stiffness of the neck in most patients
   6. Spine:
      1. Leading to complete fusion
      2. Mimicking ankylosing spondylitis
      3. Pain and stiffness of the spine present in most patients
   7. Muscles of mastication – ankylosis of the temporomandibular joint by the progressively ossifying lesion (Cramer et al. 1981)
      1. Leading to limited mouth opening
      2. Inability to feed orally
      3. Poor oral hygiene
      4. Subsequent cachexia
8. Severe restrictive pulmonary disease (Kaplan and Glaser 2005)
   1. Causes
      1. Kyphoscoliosis of the thoracolumbar spine
      2. Ankylosis of costovertebral joints
      3. Ossification of the chest wall with resultant dependence on diaphragm for respiration
   2. Severely reduced lung volume
   3. Constrictive airway dysfunction developing over time
   4. Recurrent pulmonary infections secondary to ineffective cough: a common cause of death in the third or fourth decade
9. Eventual confinement to wheelchair

3. Congenital malformation (microdactylia) of the great toes (>95%) and thumbs (50%)
    1. Association with congenital great toe malformation – abnormal hallux, hallux valgus (Schroeder and Zasloff 1980; Cohen 2002)
        1. Mainly short big toes with single phalanx (a cartilaginous anlage of the first metatarsal and proximal phalanx) present at birth
        2. An important early diagnostic clue
    2. Shortened thumbs
    3. Clinodactyly of the fifth fingers
4. Other features
    1. Patients with FOP are prone to fractures with poor outcome.
    2. Occasional baldness.
    3. Conductive hearing loss (∼50%) secondary to calcification and fusion of the ligaments, tendons, and bones of the middle ear.
    4. Markedly reduced reproductive fitness.
    5. Life-threatening complications caused by thoracic insufficiency syndrome (95%) due to:
        1. Costovertebral malformations with orthotopic ankylosis of the costovertebral joints
        2. Ossification of intercostals muscles, paravertebral muscles, and aponeuroses
        3. Progressive spinal deformity
            1. Kyphoscoliosis
            2. Thoracic kyphosis
        4. Pneumonia
        5. Right-sided congestive heart failure
    6. Reduced life span but most patients survive to adulthood.
5. Natural history
    1. Mobility becomes more restricted as the disease advances.
    2. A life-long rigid immobility caused by the progressive metamorphosis of skeletal muscle and soft connective tissue into a second skeleton of heterotopic bone.
    3. Typically confined to bed or wheelchair by early 30s.
6. Diagnostic criteria (Kartal-Kaess et al. 2010)
    1. Major characteristics
        1. Congenital malformation of the great toes (earliest phenotypic feature)
        2. Progressive extraskeletal bone formation (episodic, begin during childhood)
        3. Heterozygous *ACVR1* mutation
    2. Other features
        1. Early stage lesions associated with soft tissue swellings and inflammation in characteristic anatomic patterns
        2. Predictable regional pattern of heterotopic ossification
        3. Cervical spine fusions
        4. Short/broad femoral necks
        5. Osteochondromas
        6. Conductive hearing loss
7. Differential diagnosis of heterotopic ossification (Blaszczyk et al. 2003; Kartal-Kaess et al. 2010)
    1. Progressive osseous heteroplasia (Shore and Kaplan 2005)
        1. Presence of cutaneous ossification
        2. Absence of congenital malformations of the skeleton
        3. Absence of inflammatory tumor-like swellings
        4. Asymmetric mosaic distribution of lesions
        5. Absence of predictable regional patterns of heterotopic ossification
        6. Presence of dominance of intramembranous rather than endochondral ossification
        7. Inherited only paternally
        8. Carries inactivating mutations of the *GNAS* gene, a gene that is regulated through genomic imprinting and allele-specific gene expression
    2. Post-traumatic: myositis ossificans circumscripta
    3. Neurogenic
        1. After head trauma or spinal cord injury
        2. After long coma
    4. Postsurgical: after total joint arthroplasties
    5. Reactive
        1. Bizarre parosteal osteochondromatous proliferation
        2. Florid reactive periostitis
        3. Subungual exostosis
    6. Neoplasms
        1. Sarcoma
        2. Malignant fibrous histiocytoma

7. Degenerative processes
8. Albright hereditary osteodystrophy

Diagnostic Investigations

1. Radiography (Bridges et al. 1994)
    1. Extraskeletal ossification
        1. Progressive widespread heterotopic ossification of muscles, tendons, ligaments, and fascia
        2. Ankylosis
            1. Shoulder joints
            2. Elbow joints
            3. Hip joints: prevent ability to ambulate
            4. Knee joints
            5. Muscles of mastication
        3. Osseous bridging between the axial and appendicular skeleton might be seen in advanced stages (Al-Salmi et al. 2014).
    2. Phalangeal abnormalities
        1. Characteristically affecting the great toes
            1. Shortened first digits
            2. Delta-shaped proximal phalanges
            3. Often monophalangism with the absence of the interphalangeal joint of the great toes
        2. Shortened thumbs
        3. Clinodactyly of the fifth fingers
    3. Less common congenital malformations
        1. Small vertebral bodies and enlarged pedicles in early childhood (Connor and Smith 1982)
        2. Variable degrees of vertebral fusion, especially apophyseal joint fusion in late childhood
        3. Short, broad femoral necks
        4. Ossification of ligamentous insertions producing exostoses of the proximal tibia
        5. Delay in skeletal maturation
        6. Enchondroma formation
        7. Association with synovial chondromatosis
    4. Skeletal changes in FOP are the consequences of soft tissue ossification and that the condition is not primarily bone dysplasia (Cremin et al. 1982).
2. Bone scintigraphy (radionuclide imaging) (Tulchinsky 2007; Pawar et al. 2015)
    1. A very sensitive technique for new bone formation in FOP
    2. Reveals multiple foci of increased uptake in connective tissue at characteristic locations (ligaments, tendons, muscles), in combination with pathognomonic microdactyly of the great toes (or thumbs): highly specific
3. CT scan
    1. Useful for diagnosis because CT scan is very sensitive for calcification
    2. Soft tissue swelling in the fascial planes and muscle in the early course of FOP
    3. Evidence of soft tissue calcification, typically in the form of shell seen within days to a few weeks
    4. Calcification appearing as spicules (Carter et al. 1989) in the soft tissue or in thin planes along the fascia often encircling muscle
    5. Able to delineate the presence or absence of bone destruction, differentiating FOP from invasive processes such as infection and tumor
4. MRI: a sensitive imaging technique for soft tissue abnormalities but not particularly useful for diagnosis.
5. Ultrasonography to demonstrate echogenic and shadowing mass.
6. Audiography: mixed-type hearing loss with prominent conductive component.
7. Histopathology (Mahboubi et al. 2001)
    1. Earliest finding: an intense perivascular lymphocytic infiltration
    2. Followed by death of skeletal muscle and replacement by a highly vascular fibroproliferative soft tissue, which rapidly progresses through an endochondral process to form heterotopic bone
8. Molecular genetic diagnosis – mutational screening of *ACVR1* gene
    1. Detection of a specific heterozygous mutation (c.617G>A; p.R206H) in the activin A type I receptor gene (*ACVR1*) in all classically affected individuals

2. Detection of a variant FOP phenotype (c.983G > A; p.G328E) (Carvalho et al. 2010)
3. Atypical fibrodysplasia ossificans progressiva diagnosed by whole exome sequencing (Liu et al. 2015)

9. Definitive genetic testing of FOP is now available and can confirm a diagnosis of FOP prior to the appearance of heterotopic ossification. Clinical suspicion of FOP early in life on the basis of malformed great toes can lead to early clinical diagnosis, confirmatory diagnostic genetic testing (if appropriate), and the avoidance of harmful diagnostic and treatment procedures (Pignolo et al. 2013).

Genetic Counseling

1. Recurrence risk (Delatycki and Rogers 1998)
   1. Patient's sib: not increased unless a parent is affected or has gonadal mosaicism (a low recurrence risk) (Janoff et al. 1996)
   2. Patient's offspring: 50%
2. Prenatal diagnosis
   1. Ultrasonography: bilateral hallux valgus on ultrasound, a clue for the first prenatal diagnosis of FOP. Genetic testing for FOP revealed that the fetus was heterozygote for the recurrent de novo mutation responsible for FOP in exon 6 of *ACVR1* gene – c.617G>A, p.Arg206His (Maftei et al. 2015).
   2. Possible by molecular genetic testing of the *ACVR1* gene on fetal DNA obtained from amniocentesis or CVS (chorionic villus sampling) for fetuses at 50% risk for FOP if a clinically diagnosed relative has an identified disease-causing *ACVR1* gene alteration.
3. Management (Kocyigit et al. 2001; Taslimi et al. 2015)
   1. No effective treatment available.
   2. Mainly focused in prophylactic approaches, symptomatic management, and optimization of function.
   3. FOP can often be recognized in children with or without previously affected family members at birth or in early years before the onset of heterotopic ossifications because of the presence of shortening of the great toe and short thumbs.
4. Early recognition allows protection of the child from injuries
   1. Avoid multiple biopsies, trauma, intramuscular injections, and dysfunctional IV catheters to prevent precipitating the heterotopic ossification and exacerbating the disease.
   2. Prevention of influenza-like illnesses.
   3. Minimal soft tissue trauma during routine dental care may precipitate permanent ankylosis of the jaw.
5. Alleviate pain during episodic flare-ups (Faruqi et al. 2014).
6. Should not be subjected to excessive stretching of the jaw in dental procedures, as well as injection of local anesthesia especially mandibular block.
7. Intramuscular injections should be avoided.
8. Vaccinations should be administered subcutaneously.
9. Venipuncture and IV administration of drugs pose minimal risk.
10. Prevention of falling and improving household safety are crucial.
11. Orotracheal intubation can traumatize the TMJ (temporomandibular joint) joints and result in disease flare-up. Instead, an awake fiber-optic nasotracheal intubation should be used by an expert anesthesiologist under light sedation.
12. Physical therapy in general not recommended as stretching of the soft tissues around a joint can lead to a painful flare-up.
13. Steroids, nonsteroid anti-inflammatory agents, disodium etidronate (Rogers and Geho 1979; Brantus and Meunier 1998), warfarin, and radiotherapy
    1. Used to halt the progression of disease
    2. Without proven benefit

14. Isotretinoin
    1. Principle based on its ability to inhibit differentiation of the mesenchymal tissue into the cartilage and bone
    2. Questionable benefit to decrease the incidence of heterotopic ossification at uninvolved anatomical sites
15. Etidronate (aminobisphosphonates) (Hall et al. 1979)
    1. Blocks ectopic calcification and is approved by Food and Drug Administration for treatment of postoperative heterotopic ossification.
    2. Short-term effect of bone metabolism shows diminished bone turnover rate.
    3. Long-term effect on ectopic calcification is unchanged in most cases with few exceptions.
16. Primary therapy for the debilitating disease – supportive care
    1. Active range-of-motion exercises encouraged if the movements are comfortable.
    2. Available adaptations or modifications prescribed to a disabled patient with FOP to achieve functional independence in the home and community (Levy et al. 1999)
        1. Shoes
        2. Canes
        3. Power wheelchairs
17. Avoid trauma
18. Surgery
    1. Nearly always contraindicated since new heterotopic ossification occurs at the operative site (Connor and Evans 1982a)
    2. Surgical removal of heterotopic bone
        1. Ineffective
        2. Leading to catastrophic exacerbation of the disease
    3. Existence of intercurrent problems occasionally requiring surgery
19. Anesthesia (Liu et al. 2014)
    1. Presenting numerous difficulties to the anesthesiologist including cervical spine ankylosis and restrictive pulmonary disease (thoracic insufficiency).
    2. Avoid tissue trauma in the form of local anesthetic injections.
    3. Presence of anatomical airway abnormalities.
    4. Alternative methods preferred.
        1. Nebulized lidocaine
        2. IV sedation
        3. Nasotracheal intubation
    5. Proper positioning and padding perioperatively
    6. Vigorous chest physiotherapy and pulmonary toilet postoperatively

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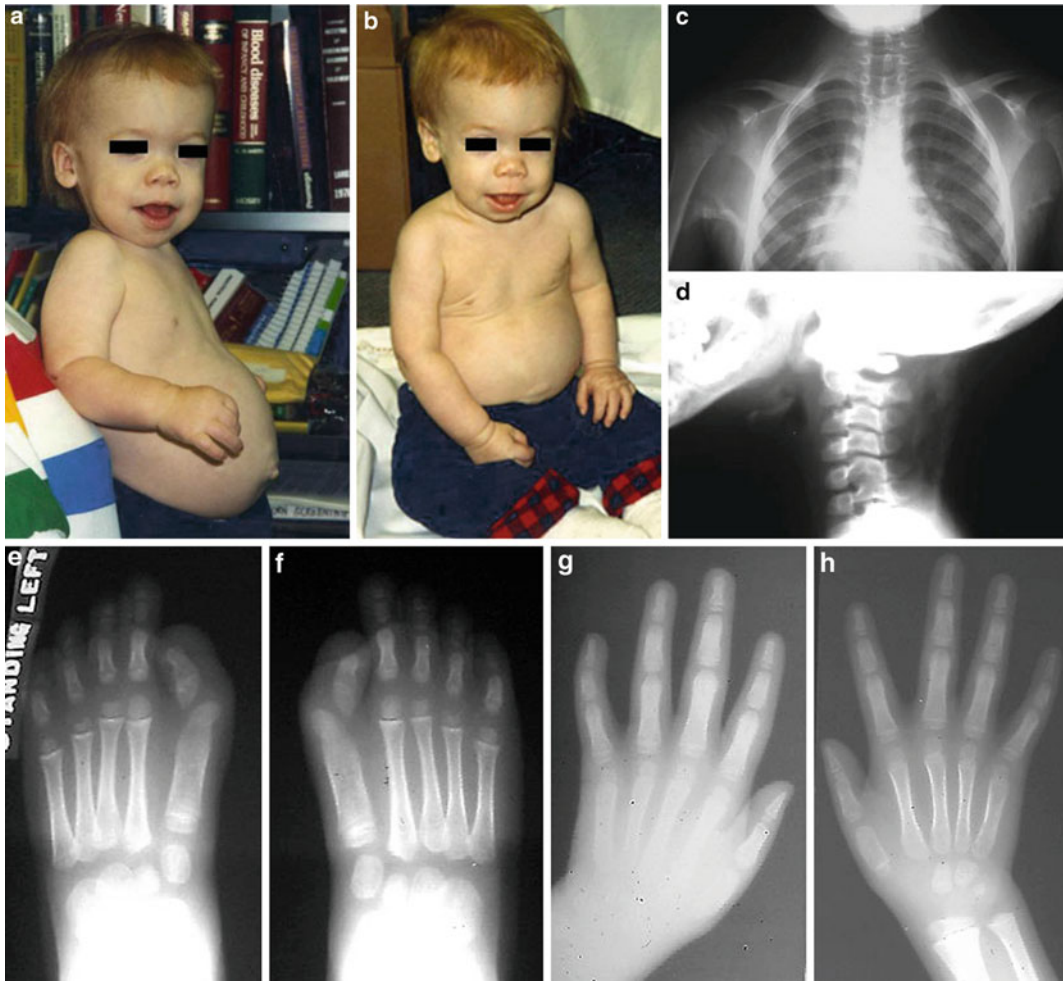

Fig. 1 (**a**–**h**) A boy (**a**, **b**) with fibrodysplasia ossificans progressiva showing a stiff neck, a narrow chest, and inability to raise arms upward due to ossification of the soft tissues on the back of the neck (**d**), the lateral chest wall, and the axillary region (**c**), illustrated by the neck, chest, and pelvic radiographs. The radiographs of both feet (**e**, **f**) showed shortened first toes and hallux valgus with delta-shaped proximal phalanges, monophalangism with the absence of the interphalangeal joint of the great toes. The radiographs of both hands (**g**, **h**) showed shortening of the first metacarpals and the middle phalanx of the fifth fingers with clinodactyly

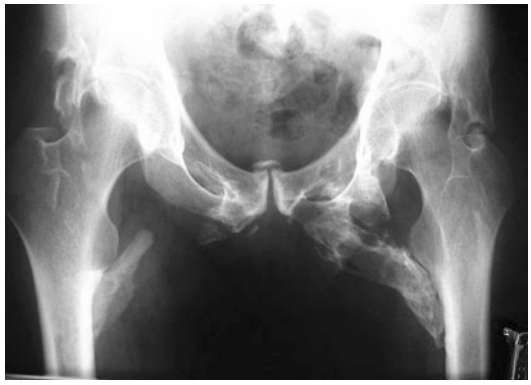

Fig. 2 A 14-year-old girl with fibrodysplasia ossificans progressiva was seen because of swelling and pain on the upper thigh, especially on the *left*. The pelvic radiograph showed extensive heterotopic calcifications on the inner upper thighs, worse on the *left*. Her father was also affected

Fibular Hemimelia

Contents

Fibular hemimelia is a rare congenital malformation of the lower limbs. It is also the most common congenital long bone deficiency and occurs more frequently than congenital anomalies of the radial, femoral, and tibial bones (Boakes et al. 1991). Fibular hemimelia syndrome includes a wide range of disorders, from an isolated shortening of the fibula up to its complete deficiency, with associated deformities of the foot, shin, and thigh (Oberc and Sulko 2013). The incidence is 7.4–20 per 1,000,000 live births (Rogala et al. 1974; Froster and Baird 1993).

Synonyms and Related Disorders

Cayler cardiofacial syndrome; Congenital fibular deficiency; Fibular hypoplasia or aplasia

Genetics/Basic Defects

1. Etiology:
   1. Most cases:
      1. Sporadic and isolated events
      2. Nonsyndromic
      3. Absence of positive family history
   2. Only 0.8% of 493 cases reviewed were associated with nonskeletal malformations, including two neural tube defects, one cardiac anomaly, and one renal anomaly (Lewin and Opitz 1986).
   3. Disruptions during the critical period of embryonic limb development (5–8 weeks of gestation) can result in a variety of limb deficiencies giving rise to varying degrees of fibular hypoplasia or aplasia.
   4. Vascular dysgenesis, viral infections, trauma, and environmental influences have been suggested as possible causes.
2. Vascular anomalies (absent peroneal artery detected by CT angiography) were observed in the dysplastic limb in three patients reported by Huda et al. (2014). These three patients with different presentations all have absent fibula and peroneal artery on the same extremity which suggests an association with a possible causal relationship. Most authors speculated that the absent fibula might be due to vascular insult in early embryogenesis during the 4–7

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weeks of gestation. Huda et al. speculate that the absent peroneal artery is secondary to absent fibular bud.

Clinical Features

1. Possible components of the complex malformation of fibular hemimelia (Birch et al. 2011) (Figs. 1–4):
    1. Femur:
        1. Shortening: the most common associated disorder (about 50 % of cases)
        2. Varus or valgus femoral neck
        3. Acetabular dysplasia
        4. External rotational deformity (retroversion)
        5. Hypoplastic lateral condyle
    2. Tibia: shortening
    3. Knee:
        1. Genu valgum
        2. Anterior cruciate ligament deficiency
        3. Anteroposterior instability of the knee
        4. Flexion contracture
    4. Ankle:
        1. Valgus deformity
        2. Ball-and-socket mortise
        3. Planar mortise
        4. Instability/dislocation
    5. Foot:
        1. Tarsal coalition
        2. Absent lateral rays
        3. Hypoplasia
        4. Equinovarus (clubfoot)
    6. Other associated anomalies:
        1. Scoliosis
        2. Roberts syndrome
        3. Upper extremity:
            1. Ulnar hemimelia
            2. Amelia
            3. Syndactyly
2. Classifications:
    1. Most classifications of congenital fibular deficiency are based primarily on the radiographic preservation of the fibula rather than on the overall clinical severity of the limb deficiency.
    2. Classification by Coventry and Johnson (1952): approximately 30 % of patients with bilateral involvement:
        1. Type I (hypoplastic fibula)
        2. Type II (rudimentary or absent fibula)
        3. Type III (bilateral fibular deficiency or the presence of "associated anomalies")
    3. Classification of fibular length deficiency by Achterman and Kalamchi (1979):
        1. Type I (minimal hypoplasia of the fibula)
        2. Type II (complete absence of the fibula)
    4. Classification of fibular aplasia by Courtens et al. (2005):
        1. Unilateral/bilateral
        2. Sporadic/familial
        3. Isolated versus syndromal
    5. Classification by Birch et al. (2011):
        1. Based on the clinical appearance of the foot and the extent of limb shortening as a percentage of the contralateral limb on radiographs
        2. Provides an opportunity to anticipate the extent of deformity at skeletal maturity and to estimate the scope of treatment necessary to reconstruct limb deformity
3. Differential diagnosis of fibular aplasia (Ekbote and Danda 2012):
    1. Autosomal dominant disorders:
        1. Fibular aplasia with ectrodactyly (Gieruszczak-Bialek et al. 2006)
        2. Fibular aplasia, tibial campomelia, and oligosyndactyly (FATCO) syndrome: proposed autosomal dominant inheritance and so far has an unknown molecular basis
        3. Reinhardt-Pfeiffer mesomelic dysplasia (mesomelic dwarfism of hypoplastic ulna and fibula type)
        4. Split hand/foot malformation with long bone deficiency I
    2. Autosomal recessive disorders:
        1. Absence of ulna and fibula with severe limb deficiency:
            1. Also called Al-Awadi/Raas-Rothschild syndrome, limb/pelvis-hypoplasia/aplasia syndrome, or Schinzel phocomelia syndrome

2. Caused by homozygous mutation in the *WNT7α* gene on chromosome 3p25
2. Fuhrmann syndrome (fibular aplasia or hypoplasia, femoral bowing, and poly-, syn-, and oligodactyly)
3. Congenital absence of the fibula and craniosynostosis
4. Femur-fibula-ulna syndrome
5. SC Roberts syndrome
3. Aneuploidy: del(21q) syndrome

Diagnostic Investigations

1. Skeletal Survey (Fig. 1b, 1c, 1d and Fig. 2)
2. 3D volume rendering reconstruction of the lower extremities (Fig. 3a and Fig. 4)
3. Computerized tomography angiogram of the lower extremities (Fig. 3b and 3c)

Genetic Counseling

1. Recurrence risk: depending on the etiology and the mode of inheritance:
   1. Patient's sib:
      1. Isolated: not increased
      2. Autosomal dominant inheritance: not increased unless a parent is affected
      3. Autosomal recessive inheritance: 25 %
   2. Patient's offspring:
      1. Isolated: unknown
      2. Autosomal dominant inheritance: 50 %
      3. Autosomal recessive inheritance: not increased unless the spouse is a carrier
2. Prenatal diagnosis:
   1. 2D ultrasonography:
      1. Isolated unilateral or bilateral complete fibular deficiency can be diagnosed antenatally (Abel et al. 2002).
      2. This condition may occur in the presence of other congenital anomalies.
      3. A comprehensive fetal anatomic survey, including examination of all long bones, is essential.
   2. 3- and 4-dimensional sonography to better image and characterize the defect (Monteagudo et al. 2006)
3. Management (Obec and Sulko 2013):
   1. The treatment should be individualized and based on the severity of the deformity.
   2. A multidisciplinary approach.
   3. Conservative management:
      1. Type IA
      2. Predicted shortening <2 cm at maturity
      3. Functional foot with more than three rays
   4. Operation approach:
      1. Elongation:
         1. Type IA or IB
         2. Functional foot with more than three rays
         3. Leg shortening <5 cm at birth
         4. Leg shortening <10 cm in the 9th year of life
      2. Epiphysiodesis:
         1. Leg shortening <5 cm in the 9th year of life
         2. Residual shortening after elongation
      3. Amputation:
         1. Type II with nonfunctional foot with < or = 3 rays
         2. Shortening >5 cm at birth
         3. Predicted shortening above 25 cm at maturity

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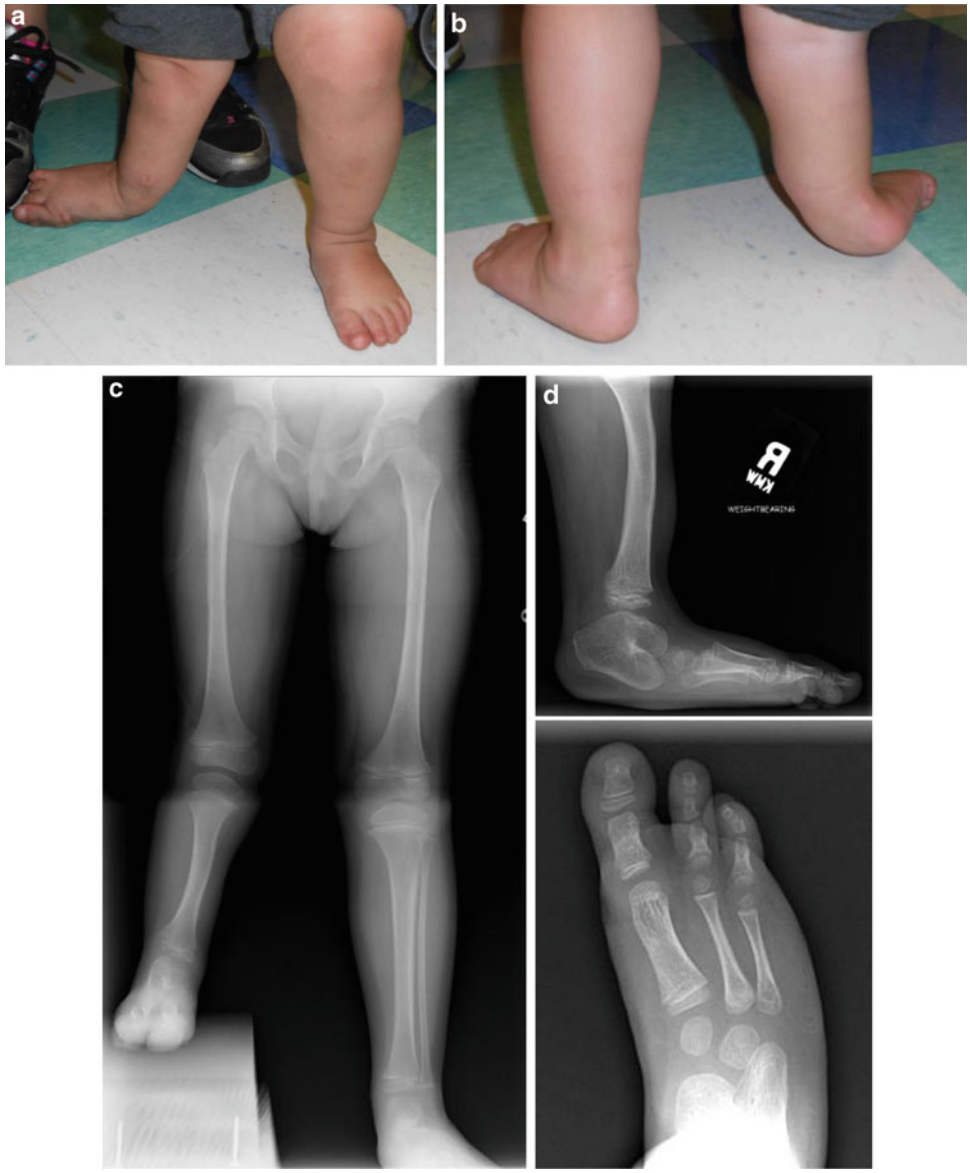

Fig. 1 (**a**–**d**) This 3-year-old girl was evaluated for short right lower leg (**a**, **b**). The AP view radiograph of both lower extremities showed absence of right fibula with shortened right tibia. In contrast the left lower extremity was normal (**c**). She has undergone realignment of her right tibia and her right foot in the past. Lateral view radiograph of the right lower leg and foot showed anterior bowing of the tibia and bone fusion of the talus and the calcaneus (**c**). AP view of the right foot showed three rays, a normal-looking first ray and two other rays consisting of metatarsals and phalanges (**d**). She was using an AFO on a regular basis and the foot position has been well maintained, according to the family. She walks well and is extremely active and not complaining of any discomfort. She has not had any recent medical or surgical problems (Courtesy of Dr. Grace Guo)

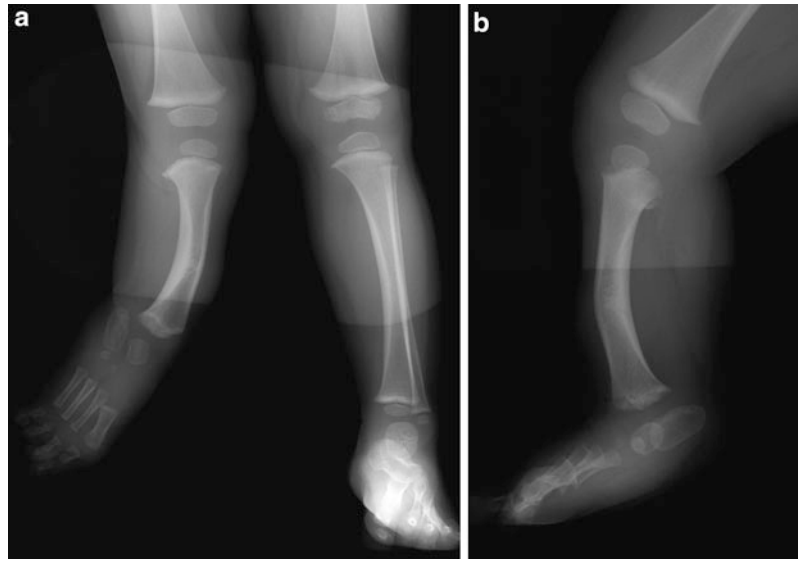

Fig. 2 (**a**, **b**) This 3-year-old male was evaluated for short right lower leg. He was born 5 days post-due date via spontaneous vaginal delivery to a 21-year-old gravida 3, para 2, AB 1 mother. He was noted to have a short leg consistent with fibular hemimelia shown on radiographs. There was absence of the right fibula. The tibia was foreshortened and broadened, with medial bowing. The right foot presented with four rays (**a**). Lateral imaging of the right lower leg showed anterior bowing of the tibia with flatfoot deformity of the foot (**b**). There was parallelism of the talus and calcaneus. Fibular hemimelia was seen on prenatal ultrasounds. After birth, he did well and went home the next day with mom. He weighed seven pounds two ounces at birth. He was lost to follow-up (Courtesy of Dr. Grace Guo)

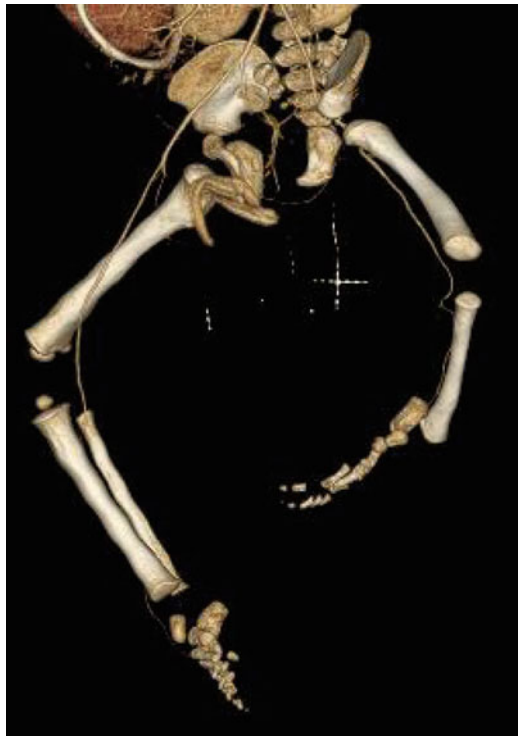

Fig. 3 The baby girl was born at 37 weeks of gestation via elective cesarean section. Prenatal ultrasounds showed lumbosacral meningocele and hydrocephalus. FISH analysis of the amniotic fluid was unremarkable. At birth, multiple abnormalities were noted including a lumbosacral meningomyelocele, length discrepancy of the lower extremities, and bilateral clubbing of the feet. Cranial ultrasound showed dilatation of lateral and third ventricles. Renal ultrasound demonstrated bilateral hydronephrosis. Frontal skeletal radiograph showed limb length discrepancy, absent left fibula, deformed bowed distal tibiae, and bilateral club feet. 3D reconstruction of both lower extremities demonstrated absence of the left fibula with shortened, hypoplastic left femur and tibia (shown here). Diffuse muscular atrophy was present in the soft tissue algorithm. Axial CT angiography of the left lower extremity revealed three vessels on the right, namely, the peroneal artery and anterior and posterior tibial arteries, but only two vessels on the left side, namely, the anterior and posterior tibial arteries with absence of peroneal artery (not shown). Curve maximum intensity projection (MIP) reconstruction of the left leg demonstrated patent anterior and posterior tibialis arteries (not shown). The peroneal artery is absent. She was discharged home at 2 weeks of age with follow-up by her pediatrician and orthopedic surgeon (Huda et al. Hemimelia and absence of the peroneal artery. Journal of Perinatology) (Courtesy of Dr. Hassan Ibrahim)

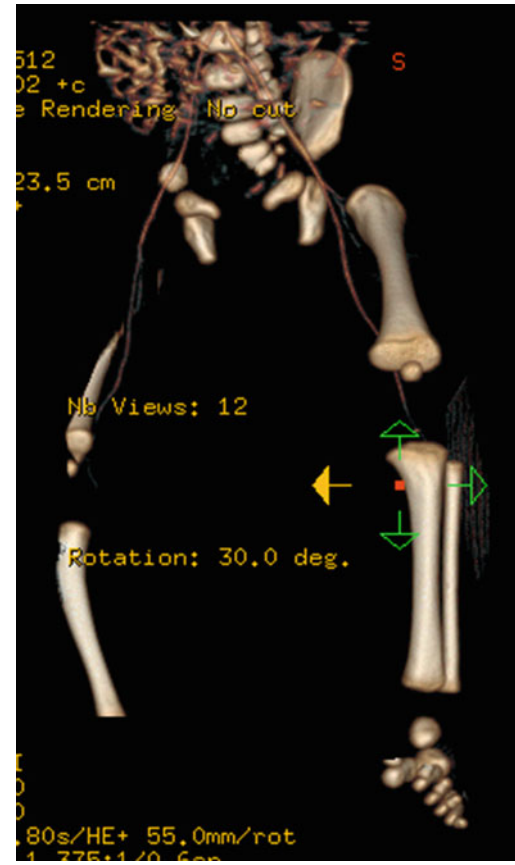

Fig. 4 This female newborn was delivered at 34 weeks of gestation via cesarean section complicated by polyhydramnios. Amniocentesis showed 46, XX. The face was asymmetric during crying. Echocardiogram showed a subaortic perimembranous ventricular septal defect (VSD). The baby was noted to have shorter right leg, absent right foot, absent thumb, and clinodactyly with a longer 4th finger. Skeletal survey showed a hypoplastic right first rib, partial fusion of the right radius and ulna, a shorter right radius, and also the absent right thumb with a corresponding absence of the first metacarpal bone. Frontal skeletal radiograph showed a congenital anomaly of the right lower extremity with unilateral fibula and foot agenesis. Soft tissue atrophy/hypoplasia of the leg is also seen. The figure here showed frontal 3D volume rendering reconstruction of both lower extremities demonstrating absence of the right fibula and foot. A computerized tomography angiogram of the lower extremities revealed normal popliteal arteries on both sides with an absent peroneal artery on the right side (not shown). She received prosthesis for the right lower extremity subsequently. The combination of absent depressor anguli oris along with the VSD prompted consideration of the possibility of Cayler cardiofacial syndrome in this patient (Courtesy of Dr. Hassan Ibrahim)

Finlay-Marks Syndrome

Contents

In *1978*, Finlay and Marks described the association of scalp defect, malformed ears, and the absence of nipples in a family. The association is also known as scalp-ear-nipple syndrome.

Synonyms and Related Disorders

Scalp-ear-nipple syndrome

Genetics/Basic Defects

1. Inheritance
   1. Autosomal dominant in most reports (Marneros et al. 2013)
   2. Severe autosomal recessive form: two children from an inbred Arab family with features suggestive of scalp-ear-nipple syndrome (Al-Gazali et al. 2007)
   3. Possible autosomal recessive form in an consanguineous family with three affected siblings with a propositus having excess of soft tissue on the nasofrontal region, widely spaced teeth, cupped protruding ears, and absent nipples (Morales-Peralta et al. 2014). Also a report of two affected siblings born to non-affected parents (Naik et al. 2012)
2. Lymphoid enhancer factor-1 (*Lef-1*), mapped to chromosome 4q23-q25 (Milatovich et al. 1991): identified as a candidate gene for scalp-ear-nipple syndrome (van Steensel et al. 1999)
   1. *Lef-1*: an HMG-domain DNA-binding protein expressed in the neural crest, mesencephalon, tooth germs, and other sites during embryogenesis.
   2. Homozygous deficiency of this gene causing postnatal lethality in mice.
   3. Mutant mice lacking teeth, mammary glands, whiskers, and hair.
   4. Lack of hair, missing teeth, and aplasia of breast tissue suggest that *Lef-1* may be a candidate gene for scalp-ear-nipple syndrome.
3. Mutations in KCTD1 cause scalp-ear-nipple syndrome (Marneros et al. 2013)

Clinical Features

1. Scalp abnormalities (Aase and Wilroy 1988; Le Merrer et al. 1991; Edwards et al. 1994; Plessis et al. 1997; Picard et al. 1999; Taniai et al. 2004)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Raised firm nodules over the scalp in the occipital region, not covered by hairs
2. The areas: raw at birth and heal during childhood
3. Crumpled scalp over occipital region

2. External ear abnormalities
   1. Hypoplastic tragus, antitragus, and lobule
   2. Over-folding of the superior helix
   3. Flattening of the antihelix
3. Athelia (absent breasts and nipples)
   1. Rudimentary or absent nipples (Tawil and Najjar 1968)
   2. Breast hypoplasia or aplasia
   3. Can be part of syndromes including other congenital or ectodermal anomalies, such as limb-mammary syndrome or ectodermal dysplasias (Borck et al. 2014)
4. Other reported features
   1. Ectodermal dysplasia features
      1. Dental anomalies
         1. Widely spaced teeth
         2. Missing secondary teeth
         3. Neonatal teeth (Berman and Silverstone 1975)
      2. Reduction of axillary apocrine secretion and axillary hair growth
      3. Hypohidrosis
      4. Nail dysplasia
   2. Aplasia cutis vertices
   3. Renal hypoplasia
   4. Hypospadias
   5. Pyeloureteral duplication
   6. Cataract
   7. Coloboma of the iris (de Macena Sobreira et al. 2006)
   8. Hypertension
   9. Diabetes mellitus
   10. Partial syndactyly
5. Hypotonia and developmental delay in severe autosomal recessive form

Diagnostic Investigations

1. No specific laboratory tests available
2. Histology of scalp defect resembling aplasia cutis congenita (Finlay and Marks 1978)
   1. An excess of normal-appearing connective tissue
   2. Lack pilosebaceous elements
3. Renal sonography for renal hypoplasia
4. Diagnosis primarily by clinical features

Genetic Counseling

1. Recurrence risk
   1. Autosomal dominant
      1. Patient's sib: low unless a parent is affected.
      2. Patient's offspring: 50%
   2. Autosomal recessive
      1. Patient's sib: 25%
      2. Patient's offspring: not increased unless the spouse is a carrier.
2. Prenatal diagnosis: not been reported
3. Management: primarily supportive

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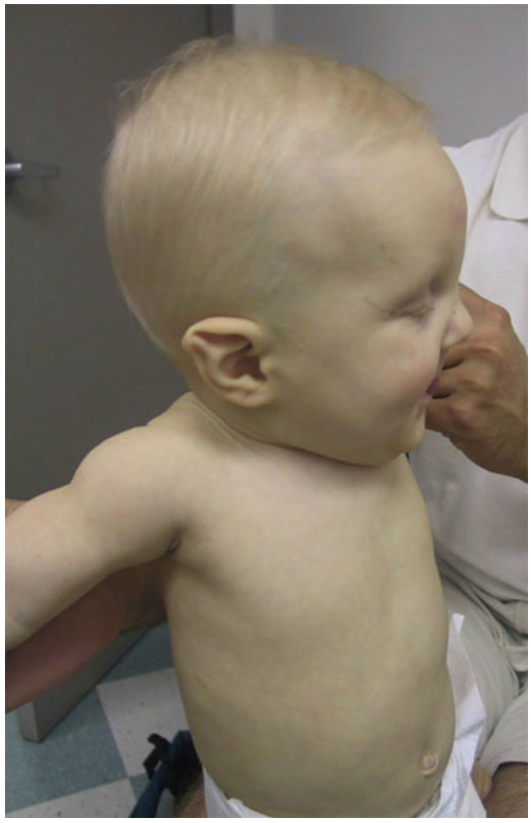

Fig. 1 A 7-month-old boy with Finlay-Marks syndrome showing absence of nipples and abnormal ears. He also had scanty eyebrows and eyelashes, neonatal teeth, which were extracted, nasolacrimal duct stenosis, and lumpy scalp on the occiput region

Floppy Infant

Contents

A floppy infant is an infant with poor muscle tone affecting the limbs, trunk, and the craniofacial musculature. The causes are numerous (heterogeneous etiologies) and the work-up in many instances can be complex. The task of evaluating infants with hypotonia is difficult and complex.

Synonyms and Related Disorders

Congenital hypotonia

Genetics/Basic Defects

1. Heterogeneous causes of hypotonia (Stiefel 1996; Richer et al. 2001; Johnston 2003; Prasad and Prasad 2003, 2011; Igarash 2004)
    1. Chromosome disorders: central hypotonia
        1. Aneuploidy: Down syndrome (one of the most frequently encountered cause of neonatal hypotonia)
        2. Microdeletions: Prader-Willi syndrome (neonatal hypotonia, feeding problems, and failure to thrive with later onset of hyperphagia and obesity)
        3. Subtelomeric cryptic deletions (relatively new category of disorders that account for unexplained mental retardation): terminal 22q13.3 deletion syndrome (neonatal hypotonia can be a prominent feature)
2. CNS malformations/encephalopathies (associated with profound neonatal hypotonia)
    1. Congenital CNS malformations
        1. Lissencephaly
        2. Holoprosencephaly
    2. Acquired CNS disorders
        1. Birth trauma
        2. Hypoxic-ischemic encephalopathy
        3. Spinal cord injury
3. Disorders affecting anterior horn cells and peripheral nerves
    1. Spinal muscular atrophy (SMA1) (Werdnig-Hoffman disease): generalized weakness, often spares the diaphragm, facial muscles, pelvis, and sphincters
    2. Charcot-Marie-Tooth disease
        1. CMT1A
        2. CMT4E (congenital hypomyelination syndrome)
        3. Dejerine-Sottas syndrome (CMT3)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Neuromuscular junction disorders
    1. Transient myasthenic syndrome.
    2. Hypermagnesemia of the newborn.
    3. Infantile botulism.
    4. Congenital myasthenic syndromes (neuromuscular junction disorders): bulbar oculomotor muscles exhibit greater degree of involvement (neonatal hypotonia, easy fatigability, recurrent aspiration, feeding difficulty, cyanosis, and apnea).
        1. Congenital myasthenic with episodic apnea
        2. Slow-channel and fast-channel syndromes
        3. Endplate cholinesterase deficiency
5. Congenital muscular dystrophies (CMD) (Brown et al. 2006) and myopathies: hypoactive reflexes. For example:
    1. Classical congenital muscular dystrophy
    2. Fukuyama muscular dystrophy
    3. Walker-Warburg syndrome
    4. Muscle-eye-brain disease
    5. Ullrich congenital muscular dystrophy
    6. Bethlem myopathy
    7. Rigid spine-muscular dystrophy (SEPN1 selenoprotein deficiency)
    8. Congenital myotonic dystrophy
        1. Triplet repeat CTG expansion of the *DMPK* and *SIX5* genes
        2. Abnormal splicing of chloride channels mRNA leading to the myotonia
6. Congenital myopathies (Taratuto 2002): prominent weakness. For example:
    1. Central core myopathy
    2. Nemaline myopathy
    3. Myotubular (centronuclear) myopathy
    4. Multicore myopathy
    5. Congenital myopathy with fiber-type disproportion
7. Metabolic disorders/myopathies: proximal musculature weakness. For example:
    1. Acid maltase deficiency (Pompe disease) (Howell et al. 2006)
    2. Pyruvate dehydrogenase complex deficiency
    3. Pyruvate carboxylase deficiency
    4. Respiratory chain defects (mitochondrial disorder)
    5. Zellweger syndrome
    6. Smith-Lemli-Opitz syndrome
    7. Congenital disorders of glycosylation
    8. Phosphomannomutase-2 deficiency
8. Combined CNS and motor unit disorder
    1. Metachromatic leukodystrophy
    2. Giant axonal neuropathy
    3. Familial dysautonomia
    4. Mitochondrial encephalopathy
    5. Congenital muscular dystrophies
9. Congenital hypotonia with a favorable outcome (benign congenital hypotonia): characterized by an early neonatal onset and a benign clinical course, no longer considered as a specific diagnostic entity
10. Acute and systemic diseases especially in the newborn period
    1. Sepsis
    2. Congestive heart failure
11. Chronic
    1. Hypothyroidism
    2. Connective tissue disorder

2. Localization of hypotonia in the floppy infant (Bodensteiner 2008)
    1. Supraspinal/suprasegmental hypotonia in which deep tendon reflexes are preserved:
        1. Central hypotonia caused by brain lesions
            1. Sepsis
            2. Congenital heart failure
            3. Hypoxic-ischemic encephalopathy
        2. Syndromic central hypotonia caused by brainstem lesions (extensive list of etiologic possibilities associated with constellation of dysmorphic features)

3. Nonsyndromic central hypotonia
    1. Cerebral dysgenesis (developmental anomalies of the brain).
    2. Grossly normal brain by MRI includes myelination within normal range, normal development (essential hypotonia), delayed myelination, motor delay only (usually catch up to peers in tone and development by school age), developmental delay (may later be diagnosed as nonsyndromic mental retardation, frequently labeled as autistic), or global developmental delay (usually do not catch up intellectually and cognitively to peer by school age).
4. Central hypotonia caused by craniocervical junction lesions
    1. Spinal cord injury (critically ill infant with severe hypotonia at first and the nature of the injury is not usually suspected until the development of the hyperactive reflexes and the lack of the expected maturation of the corticospinal tract influences on the motor unit).
    2. Chiari I malformation (may be an isolated finding that may cause hypotonia early on by compression of the lower brainstem at the level of the foramen magnum).
    3. Chiari II malformation (usually associated with spina bifida and easily suspected).

2. Segmental or motor unit hypotonia in which deep tendon reflexes are depressed or lost
    1. Anterior horn cell (spinal muscular atrophy)
    2. Peripheral nerve (hereditary motor sensory neuropathy)
    3. Neuromuscular junction
        1. Myasthenia gravis
        2. Congenital myasthenic syndromes
        3. Botulism
    4. Muscle
        1. Congenital myopathies
        2. Metabolic myopathies
        3. Neonatal presentation of muscular dystrophy

Clinical Features

1. Hypotonia (decreased or loss of muscle tone)
    1. Full abduction and external rotation of the legs.
    2. Flaccid extension of the arms.
    3. Prominent head lag on pull to sit (normally diminished or absent by about 2 months of age): “Pull to sit” maneuver tests axial tone of the neck and back and appendicular tone of the shoulder and arms and also tests strength to some extent. Normal response from the infant being tested is to resist the pull on the arms and shoulder.
    4. Scarf sign: Produced by grasping the supine infant’s hand and pulling it across the chest and bring the baby’s elbow well beyond the baby’s chin and the midline of the chest before encountering the resistance. The maneuver tests the appendicular tone in the shoulder and is somewhat sensitive to the gestational age of the infant, the degree of laxity of the ligaments, and the state of alertness of the child.
    5. Shoulder suspension test: Produced by picking the infant up holding under the infant’s arms and observe the tendency of the hypotonic infant to slip through the examiner’s hands. The maneuver tests the appendicular tone but also gives some indication of head control (axial) as well as strength.
    6. Ventral suspension test: Produced by lifting off the infant from the table by examiner’s one hand under the infant’s chest and abdomen and observe the

hypotonic infant unable to lift the head above the horizontal plane and unable to flex the arms and legs.

2. Central hypotonia (disorders of central nervous system that cause decreased tone by interrupting pathways involved in the modulation) with following general characteristics:
    1. Hypotonia
    2. Obtundation
    3. Neonatal seizures
    4. Hyperactive deep tendon reflexes
    5. Neonatal encephalopathy
    6. Clinical or neuroimaging evidence for hypoxia-ischemia
3. Peripheral hypotonia (disorders of the motor unit)
    1. General characteristics.
        1. Hypotonia (absence of features of central hypotonia)
        2. Areflexia or diminished reflexes
        3. Convincing weakness
        4. Decreased antigravity limb movements
        5. Weak cry
        6. Weak suck
        7. Fasciculations
        8. External ophthalmoplegia
        9. Alert look
        10. Arthrogryposis
    2. Anterior horn cell disease.
        1. SMA: the most common serious cause of hypotonia in the infant and child
        2. Very few conditions other than SMA that would result in widespread denervation on EMG in the clinical setting of hypotonia and weakness in infancy
        3. Muscle biopsy no longer necessary to make the diagnosis of SMA in the clinical situation
    3. Peripheral nerve diseases, such as CMT, rarely cause hypotonia in infancy.
    4. Neuromuscular junction disease.
        1. Not a common cause of hypotonia in infancy
        2. The only category of motor unit disease in which the reflexes may be preserved
    3. Neonatal myasthenia gravis
        1. Uncommon cause of hypotonia in infancy in recent years
        2. Caused by antibodies to the acetylcholine receptor (AchR) which are passively transferred to the infant by the mother who has autoimmune myasthenia gravis
    4. Congenital myasthenic syndromes
        1. Much more common cause of hypotonia in infancy.
        2. Caused by genetic defects of neuromuscular transmission resulting in a decrease in the safety margin in neuromuscular transmission.
        3. Manifest clinically by easy fatigability and weakness to variable degree depending on the severity of the defect in transmission.
        4. Diagnosis based on fatigue with exercise.
        5. Affected infants may be very sensitive to neuromuscular blocking agents and may respond to AchE antagonists.
    5. Selected congenital myasthenic syndromes
        1. AchR deficiency: early onset, variable severity, ptosis, extraocular palsy, and involvement of the bulbar, arm, and legs.
        2. Slow-channel syndrome: selective severe weakness of the neck, wrist, and finger extensor, variable onset and severity, and common, often progressive ventilatory problems.
        3. Fast-channel syndrome: variable onset and severity and may respond to AchE inhibitors.
        4. Endplate rapsyn deficiency: early onset with hypotonia, respiratory failure, apnea, and arthrogryposis.
        5. Congenital myasthenia syndrome with episodic apnea: early respiratory failure, episodic apnea, improvement with age, and may respond to AchE inhibitors.
        6. Endplate acetylcholinesterase deficiency: ophthalmoparesis, severe

axial musculature weakness, slow papillary responses.

5. Abnormalities of muscle structure or function
    1. A major cause of motor unit hypotonia, second only to SMA in overall frequency
    2. Congenital myopathies
        1. More likely than Duchenne muscular dystrophy as a cause of hypotonia in the first year.
        2. Comprised of a group of muscle diseases that typically only slowly progressive over time, although present at birth with variable severity.
        3. Classical congenital myopathies (central core disease, nemaline myopathy, centronuclear myopathy) (Riggs et al. 2003).
        4. Other well-established congenital myopathies (multicore, congenital myopathy with fiber-type disproportion (CFTD), reducing body, fingerprint, cytoplasmic body).
        5. Congenital muscular dystrophies (CMD): CMD is an important subgroup of congenital myopathies. The conditions are usually present at birth, often quite severe with muscle weakness, wasting, respiratory difficulty, and contractures, with variable involvement of the brain, eyes, and other tissues. Muscle biopsies show dystrophic muscle with muscle fiber necrosis and regeneration with replacement of muscle with fibrous and fatty connective tissue. The CMD is typically subdivided into two categories: those with brain involvement (syndromic CMD, comprised of merosin-deficient CMD, CMD with partial merosin deficiency, CMD 1C, CMD with ITGA7 mutations, CMD with spine rigidity) and those without brain involvement (nonsyndromic CMD, comprised of Fukuyama CMD, muscle-eye-brain disease, Walker-Warburg syndrome 2, congenital muscular dystrophy).
    3. Central core disease
        1. Variable presentation
        2. Somatic abnormalities
        3. Characteristic malignant hyperthermia
        4. Occasional cardiomyopathy
    4. Nemaline myopathy
        1. Variable presentation
        2. Somatic abnormalities (infantile)
        3. Muscle wasting
        4. Ocular muscle weakness
        5. Adult onset of pain/cramp
        6. Rare cardiomyopathy
    5. Centronuclear (myotubular) myopathy
        1. Variable presentation
        2. Somatic abnormalities (infantile)
        3. Muscle wasting
        4. Ocular muscle weakness with ptosis
    6. Multicore myopathy
        1. Mild early presentation
        2. Somatic abnormalities
        3. Ocular muscle weakness with ptosis
        4. Malignant hyperthermia reported
        5. Cardiomyopathy reported
    7. Congenital myopathy with fiber-type disproportion (CFTD)
        1. Variable presentation
        2. Muscle wasting
        3. Somatic abnormalities
        4. Stiffness
        5. Mental retardation
    8. Reducing body myopathy (X-linked)
        1. Variable presentation
        2. Somatic abnormalities
        3. Ocular muscle weakness with ptosis
        4. Cardiomyopathy reported
    9. Fingerprint body myopathy
        1. Mild early presentation
        2. Muscle wasting
        3. Somatic abnormalities
        4. Mental retardation

10. Cytoplasmic inclusion body myopathy
    1. Early, moderate to severe onset
    2. Somatic abnormalities
    3. Cardiomyopathy
11. Merosin-deficient DMD
    1. Severe manifestation
    2. Hypotonia
    3. Global weakness
    4. Contractures
    5. Scoliosis
    6. Inability to walk
    7. Normal intelligence
    8. Abnormal white matter signal (MRI)
12. CMD with partial merosin deficiency
    1. Milder manifestation
    2. Ability to walk in most cases
    3. Cardiomyopathy
    4. Contractures of elbow, knees, and fingers
    5. Normal intelligence
    6. Normal MRI of the brain
13. CMD type 1C
    1. Severe weakness
    2. Global involvement
    3. Contractures of elbow, knees, fingers
    4. Cardiomyopathy
    5. Normal intelligence
    6. Normal MRI of the brain
14. CMD with *ITGA7* mutation
    1. Proximal muscle weakness
    2. Torticolis
    3. Congenital hip dislocation
15. CMD with spine rigidity
    1. Rigid spine, elbows, hips, and ankles
    2. Progressive sleep hypoventilation
16. Ullrich CMD
    1. Global weakness with contractures
    2. Distal hyperextensibility
    3. Calf atrophy
    4. Normal intelligence
17. Fukuyama CMD
    1. Severe generalized weakness
    2. Contractures
    3. Cobblestone lissencephaly
18. Muscle-eye-brain disease
    1. Mild presentation early (ability to walk in some cases but lose walking by age 20)
    2. Eye malformations (without cataracts)
    3. Hydrocephalus
    4. White matter abnormality (MRI)
    5. Cobblestone lissencephaly
19. Walker-Warburg syndrome
    1. Severe generalized weakness
    2. Contractures at elbows only
    3. Lissencephaly
    4. Dandy-Walker malformation or cerebellar hypoplasia and flat pons (MRI)
    5. Early demise
20. CMD 1D
    1. Global delay
    2. Proximal weakness greater than distal weakness
    3. Muscle hypertrophy
    4. Facial sparing
    5. White matter changes (MRI)

4. Differentiating congenital hypotonia of central versus peripheral origin (Harris 2008)
    1. Weakness
        1. Central: mild to moderate
        2. Peripheral: significant (“paralytic”)
    2. Deep tendon reflexes
        1. Central: decreased or increased
        2. Peripheral: absent
    3. Placing reactions
        1. Central: sluggish or slow
        2. Peripheral: absent
    4. Motor delays
        1. Central: present
        2. Peripheral: present
    5. Antigravity movements in prone and supine
        1. Central: some but less than a typical infant
        2. Peripheral: often absent
    6. Pull to sit
        1. Central: some head lag (more so than typical infant)
        2. Peripheral: marked head lag

7. Cognition/affect
    1. Central: delayed
    2. Peripheral: typical
8. Ability to "build up" tone, e.g., tapping under knees with infant in supine to assist them in holding hips in adduction
    1. Central: present
    2. Peripheral: absent

5. Pattern of muscle weakness and localization in the floppy infant (Prasad and Prasad 2003)
    1. Central nervous system
        1. Corresponding disorders
            1. Chromosome disorders
            2. Inborn errors of metabolism
            3. Cerebral dysgenesis
            4. Cerebral/spinal cord trauma
        2. Pattern of weakness and involvement
            1. Central hypotonia
            2. More prominent axial weakness
            3. Hyperactive reflexes
    2. Motor neuron
        1. Corresponding disorders (SMA)
        2. Pattern of weakness and involvement (generalized weakness, often sparing diaphragm, facial muscles, pelvis, and sphincters)
    3. Nerve
        1. Corresponding disorders: peripheral neuropathies
        2. Pattern of weakness and involvement (weakness with wasting involving distal muscle)
    4. Neuromuscular junction
        1. Corresponding disorders
            1. Myasthenia syndrome
            2. Infantile botulism
        2. Pattern of weakness and involvement (weakness with greater involvement of bulbar and oculomotor muscles)
    5. Muscle
        1. Corresponding disorders
            1. Congenital myopathies
            2. Metabolic myopathies
            3. CMD
            4. Congenital myotonic dystrophy
        2. Pattern of weakness and involvement
            1. Prominent weakness
            2. Proximal musculature
            3. Hypoactive reflexes
            4. Joint contractures
6. Congenital hypotonia with a favorable outcome (benign congenital hypotonia) (Shuper et al. 1987; Parush et al. 1998; Carboni et al. 2002)
    1. No longer considered as a specific diagnostic entity
    2. The term applied to a group of patients in whom a specific diagnosis cannot be made despite best effort in work-up
    3. Common features
        1. Generalized hypotonia since birth
        2. Mild delayed or normal developmental milestones
        3. Active movement with preserved reflexes
        4. Significant joint laxity or hypermobility
        5. Normal investigations (muscle enzymes, EMG, nerve conduction studies, muscle biopsy)
        6. Favorable outcome common
7. Other diagnostic features
    1. Areflexia, decreased limb movement, and demonstration of denervation on EMG suggest anterior horn cell disorders such as SMA type I.
    2. Decreased conduction velocities on nerve conduction test suggest a demyelinating neuropathies such as Charcot-Marie-Tooth (CMT) type 2 (also known as Dejerine-Sottas disease), congenital hypomyelinating neuropathy (CMT 4E), and other subtypes of CMT4.
    3. Demonstration of cerebral myelin abnormalities and peripheral demyelination suggest Pelizaeus-Merzbacher disease or other known leukodystrophies such as Krabbe disease.
    4. Pompe disease (acid maltase deficiency) (Hebert et al. 2015).
        1. A mutation in the gene responsible for production of lysosomal alpha-1,4- glucosidase (GAA), an enzyme responsible for glycogen breakdown, leads to decreased enzyme activity resulting in glycogen buildup in the body, with the heart and skeletal muscles being most severely affected.

2. Can be easily mistaken for a primary myopathy in the first year.
3. Major differential clinical features.
    1. A large heart
    2. Firm skeletal muscles secondary to glycogen stored in the muscle fibers
    3. Distinctive EMG findings

8. Differential diagnosis of hypotonia based on specific associated features (Dubowitz 1985)
    1. Hypotonia and respiratory difficulties
        1. Muscular disorders
            1. Spinal muscular atrophy
            2. Myotonic dystrophy
            3. Myotubular myopathy (especially X-linked form)
            4. Nemaline myopathy
            5. Congenital muscular dystrophy
            6. Other
        2. Nonmuscular disorders
            1. Intracranial hemorrhage
            2. Intracranial ischemia
    2. Hypotonia and facial weakness: muscular disorders
        1. Congenital myotonic dystrophy
        2. Myotubular myopathy
        3. Congenital muscular dystrophy
        4. Congenital facial diplegia syndrome
    3. Hypotonia and swallowing difficulty
        1. Muscular disorders
            1. Spinal muscular atrophy
            2. Myotubular myopathy
            3. Myotonic dystrophy
            4. Myasthenia gravis (neonatal)
        2. Nonmuscular disorders
            1. Prader-Willi syndrome
            2. Intracranial hemorrhage
            3. Intracranial ischemia
    4. Hypotonia and ptosis/ophthalmoplegia: muscular disorders
        1. Myotubular myopathy
        2. Mitochondrial myopathy
        3. Myotonic dystrophy
        4. Congenital muscular dystrophy
        5. Myasthenia gravis
    5. Hypotonia and arthrogryposis
        1. Muscular disorders
            1. Congenital muscular dystrophy
            2. Myotonic dystrophy
            3. Congenital fiber-type disproportion
            4. Denervation syndromes
        2. Nonmuscular disorders
            1. Oligohydramnios
            2. Bicornuate uterus
            3. Renal agenesis
    6. Hypotonia and CNS dysfunction/convulsions
        1. Hypoxic-ischemic encephalopathy
        2. Intracranial hemorrhage
        3. Intracranial ischemia
        4. Organic acidurias
        5. Mitochondrial encephalopathies
        6. Zellweger disease
        7. Other rare metabolic disorders

Diagnostic Investigations

1. A stepwise approach to the evaluation of a neonate with hypotonia (modified from Paro-Panjan and Neubauer 2004)
    1. Step 1 comprised of history taking and physical examination
        1. Family history (FH)
            1. Drug or teratogen exposure
            2. Breech presentation
            3. Reduced fetal movements
            4. Polyhydramnios
            5. Maternal diseases such as diabetes and epilepsy
            6. Parental age
            7. Neuromuscular disease
            8. Affected siblings
        2. Prenatal history
            1. Decreased fetal movement
            2. Abnormal ultrasonographic findings such as hydrocephalus or polyhydramnios
            3. Possible evidence for hypoxic-ischemic insult, either in utero or during birth: detail perinatal birth trauma, birth anoxia, delivery complications, low APGAR scores (lower scores for

tone, reflexes, and respiratory effort), and onset of hypotonia
3. Neonatal history
1. A shortened umbilical cord and abnormal fetal presentation: reflects poor fetal movement or immobility.
2. Infants requiring ventilator assistance soon after birth to maintain respiration in addition to hypotonia: suggest the presence of significant muscle weakness.
3. In addition to hypotonia, infants with severe CNS abnormalities develop signs of impairment in level of consciousness, feeding difficulties, seizures, apneas, abnormal posturing, abnormalities of ocular movements, and of brain stem reflexes.
4. Presence of congenital malformations in other organ systems, deformations, and craniofacial dysmorphic features: need to establish a syndromic diagnosis.
4. Postnatal history
5. Clinical and neurological examinations
2. Step 2 comprised of neurological imaging tests: important to determine whether there is evidence for a cerebral lesion contributing to hypotonia
1. Computed tomography (CT)
2. Magnetic resonance imaging (MRI)
3. Step 3 comprised careful search of dysmorphology databases
4. Step 4 comprised of karyotyping with fluorescence in situ hybridization (FISH) for chromosome anomalies
5. Step 5 comprised of biochemical investigations for inborn errors of metabolism
6. Step 6 comprised of other specific studies
1. Specific nerve and muscle investigations
1. Serum kinase levels
2. Electromyography
3. Nerve conduction velocities
2. DNA markers
1. Spinal muscular atrophy
2. Congenital myotonic dystrophy
3. Duchenne muscular dystrophy
3. Muscle and nerve biopsy with mitochondrial enzymes

2. Initial work-up of the floppy infant based on clinical presentation, localization, and diagnostic yield (Prasad and Prasad 2003)
1. Clinical history and physical examination
1. Central hypotonia
1. Hypotonia
2. Obtundation
3. Seizures
4. Hyperactive deep tendon reflexes
2. Disorders of the lower motor unit
1. Hypotonia
2. Weakness
3. Areflexia
4. Fasciculations
5. Weak cry
6. Weak suck
7. External ophthalmoplegia
8. Alert look
9. Arthrogryposis
2. Multidisciplinary assessment including pedigree/family history and targeted investigations
1. CT/MRI, EEG, and infection screen (CSF, blood)
1. Birth trauma
2. Hypoxic-ischemic encephalopathy
3. Sepsis
4. Cerebral dysgenesis
2. Genetic studies (karyotyping, FISH, methylation studies, mutation analysis)
1. Chromosomal rearrangements
2. Prader-Willi syndrome
3. Congenital myotonic dystrophy
4. Subtelomeric deletions
3. Creatine kinase assay, electrophysiology, nerve conduction studies, and EMG
1. Nerve biopsy and/or direct mutation analysis (inherited neuropathies, disorders of neuromuscular junction)
2. Muscle biopsy followed by DNA-based mutation analysis when available (congenital muscular dystrophy, congenital myopathies)

3. Investigation scheme in the floppy infant with multisystem involvement (Prasad and Prasad 2003)
    1. Cranial MRI, echocardiography, abdominal ultrasound, and ophthalmic examinations for infants with hypotonia plus manifestations
        1. CNS obtundation
        2. Abnormal odors
        3. Seizures
        4. Craniofacial dysmorphisms
        5. Cataracts
        6. Hepatomegaly
        7. Renal cysts
        8. Retinopathy
        9. Arthrogryposis
        10. Lipodystrophy
    2. Plasma lactate levels, mt DNA mutations, DNA depletion studies, respiratory chain analysis (muscle), DNA-based mutation analysis for mitochondrial, and "energy deficient" encephalopathies (e.g., congenital lactic acidosis)
    3. Plasma ammonia, amino acids (blood, urine), urine organic acids, blood acylcarnitine profile, plasma uric acid, urinary sulfites, enzyme assays in skin fibroblasts for aminoacidopathies, organic acidemias, and sulfite oxidation/molybdenum cofactor deficiency
    4. Lysosomal enzyme assay in WBC, skin biopsy (EM for inclusion), and skin fibroblast culture + enzyme assays for lysosomal disorders (e.g., Pompe disease)
    5. Phytanic acid and plasma VLCFA for peroxisomal disorders (e.g., Zellweger syndrome)
    6. Isoimmune electrophoresis for transferrin for congenital disorders of glycosylation
    7. 7-Dehydrocholesterol for Smith-Lemli-Opitz syndrome
4. Cytogenetic analyses (Zand and Zackai 2004): for floppy infants with dysmorphic features and/or multiple congenital anomalies
    1. Aneuploidy disorders such as Down syndrome
    2. Microdeletion disorders such as Prader-Willi syndrome
        1. Methylation patterns study to determine the presence of PWS
        2. FISH and mutation analysis to identify the class of mutation
    3. Subtelomeric deletion disorders: easily detected using in situ hybridization using chromosomal telomeric probes
5. Molecular analyses: genetic testing aid significantly in timely diagnosis for a critically ill newborn and allow for anticipation of medical interventions by the multidisciplinary team caring for the infant
    1. Chromosomal microarray studies
    2. Mutation or deletion analysis of the survival motor neuron gene (*SMN*) for SMA
        1. All patients with SMA have deletions or mutations of *SMN1* (also known as *SMN t*, the telomeric copy of *SMN* gene). Homozygous deletion of exon 7 in the telomeric survival motor neuron gene found in 95% of SMA type I patients
        2. The major phenotype determinant is the presence of the number of copies of *SMN2* (also known as *SMN c*, the centromeric copy of *SMN* gene)
            1. One copy: likely to produce SMA1
            2. No copy of SMA1: likely results in spontaneous abortion or fetal wastage
            3. Five or six copies: likely allow normal survival with little or no progressive weakness
    3. Mutation analysis in CMT hereditary motor sensory neuropathies
        1. CMT 1A: mutations in the peripheral myelin protein-22 gene
        2. CMT 1B: mutation in the myelin protein zero gene
        3. CMT 2B: mutation in the RAS-associated protein RAB7
        4. CMT 4A: mutation in the ganglioside-induced differentiation-associated protein-1 gene
        5. CMT-X1: mutation in the connexin-32 gene

4. Mutation analysis for disorders of neuromuscular junction (congenital myasthenic syndromes)
    1. Congenital myasthenia with episodic apnea
    2. Slow-channel and fast-channel syndrome
    3. End plate cholinesterase deficiency
5. Mutation analysis for disorders with prominent muscle involvement
    1. Bethlem myopathy
    2. Triplet repeat CTG expansion of the DM protein kinase mutations (>37)
    3. Congenital DM protein kinase repeat expansion (>750)
6. Gene sequencing, mutation analysis, or mutation scanning
    1. Dystrophinopathies
    2. Muscular dystrophies
    3. Myopathies
7. mtDNA mutation analysis or mutation analysis in nuclear gene for mitochondrial disorders

6. Electrophysiological studies (Darras and Jones 2000)
    1. Needle electromyogram (EMG)
        1. Neurogenic changes.
            1. Spontaneous fibrillation at rest
            2. Long-duration polyphasic motor unit potentials
            3. Decreased interference pattern
        2. Myopathic changes: consider muscle biopsy.
            1. Low-amplitude, short-duration polyphasic
            2. Normal interference pattern
        3. Myopathy plus muscle irritability (large amplitude of CMAPs, increased insertional activity) should consider Pompe disease (acid maltase enzyme assay).
        4. Demonstration of denervation on EMG (large amplitude of CMAPs, fasciculation, positive sharp wave) should prompt investigation for anterior horn cell disorders (proceed to SMA genetic test, SMN type I and type II copy number).
    2. Motor and sensory nerve conduction studies (NCS): decreased nerve conduction velocities on NCS suggest a demyelinating neuropathy
7. Pathologic studies of muscles (muscle biopsy) (Darras and Jones 2000):
    1. The most useful test in the diagnosis of motor unit hypotonia.
    2. Used much less often today with the availability of specific gene test for many of the conditions under consideration.
    3. A sequential scheme for the proper use of the muscle biopsy.
        1. Nonspecific myopathy: consider myotonic, dystrophinopathy, and other congenital myopathy.
        2. Characteristic pathology.
            1. Central core disease
            2. Nemaline rod myopathy
            3. Centronuclear myopathy
        3. Dystrophic muscle.
            1. Brain involvement: consider muscle-eye-brain disease, Fukuyama congenital muscular dystrophy, and Walker-Warberg syndrome.
            2. Without brain involvement: consider histoimmunological stain for merosin-deficient and merosin-positive muscular dystrophies.
    4. SMA: extensive large grouped atrophy involving both type I and type II fibers and scattered clusters of enlarged type I fibers.
    5. Congenital muscular dystrophy: considerable variations in fiber size with extensive fatty infiltration.
    6. Glycogen storage disease: vacuolar myopathy with muscle fibers containing type vacuoles of varying sizes.
    7. Central nuclear myopathy: presence of central nucleus in the majority of muscle.
    8. Central core myopathy: deficient oxidative enzyme in the center of many fibers.
    9. Nemaline myopathy: muscle fibers with thickened striations and aggregates of rod bodies.

10. Congenital fiber-type disproportions: increased number of small lightly stained type I fibers and reduced number of larger darkly stained type II fibers.

8. Biochemical studies
    1. Muscle enzymes (creatine kinase)
        1. Rarely helpful in work-up of a floppy infant
        2. Elevated in:
            1. Congenital muscular dystrophies
            2. Some forms of congenital myopathies
    2. Inborn errors of metabolism screening
        1. Categories of biochemical defects
            1. Toxic encephalopathies
            2. Energy deficient encephalopathies
            3. Disorders affecting intracellular processing of complex molecules
        2. Blood ammonia
            1. Urea cycle defects
            2. Organic acidemias
            3. Fatty acid oxidation disorders
        3. Lactate (blood, urine, CSF)
            1. Carbohydrate metabolism disorders
            2. Mitochondrial disease
        4. Blood and urine quantitative analysis of amino acids for aminoacidopathies
        5. Blood organic acid and acylcarnitine profiles using tandem mass spectrometry
            1. Organic acidemias
            2. Fatty acid oxidation defects
        6. Plasma very long chain fatty acids (VLCFA) for peroxisomal disorders
        7. Transferrin (low in glycosylation disorders)
        8. Blood 7-dehydrocholesterol (elevated in Smith-Lemli-Opitz syndrome)
9. Cranial ultrasound or CT studies (Rumack 1985): to detect CNS lesions causing infantile hypotonia
    1. Hypoxic-ischemic encephalopathy
        1. Fetal or neonatal hypoxia
        2. Sudden infant death syndrome
        3. Infarction from other causes
    2. Neonatal intracranial hemorrhage
        1. Subependymal hemorrhage (premature infants)
        2. Subarachnoid hemorrhage or atypical intracranial hemorrhage (term infants)
    3. Intracranial infection
        1. Prenatal
            1. Cytomegalovirus
            2. Toxoplasmosis
            3. Herpes
            4. Rubella
        2. Neonatal and infant: bacterial
    4. Trauma
        1. Subdural hematoma
        2. Epidural hematoma
        3. Parenchymal hemorrhage or edema
10. Cranial CT/MRI studies
    1. Structural malformations
    2. Altered signals
        1. White matter: laminin deficiency
        2. Basal ganglia: mitochondrial cytopathies
        3. Brain stem and cerebellar abnormalities
            1. Joubert syndrome
            2. Pontocerebellar hypoplasia
11. Genetic testing in neuromuscular diseases (Krajewski and Shy 2004)
    1. Polymerase chain reaction (PCR)
    2. Mutation analysis
    3. Sequence analysis
    4. Restriction fragment length polymorphism (RFLP)
    5. Single-strand conformational polymorphism (SSCP)
    6. Denaturing gradient high-performance liquid chromatography
    7. Cytogenetics and fluorescent in situ hybridization
    8. Southern blotting
    9. RNA analysis
    10. Linkage analysis
12. Genetic evaluation in floppy infant (Jain and Jayawant 2011)
    1. Recently, array CGH (comparative genomic hybridization) has come up as a powerful diagnostic tool having detection rate of 5–17% in cases of normal karyotype.

2. Exon sequencing is promising in detecting causal genetic variants of rare monogenic disorders.
3. Newborn screening using tandem mass spectrometry can be helpful for metabolic disorders.
4. Recent advances in genetics have uncovered new conditions causing hypotonia and weakness such as congenital myasthenic syndromes and spinal muscular atrophy variants.

13. Differential diagnosis of hypotonia (Sparks 2015)
    1. Central hypotonia
        1. Hypoxic-ischemic encephalopathy
            1. Premature birth
            2. Difficult delivery
            3. Brain MRI
        2. Intracranial hemorrhage
            1. Brain MRI
        3. Cerebral malformations
            1. May be noted on prenatal ultrasonography
            2. Brain MRI
        4. Chromosomal abnormalities
            1. Dysmorphic features
            2. Congenital malformations
            3. Karyotype/array CGH
        5. Congenital infections
            1. Prenatal history
            2. Infectious cultures/evaluation
        6. Acquired infections
            1. Infectious cultures
        7. Peroxisomal disorders
            1. Dysmorphic features
            2. Very long chain fatty acids
        8. Inborn errors of metabolism
            1. Metabolic acidosis (hyperammonemia, hypoglycemia, lactic acidosis)
        9. Maternal and infant drug effects
            1. Prenatal and perinatal history of drug exposure
            2. Toxicology screen
    2. Spinal cord lesions
        1. Birth trauma
            1. History of trauma
        2. Hypoxic-ischemic encephalopathy
            1. Brain MRI
        3. Syringomyelia
            1. Spine MRI
    3. Anterior horn cell disease
        1. Spinal muscular atrophy
            1. Diminished/absent deep tendon
            2. Reflexes
            3. Muscle fasciculations
            4. *SMN1* copy number analysis
    4. Neuromuscular junction diseases
        1. Myasthenia gravis (transient acquired neonatal myasthenia, congenital myasthenia gravis)
            1. Easy fatigability.
            2. Recurrent aspiration.
            3. Feeding difficulty.
            4. EMG.
            5. Responds to anticholinesterase inhibitors.
            6. ECG may show heart block.
        2. Infantile botulism
            1. Facial weakness and pupillary abnormality
            2. Presence of toxin in food
        3. Drug toxicity (magnesium, aminoglycosides)
            1. History of drug exposure
            2. Plasma and urine drug levels
    5. Peripheral nerve diseases
        1. Hereditary motor and sensory neuropathies
            1. Diminished/absent DTRs.
            2. Absent Babinski and infantile reflexes.
            3. EMG/NCV may be helpful.
            4. DNA sequencing.
        2. Congenital hypomyelinating neuropathy
            1. FH
            2. DNA sequencing
        3. Giant axonal neuropathy
            1. FH
            2. DNA sequencing
    6. Muscle diseases
        1. Muscular dystrophies
            1. FH.

2. May have elevated serum CK and aldolase.
3. ALT and AST may be elevated from muscle rather than liver.
4. Muscle biopsy.

2. Congenital myopathies
   1. FH
   2. Muscle biopsy
3. Metabolic myopathies
   1. FH
   2. May have elevated serum CK, aldolase, ALT, and AST
   3. Muscle biopsy
4. Congenital myotonic dystrophy
   1. FH and maternal myotonia
   2. CTG-repeat analysis of *DMPK*

7. Microdeletion syndromes (Prasad and Prasad 2011)
   1. Clinical features: hypotonia in association with specific phenotypes
      1. Facial dysmorphisms
      2. Supravalvular aortic stenosis (in Williams syndrome)
   2. Disorders: 1p36, 22q13, 22q11.2, Williams syndrome, Smith-Magenis syndrome, and Wolf-Hirschhorn syndrome
   3. Laboratory testing: array CGH
   4. Genetic basis/inheritance: continuous gene syndrome

Genetic Counseling

1. Recurrence risk: depends on underline etiology
   1. Patient's sib
      1. Autosomal recessive (e.g., spinal muscular atrophy, congenital muscular dystrophy): 25%.
      2. Autosomal dominant (e.g., congenital myotonic dystrophy): not increased unless a parent is affected.
      3. X-linked recessive (e.g., severe infantile form of myotubular myopathy): 50% of male sibs affected if the mother is a carrier.
      4. Mitochondrial: all sibs are at risk of being affected if the mother has the mitochondrial DNA mutation.
      5. Chromosomal: increased risk, especially a parent is a translocation carrier.
   2. Patient's offspring
      1. Autosomal recessive: not increased unless the spouse is also a carrier.
      2. Autosomal dominant: 50%.
      3. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
      4. Mitochondrial:
         1. Offspring of males with a mtDNA mutation are not at risk.
         2. All offspring of females with a mtDNA mutation are at risk of inheriting the mutation.
         3. A female harboring a heteroplasmic mtDNA point mutation may transmit a variable amount of mutant mtDNA to her offspring, resulting in considerable clinical variability among sibs within the same nuclear family (Poulton and Turnbull 2000; Chinnery 2006).
      5. Chromosomal: an increased risk.
2. Prenatal diagnosis as well as preimplantation genetic diagnosis in certain cases (Prasad and Prasad 2011)
3. Management (Pediatric Care Online 2008)
   1. Supportive treatment in most causes of hypotonia.
   2. Multidisciplinary team approach for coordination of interventions.
   3. Infantile progressive spinal muscular atrophy.
      1. Physical therapy
      2. Respiratory therapy
      3. Nutritional support as needed
      4. Scoliosis treatments:
         1. Body jacket
         2. Molded back support
         3. Surgery
         4. Motorized wheelchair for children with type II at approximately 2–3 years of age

4. Peripheral nerve disorders: bracing for children with foot drop.
5. Neuromuscular junction disorders: hospitalization, with respiratory and nutritional support as needed.
    1. Passively acquired autoimmune myasthenia gravis (transient neonatal myasthenia): give pyridostigmine until asymptomatic and then taper over 1–2 weeks.
    2. Acquired autoimmune myasthenia gravis (juvenile myasthenia).
        1. Anticholinesterase drugs
        2. Immunosuppressive treatment
        3. Intravenous γ-globulin
        4. Corticosteroids
        5. Thymectomy
    3. Nonautoimmune myasthenic syndromes (congenital myasthenia gravis).
        1. Anticholinesterase inhibitors
        2. Corticosteroids
        3. Diaminopyridine (experimental)
    4. Infantile botulism: antibotulism immune globulin may be therapeutic.
6. Myopathies.
    1. Infantile form of myotonic dystrophy-type hypotonia
        1. Assisted ventilation as indicated
        2. Gastrostomy tube feedings as indicated
    2. Glycogen storage disease: consider enzyme replacement therapy (myozyme) (prognosis dismal without such therapy).
7. Some of recent advances in genetics have allowed for specific therapeutic interventions (Jain and Jayawant 2011).
    1. Use of acetylcholinesterase inhibitors, 3,4-diaminopyridine and ephedrine, salbutamol, or fluoxetine in some congenital myasthenic syndromes.
    2. Antisense oligonucleotide therapy has been under trial for Duchenne muscular dystrophy.
    3. Enzyme replacement therapy (myozyme) for infantile Pompe disease.

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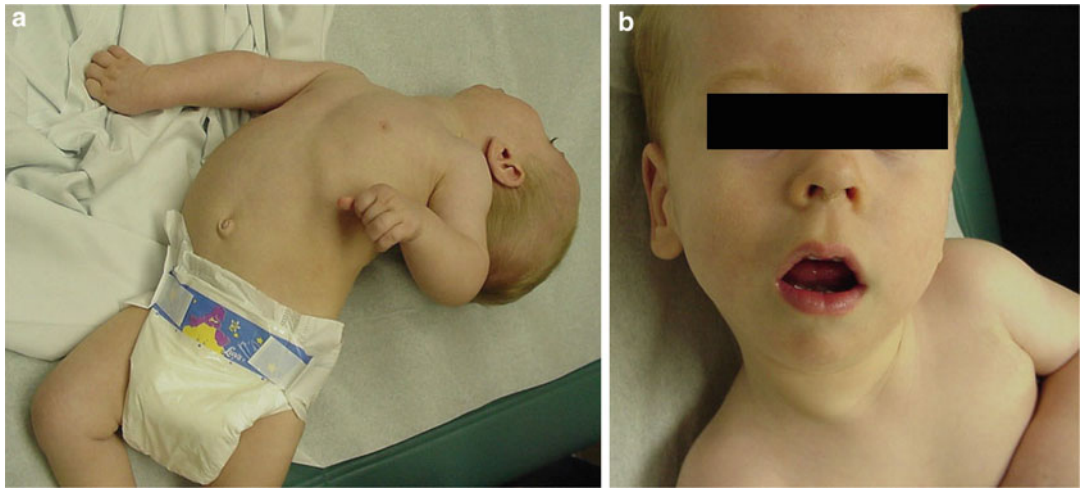

Fig. 1 (**a**–**b**) An infant boy with hypotonia

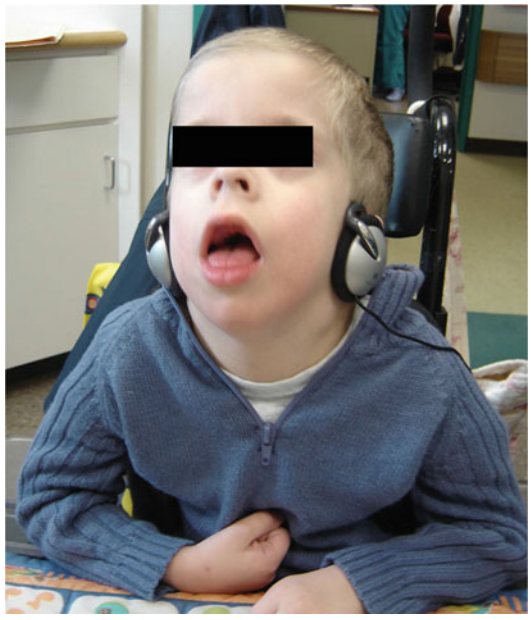

Fig. 2 The same boy with hypotonia at 6 years of age

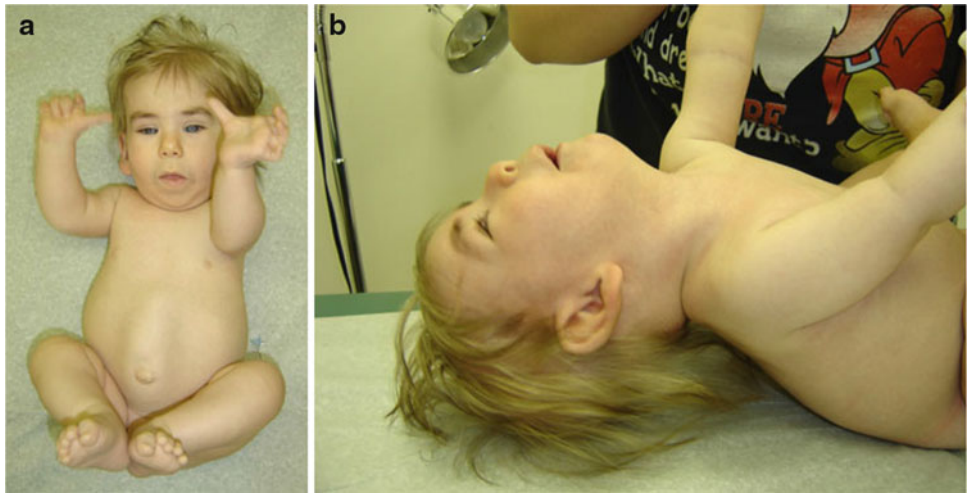

Fig. 3 (**a**–**b**) Hypotonia associated with cerebellum and optic nerve hypoplasia in an infant at 9 months of age

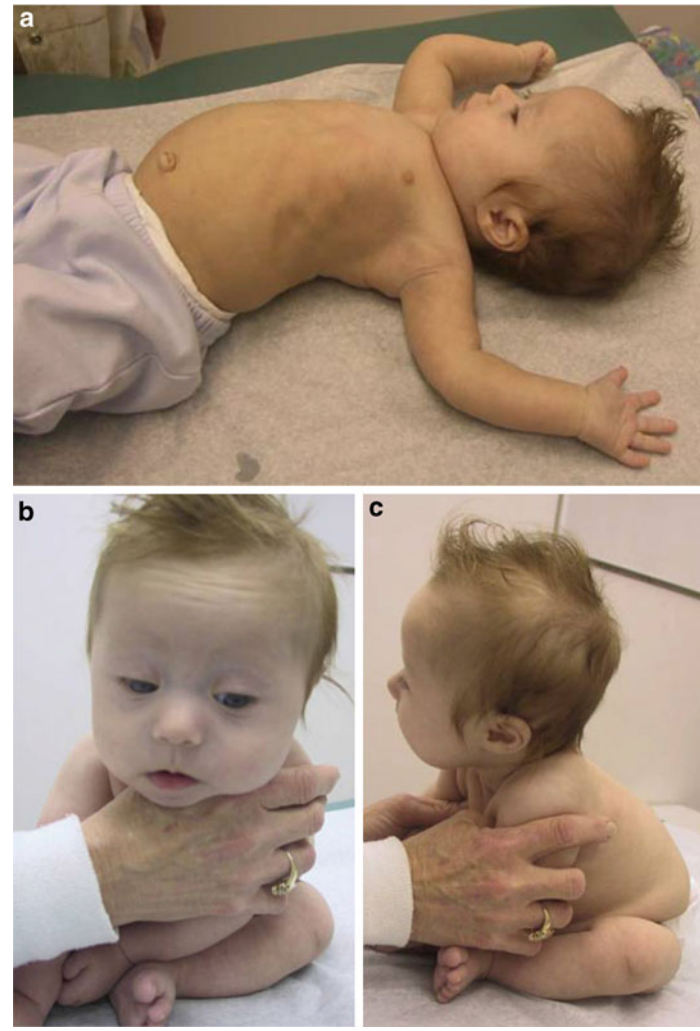

Fig. 4 (**a**–**c**) Hypotonia associated with Down syndrome in an infant

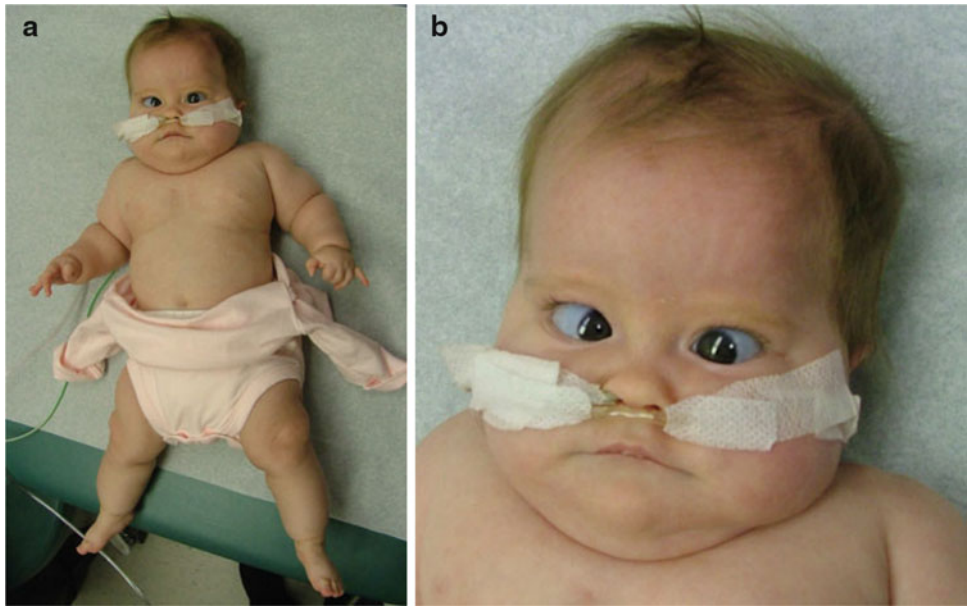

Fig. 5 (**a**–**b**) Hypotonia associated with Prader-Willi syndrome in a 7-month-old boy

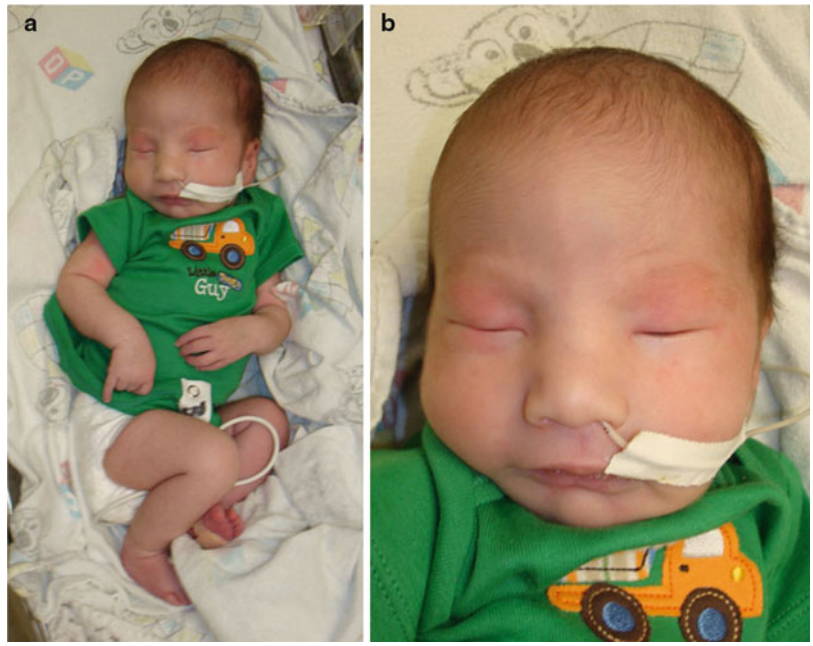

Fig. 6 (**a**–**b**) Hypotonia associated with dysmorphic facies (ocular hypertelorism, slightly upslanted palpebral fissures, bulbous nose, micro-/retrognathia, and small ears) secondary to microdeletion of 15q demonstrated by chromosome microarray analysis [arr cgh l5q11.2q13.1 (19,623,685 → 26,605,469) × 1]. Regular chromosome analysis was normal

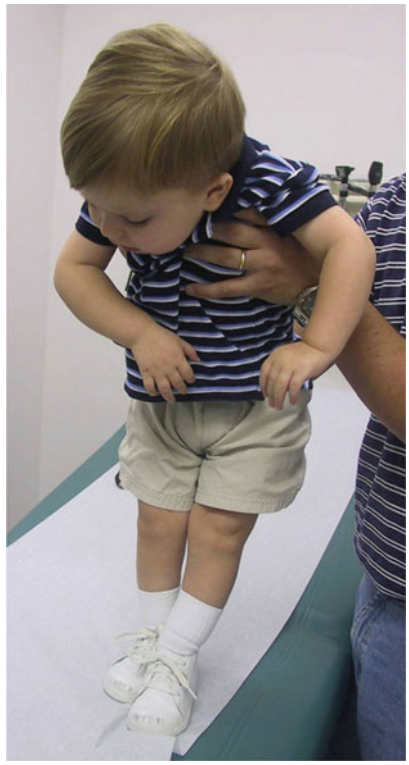

Fig. 7 A 28-month-old infant with metachromatic leukodystrophy with hypotonia

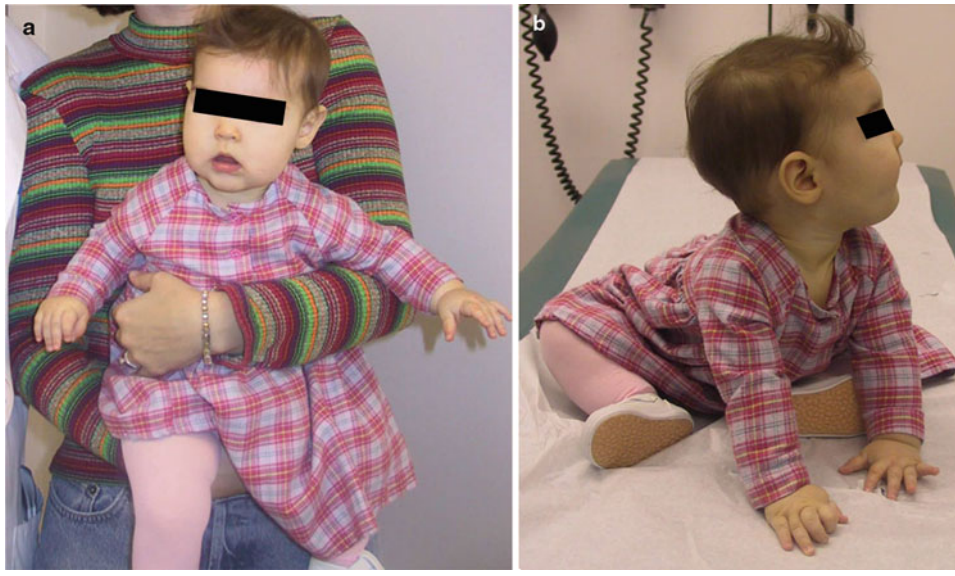

Fig. 8 (**a**–**b**) "Congenital benign hypotonia" in a 7-month-old infant

Fragile X Syndrome

Contents

Fragile X syndrome is the most common form of heritable intellectual disability, affecting approximately 1 in 1,250 males and 1 in 2,000 females (Webb 1989). The prevalence appears to be 1 in 4,000–6,000 males and 1 in 8,000–10,000 females. Martin and Bell first documented X-linked mental retardation in 1943. Subsequent identification of a fragile site on the long arm of the X chromosome (Lubs 1969), discovery of cell culture medium-dependent fragile site, and recognition of a unique constellation of physical features served to distinguish fragile X syndrome from other X-linked mental retardation syndromes.

Verkerk et al. (1991) identified a single gene that was associated with symptoms of the disorder. The gene, known as fragile X mental retardation gene 1 (*FMR1*), exhibited a novel form of mutation, a sequence of three nucleotides (CGG) that was repeated many times in patients with fragile X syndrome.

Synonyms and Related Disorders

Fragile X mental retardation syndrome; Fragile X spectrum disorders; Marker X syndrome; Martin-Bell syndrome; X-linked mental retardation and macroorchidism

Genetics/Basic Defects

1. Inheritance not conforming to usual rules governing X-linked traits
    1. Presence of asymptomatic transmitting males
    2. Presence of affected female carriers who inherited the gene
2. Caused by mutations in a trinucleotide $(CGG)_n$ repeat found in the coding region of the *FMR1* gene, mapped to Xq27.3 (De Boulle et al. 1993)
    1. Expanded CGG repeats >200 (full mutation): associated with fragile X syndrome.
    2. High repeat number (full mutation) leads to hypermethylation of an upstream promoter region and subsequent silencing (inactivating) of the *FMR1* gene.
    3. Fragile X premutation.
        1. A small expansion (premutation): between 55 and 200 CGG repeats
        2. Usually not associated with cognitive deficits

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4. Expansion to a full mutation from the premutation in normal carriers occurs only when it is transmitted by a female.
5. Presence of anticipation phenomenon.

3. The Sherman paradox (Laxova 1994)
   1. A perplexing and confusing fragile X pedigree pattern was discovered during the mid-1980s by Sherman et al. (1984, 1985) who discovered the large discrepancy in risks for mental retardation within fragile X families containing transmitting males. This phenomenon was termed the "Sherman paradox" by Opitz (1986).
      1. 20% of males within fragile X families who carried the mutation are unaffected clinically and intellectually and became known as transmitting males.
      2. An increasing risk of mental retardation in grandsons of normal transmitting males: a special form of genetic anticipation (the increase in disease severity through successive generations).
      3. About a third of obligate carrier females are mentally impaired.
      4. More than half of known carrier females are either mildly impaired or expressed the fragile site on one of their X chromosomes.
   2. Possible explanations of the Sherman paradox.
      1. An unaffected transmitting male who inherits a premutation from his unaffected carrier mother, who has 50–200 repeats but probably a number closer to the lower end of the premutation range.
      2. Offspring of a carrier mother with the number of repeats still within the premutation range, even if amplification occurs during oogenesis.
      3. Transmission of the premutation to the daughters by the transmitting male. No amplification has occurred during spermatogenesis; hence, the daughters also have a premutation and are unaffected.
      4. Amplification to more than 200 repeats occurs during oogenesis of the transmitting male's daughters whose sons will receive a null mutation and be affected and their daughters may or may not be affected.
      5. The risk of expansion during oogenesis to the full mutation associated with mental retraction increases with the number of repeats, and this variation in risk accounts for the Sherman paradox (Fu et al. 1991).
4. Genotypic-phenotypic correlations (Kaufmann and Reiss 1999)
   1. Fragile X full mutation and mental retardation with a wide spectrum of phenotypic effects in both sexes
      1. Mental retardation in 100% of males
      2. Usually a milder form of retardation in 60% of females
   2. Large CGG amplification
      1. Associated with hypermethylation
      2. Almost invariably correlated with the most severe fragile X phenotype
      3. Seen in males with the full mutation pattern
   3. Premutation expansions that are not usually accompanied by methylation: minimal or no neurologic repercussion
   4. Correlation of methylation in *FMR1* expression and cognitive function
      1. Individuals with full mutation without methylation scored better than those with full mutation and complete methylation
      2. Individuals with full mutation and partial methylation showed intermediate values
   5. Presence of the *FMR1* protein (FMRP) responsible for:
      1. Lack of neurologic abnormalities in individuals with premutation
      2. Milder phenotype of males having full mutation without full methylation
5. Pathogenesis
   1. A consequence of the absence or deficit of the FMRP (de Vries et al. 1998)
   2. Absence of FMRP in the brain: the likely cause of mental retardation in patients with fragile X syndrome

6. Genetic and environmental influences on the cognitive outcomes of children with fragile X syndrome (Dyer-Friedman et al. 2002)

Clinical Features

1. Affected males (Hagerman and Cronister 1996)
    1. CNS involvement
        1. Delayed developmental milestones
        2. Mild to severe mental retardation
        3. Difficulty with abstract thinking, sequential processing, mathematics, short-term memory, and visual motor coordination
        4. Seizures
    2. Connective tissue dysplasia (Davids et al. 1990)
        1. Hyperextensible finger joints
        2. Double-jointed thumbs
        3. Flat feet
        4. High-arched palate
        5. Mitral valve prolapse (55%, diagnosed by echocardiography)
        6. Dilatation of the ascending aorta
        7. Inguinal hernia
        8. Soft and velvet-like skin
    3. Typical facial features
        1. Long face
        2. Prominent forehead
        3. Prominent/long ears
        4. Prominent jaw
    4. Other features
        1. Macroorchidism present in over 80% of adult fra(X) males
        2. Pectus excavatum
        3. Scoliosis
        4. Strabismus
        5. Recurrent otitis media in early childhood
        6. Reproduction documented but rare because of significant mental retardation
    5. Behavior abnormalities (Dykens et al. 1994; Kau et al. 2002)
        1. Stereotyped with odd mannerisms (hand flapping/biting)
        2. Tactile defensiveness
        3. Poor eye contact (excessive shyness)
        4. Attention deficit/hyperactivity disorder
            1. Hyperactivity
            2. Temper tantrums
            3. Distractibility
            4. Mood lability
        5. Speech disorder
            1. Perseveration
            2. Litany speech
            3. Echolalia
        6. Autism
        7. Autistic-like features
        8. Schizotypal personality disorder
        9. Anxiety disorder
2. Females heterozygous for full mutation alleles (Hagerman et al. 1992)
    1. Fifty percentage with cognitive deficits with learning disabilities, borderline IQ, or mental retardation
    2. Fifty percentage with normal intellectual function
3. Females heterozygous for premutation alleles (carriers) at risk for premature ovarian failure (early onset of menopause before age 40 years) (*FMR1*-related premature ovarian failure) (Hagerman et al. 1998; Holden et al. 1999; Bardoni et al. 2000; Kenneson and Warren 2001)
4. Fragile X-associated tremor/ataxia syndrome (FXTAS) (Saul and Tarleton 2012; Hagerman and Hagerman 2013)
    1. Carriers of the fragile X premutation may develop a neurodegenerative disease called FXTAS (Brown and Stanfield 2015).
    2. Established and expanded features of FXTAS.
        1. Autonomic problems
            1. Constipation/irritable bowel syndrome
            2. Erectile dysfunction
            3. Problems swallowing
            4. Gastrointestinal reflux
            5. Orthostatic hypotension
            6. Hypertension
            7. Urinary urgency and incontinence
            8. Cardiac arrhythmia
            9. Dizzy spells or vertigo

2. Sensory
    1. Olfactory dysfunction
    2. Hearing loss
    3. Neuropathy
3. Sleep problems
    1. Insomnia
    2. Sleep apnea
    3. Daytime sleeping
4. Motor symptoms
    1. Tremor or ataxia
    2. Muscle weakness
    3. Parkinsonism
5. Psychiatric
    1. Depression or anxiety
    2. Irritability
6. Chronic pain
    1. Fibromyalgia
    2. Neuropathic pain
7. Immune-mediated disorder
    1. Hypothyroidism
    2. Fibromyalgia

3. A definite diagnosis based on the following four observations (major criteria)
    1. Molecular: presence of FMR1 premutation (55–200 CGG repeats)
    2. Radiological: white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem (the major neuroradiologic sign)
    3. Clinical: presence of two major clinical signs
        1. Intention tremor
        2. Gait ataxia
    4. Neuropathological: FXTAS inclusions
4. Other minor clinical criteria
    1. Clinical
        1. Parkinsonism
        2. Moderate to severe short-term memory deficits
        3. Executive cognitive function deficits
    2. Radiological
        1. MRI white matter lesions in cerebral white matter
        2. Moderate-to-severe generalized atrophy
5. Diagnostic category: presence of expanded CGG repeat (molecular)
    1. Definite: presence of one major radiological sign plus (i) one major clinical symptom or (ii) the presence of FXTAS inclusions
    2. Probable: presence of one major radiological sign and one minor clinical symptom, or two major clinical symptoms
    3. Possible: presence of one minor radiological sign and one major clinical symptom
5. Fragile X spectrum disorders (FXSD) (Lozano et al. 2014): FXSD should be used to include the wide range of overlapping phenotypes observed in affected individuals with *FMR1* mutations
    1. Fragile X-associated primary ovarian insufficiency.
    2. Fragile X-associated tremor/ataxia syndrome.
    3. Developmental problems including ASD and ADHD especially in boys and psychopathology including anxiety and depression in children and adults.
    4. Some premutation carriers can have a deficit of FMRP and some unmethylated full mutation individuals can have elevated FMR1 mRNA that is considered a premutation problem.

Diagnostic Investigations

1. Pedigree analysis.
2. Karyotyping of cells grown in folate- or thymidine-depleted cell culture media.
    1. A “fragile” site on one of the X chromosomes (Xq27.3) that appeared as a constriction on the distal long arm in many patients
    2. Cells exhibiting fragile X chromosome: 5–50%
    3. Cytogenetic studies now rendered obsolete by direct DNA testing
3. Indications for molecular genetic testing (Park et al. 1994).

1. Individuals of either sex with mental retardation, developmental delay, or autism
    1. Any physical or behavioral characteristics of fragile X syndrome
    2. A family history of fragile X syndrome
    3. Male or female relatives with undiagnosed mental retardation
2. Individuals seeking reproductive counseling who have a family history of fragile X syndrome or undiagnosed mental retardation
3. Fetus of a known carrier mother
4. Patients with cytogenetic fragile X test result discordant with phenotype
    1. Patients with a strong clinical impression of being affected with or carrier of fragile X syndrome but had a negative or ambiguous cytogenetic test result
    2. Patients with an atypical phenotype of fragile X syndrome but had a positive cytogenetic test result

4. Prenatal carrier testing for fragile X (Musci and Moyer 2010).
    1. Carrier testing is recommended for:
        1. Women with a family history of FXS
        2. Women with ovarian insufficiency
        3. Women with a family history of undiagnosed mental retardation, developmental delay, or autism.
    2. Testing for premutations is also recommended in men and women with late-onset intention tremor and cerebellar ataxia, especially those individuals with a family history of FXS, unknown mental retardation, and movement disorders.
5. Direct DNA analysis for point mutation or deletion in *FMR1* gene (Saul and Tarleton 2012).
    1. Targeted mutation analysis: mutation analysis to determine the CGG repeat size (mutation detection rate >99%).
        1. Southern blot hybridization
        2. Polymerase chain reaction (PCR)
        3. AGG trinucleotide repeat genotyping
    2. Methylation analysis by Southern blot analysis to determine the *FMR1* methylation status, independent of measuring the number of CGG repeats.
    3. Sequence analysis: very few individuals with fragile X syndrome have been identified with an intragenic *FMR1* mutation.
    4. Deletion/duplication analysis: fewer than 1% of individuals with fragile X syndrome have a partial or full deletion of FMR1 (Hammond et al. 1997).
6. Types of *FMR1* repeat expansion mutations (Tarleton and Saul 1993; Saul and Tarleton 2012).
    1. Normal alleles: 5–40 CGG repeats
        1. Stably transmitted without any increase or decrease in repeat number.
        2. In stable normal alleles, the CGG region is interrupted by an AGG triplet after every nine or ten CGG repeats. These AGG triplets are believed to maintain repeat integrity by preventing DNA strand slippage during replication.
        3. Normal alleles with more than 35 CGG repeats are associated with increased risk of *FMR1*-related premature ovarian failure.
    2. Mutable normal alleles (intermediate alleles, also termed "gray zone"): broadly defined as 41–58 repeats (no consensus exists regarding the precise size)
    3. Premutation alleles
        1. 59–200 CGG repeats.
        2. Methylation status of *FMR1*: premutation alleles are usually unmethylated and FMRP production is normal.
        3. Therefore, individuals (males or females) with premutation are clinically unaffected (Caskey et al. 1992).
        4. Do convey increased risk for FXTAS and POF, because of:
            1. Potential repeat instability upon transmission of premutation alleles.
            2. Women with alleles in this range are considered to be at risk of having

children affected with fragile X syndrome.

4. Full mutation alleles
   1. >200 CGG (several hundreds to several thousands) repeats. Expansion of the repeat more than 200 generally results in hypermethylation of both the CpG island and the CGG repeat within the *FMR1* gene.
   2. Methylation status of *FMR1*: completely methylated.
   3. Males: affected.
   4. Females: affected in about 50% of cases; unaffected in about 50% of cases.
5. Mosaicism
   1. Number of CGG repeats varies between premutation and full mutation in different cell lines.
   2. Methylation status of *FMR1*: partially methylated (unmethylated in the premutation cell line and methylated in the full mutation cell line).
   3. Males: affected but may function higher than individuals with full mutation.
   4. Females: highly variable clinical expression ranging from normal intellect to affected.
6. Methylation mosaicism
   1. Number of CGG repeats >200
   2. Methylation status of *FMR1* gene: partially methylated (mixture of methylated and unmethylated cell lines)
   3. Males: affected but may function higher than individuals with full mutation
   4. Females: highly variable clinical expression ranging from normal intellect to affected
7. Unmethylated full mutation
   1. Number of CGG repeats >200.
   2. Methylation status of *FMR1* gene: unmethylated.
   3. High functioning fragile X males (Hagerman et al. 1994): nearly all are affected but may have high functioning mental retardation to low normal intellect.
   4. Females: highly variable clinical expression ranging from normal intellect to affected.
7. Immunocytochemical tests based on the direct detection of FMRP using monospecific antibodies (Willemsen and Oostra 2000; Oostra and Willemsen 2001). This FMRP detection assay is based on the presence of FMRP in cells from unaffected individuals and its absence in cells from patients with fragile X syndrome. This assay is proven to be a reliable alternative method to identify male patients with fragile X syndrome. The new test on hair roots is suitable for use in large screening programs among males. The immunocytochemical tests can also be used in patients with mosaic pattern, affected premutation males, and intragenic mutations.
8. Functional neuroimaging (fMRI) of fragile X premutation carriers (Brown and Stanfield 2015).
   1. Given the complex nature of the premutation and FXTAS, functional imaging in particular can be further utilized to probe a broad range of clinically relevant features.
   2. For example, analysis of emotional processing may help to unravel the neurodevelopmental aspects of the premutation.
9. Molecular genetic testing (Oostra et al. 1993; Brown 1995; Naber 1995; Crawford et al. 2001).
   1. Targeted mutation analysis
      1. PCR analysis
      2. Southern blot analysis (Rousseau et al. 1991)
   2. Methylation status/analysis (Das et al. 1997)
   3. Sequence analysis
   4. Deletion/duplication analysis
   5. FISH analysis
   6. X-chromosome inactivation

Genetic Counseling

1. Recurrence risk: adequate genetic counseling depends on accurate diagnosis at the molecular level.

1. Individuals identified as noncarriers: the zero risk of transmitting fragile X syndrome to the next generation
2. Individuals identified as carriers: the risk of having children with fragile X syndrome depending on the sex of the carrier parent, the sex of the child, and the size of the CGG repeats.
    1. Premutation carrier males: considered "transmitting males." All daughters of transmitting males are unaffected premutation carriers. However, the grandsons and granddaughters of a transmitting male are at risk for developing fragile X syndrome.
    2. All mothers of a child with *FMR1* full mutation (expansion >200 CGG trinucleotide repeats) are considered carriers of an *FMR1* gene expansion (either full mutation or premutation and may be affected).
    3. Females with premutation (Kallinen et al. 2000; Nolin et al. 2003): an increased risk of passing on the full mutation and having offspring with the fragile X phenotype (the fragile X premutation can expand to the full mutation during maternal meiosis) (Warren and Nelson 1994).
    4. Carrier males who may reproduce: essentially zero risk of having male offspring with fragile X syndrome, since all their sons receive their Y chromosome [except in the rare instance of the fragile X chromosome coming into the family from the other source (mother)]. All the daughters of male carriers will have premutations regardless of the size of paternal amplifications and will not have fragile X syndrome. Only a few reports with premutation males have full mutation daughters.
3. Females with full mutation: her offspring, if they inherit the fragile X locus, all will have full mutation.
    1. All her sons will have fragile X syndrome.
    2. About 50–60% of her daughters will have fragile X syndrome, exceeding the 35% applicable to all female carriers of the fragile X chromosome. Affected females generally have less severe intellectual disability than found in affected males.
    4. Males with full mutations.
        1. Mentally retarded
        2. Generally do not reproduce
2. Risks to pregnant women with an expanded *FMR1* gene.
    1. A repeat size of 40–59: safe (0% risk) with no fetal full mutations
    2. A repeat size of 60–80: low risk (14%) of full mutation in the fetus
    3. A repeat size of over 80–100: a significant increase in risk (89%) of developing full mutation in the fetus
    4. A repeat size of 100–200: 100% risk of developing full mutation in the fetus
3. Prenatal diagnosis by amniocentesis or CVS (Saul and Tarleton 2012).
    1. Available to at-risk pregnancies: requires prior confirmation of the presence of an expanded (or altered) *FMR1* allele in the family
    2. Prenatal diagnosis using direct DNA analysis to women discovered to be premutation carriers
    3. The limitation: inability to accurately predict phenotype in female fetuses with full mutation
    4. CVS: follow-up amniocentesis or testing using PCR, necessary to determine the size of the *FMR1* alleles in a methylation-independent manner
4. Prenatal identification of male or female fetuses with a premutation fragile X allele of a premutation carrier woman (Musci and Moyer 2010).
    1. The mother has knowledge of the repeat size and gender of her fetus.
    2. The fetus does not carry a full mutation but instead has inherited an allele in the premutation range.
    3. Involves disclosure of information pertaining to the risk that the fetus may have to develop 2 adult-onset conditions, fragile X-associated primary ovarian insufficiency (FXPOI) and FXTAS.

5. Prenatal Identification of female fetuses with a full mutation of a premutation carrier woman (Musci and Moyer 2010).
    1. Identification of female fetuses with full mutations (>200) can pose a significant counseling challenge and a difficult set of choices for the parents.
    2. As anticipated for X-linked conditions, skewed X inactivation may modify the clinical phenotype of FXS in female carriers.
    3. In general, up to 50% of females with a full mutation allele will be significantly affected with cognitive and behavioral features of FXS (Sherman et al. 2005).
    4. Ultimately, for those women identified as carrying a female fetus with a full mutation, uncertainty about the resulting phenotype may certainly produce anxiety.
6. Prenatal identification of female fetuses with a full mutation (Musci and Moyer 2010).
    1. Genetic counseling for individuals shown to have an intermediate allele has proven especially challenging.
    2. This repeat range (45–54), often referred to as the "gray zone," can cause moderate anxiety in patients because this result is not called "normal," and intermediate repeat sizes may be unstable and can expand in subsequent generations.
    3. To date, there have been no reports of a CGG repeat of less than 56 expanding into a full mutation in a single generation.
7. Preimplantation genetic diagnosis (Saul and Tarleton 2012): available to at-risk pregnancies in which prior confirmation of the presence of an expanded (or altered) *FMR1* allele was identified in the family.
8. Management (Hagerman and Silverman 1991; Goldson and Hagerman 1992; American Academy of Pediatrics 1996; Hagerman 2001).
    1. To date, no drug is approved for the treatment of fragile X syndrome although many drugs are used to manage challenging behaviors from a symptomatic perspective in this population. A wide array of drug mechanisms is currently being assessed in FXS clinical study, although most are still in early phases (Davenport et al. 2016).
    2. Psychopharmacologic treatment with medications such as stimulants for attention and hyperactivity, selective serotonin reuptake inhibitors for anxiety, alpha-agonists for hyperactivity and overarousal, and antipsychotics for irritable and aggressive behaviors appear to be helpful by assessment in a clinical setting in approximately 50–70% of patients (Berry-Kravis et al. 2012).
    3. Emerging pharmacological treatment options (symptoms-based treatments) for fragile x syndrome (Schaefer et al. 2015).
        1. ADHD treatments: Overall, clinical treatment of ADHD symptoms in the context of FXS continues to focus on stimulant usage. Published data supporting use of agents approved by the FDA, including atomoxetine, clonidine, and guanfacine, specifically in persons with FXS, remains limited. Use of novel agents such as L-acetylcarnitine (LAC) or valproic acid (VPA) remains limited in the clinical setting for symptoms and behaviors of ADHD in this population.
        2. Sleep treatments: melatonin treatment leads to significantly longer sleep duration, shorter sleep latency, and earlier onset of sleep.
        3. Anxiety treatments: Oxytocin (OT) is a hormone produced in the hypothalamus that could diminish stress-induced behavior. Despite limited published data, selective serotonin reuptake inhibitor (SSRI) use targeting anxiety in persons with FXS is widespread. Clinical consensus on FXS appears to hold that SSRIs may be better tolerated in persons with FXS compared with youth with idiopathic ASD, where SSRI controlled trials have noted significant adverse effect rates and a lack of efficacy targeting repetitive behavior.

4. Irritability treatments: Atypical or newer-generation antipsychotics are often used by clinicians to treat the irritability associated with FXS. Despite their high rate of clinical use, there has been little systematic study of the efficacy of these antipsychotics within the FXS population.
4. Early intervention programs for developmental delay including speech and language therapies, physical therapy, and occupational therapy.
5. Behavioral interventions including psychopharmacological therapy.
6. Special educations.
7. Vocational planning.
8. Anticonvulsants for seizure control.
9. Prophylactic antibiotics for surgical or dental procedures in patients with mitral valve prolapse.
10. Orthopedic care for joint dislocations, flat feet, and scoliosis.

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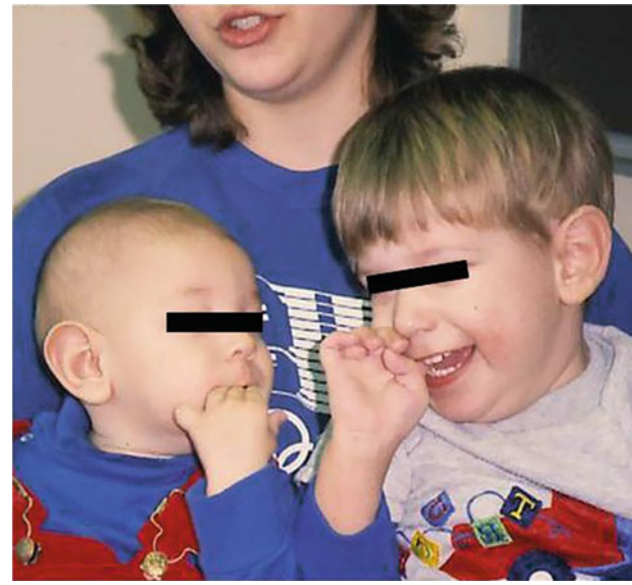

Fig. 1 Two brothers with fragile X syndrome showing large ears, accompanied by their mother

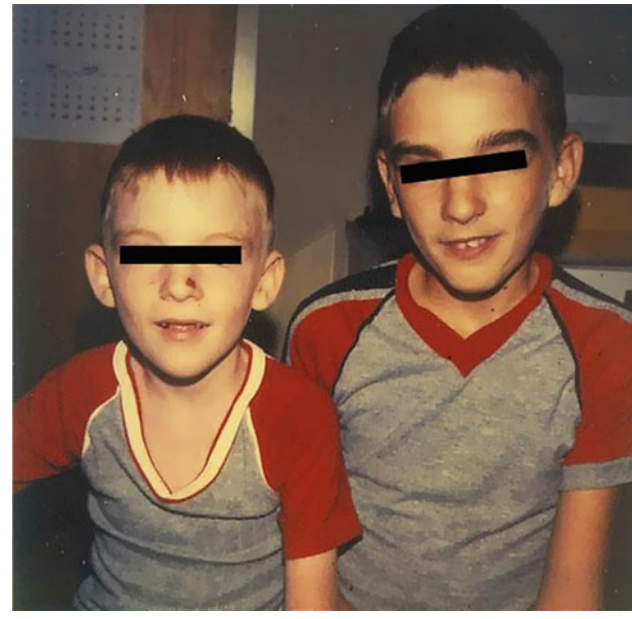

Fig. 2 A pair of brothers with fragile X syndrome showing a long face with large ears

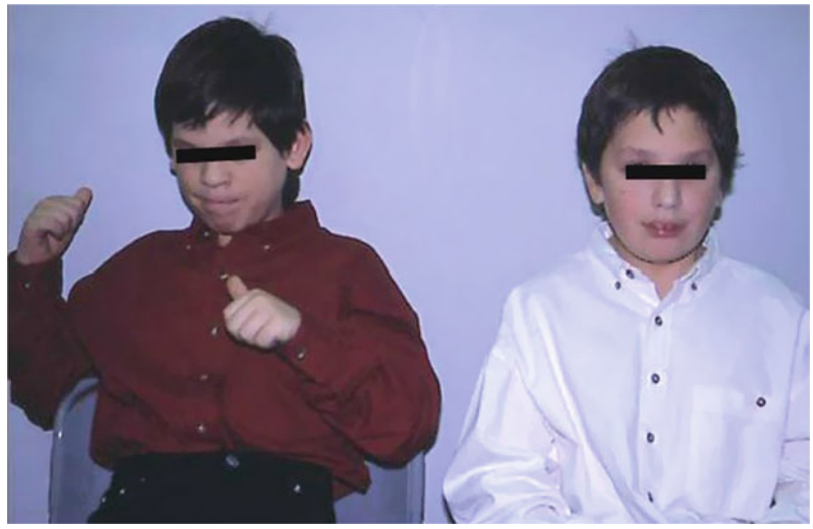

Fig. 3 Another pair of male siblings with fragile X syndrome

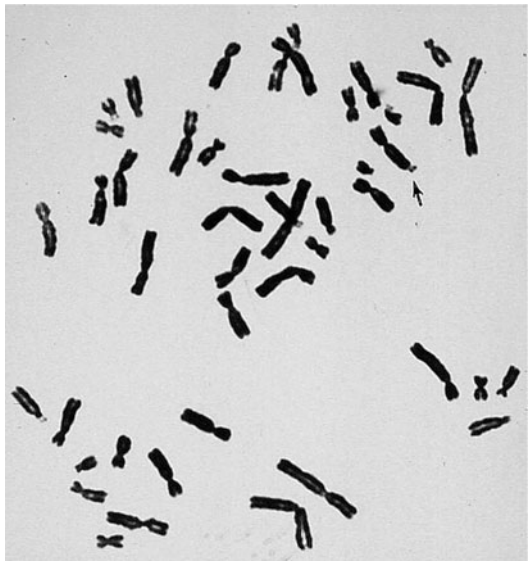

Fig. 4 A chromosome spread showing a fragile X chromosome (*arrow*)

Fig. 5 (**a**–**d**) A large family affected by fragile X syndrome. The first boy (**a**, age 15) is the most affected one with CGG repeats of >1,500. He was not toilet trained until age 5 or 6 years. He never spoke until after auditory training. He may watch TV for 6–8 h straight and get agitated if someone approaches him. The brother (**b**, age 10) and sister (**c**, age 16) have CGG repeats of 1,200 and 600, respectively. Another sister (**d**) is a carrier with CGG repeats of 110 who has four children. The daughter (age 3, the first one from the *left*) has CGG repeats of 700. She has a long face with prominent ears, a high-arched palate, and flat feet. She suffers from hyperactivity, tactile/oral/olfactory defensiveness, gaze aversion, poor postural alignment, food cramming, hand biting, excessive drooling, poor self-regulation, and speech difficulties including echolalia. The other three children are normal with normal CGG repeats. The maternal grandmother has CGG repeats of 126

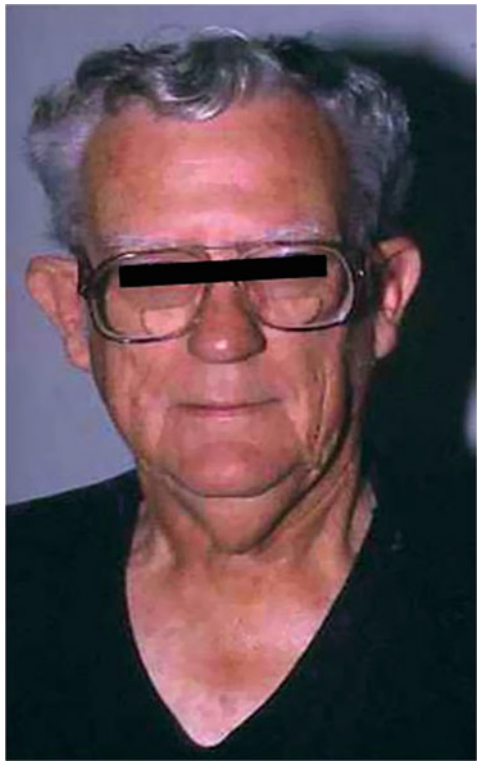

Fig. 6 A 66-year-old male with fragile X syndrome. The patient has mental retardation, a long face with large ears, and macroorchidism. Molecular analysis revealed CGG repeats of about 400

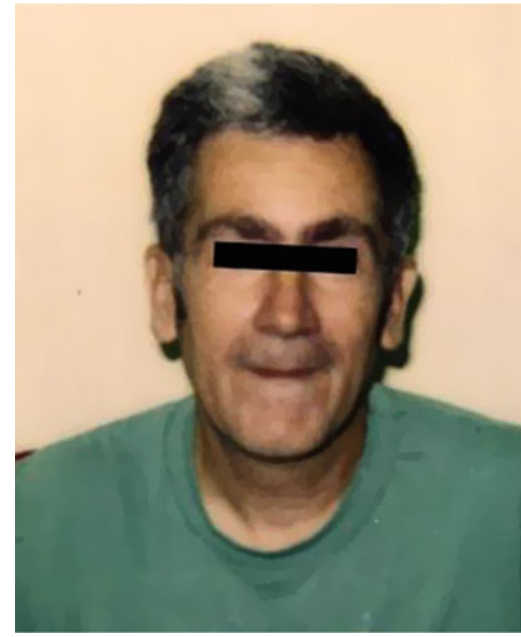

Fig. 7 A 46-year-old male with methylation mosaic fragile X syndrome (mixture of methylated full mutation allele of approximately 450 repeats in some cells and unmethylated premutation size allele of approximately 200 repeats in some cells). He is tall and has mental retardation, a long narrow face, slightly large ears, and macroorchidism

Fraser Syndrome

Contents

Fraser syndrome is a malformation syndrome characterized by cryptophthalmos ("hidden eye," a term coined by Zehender et al. 1872), cutaneous syndactyly, and anomalies of the genitourinary system. It was first described by Fraser in 1962. It is also known as cryptophthalmos-syndactyly syndrome, cryptophthalmos syndrome, or Fraser cryptophthalmos syndrome. Fraser syndrome occurs with a minimal estimated frequency of 0.43 per 100,000 live-born infants and 11.06 per 1,000,000 stillbirths (Martínez-Frías et al. 1998).

Synonyms and Related Disorders

Cryptophthalmos with other malformations; Cryptophthalmos-syndactyly syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Azevedo et al. 1973; Francannet et al. 1990; Barisic et al. 2013)
2. Caused by mutations in *FRAS1* and FRAS1-related extracellular matrix protein 2 (*FREM2*) genes:
    1. *FRAS1* gene, encoding a putative extracellular matrix (ECM) protein, located on the long arm of chromosome 4 (4q21)
    2. *FREM2* gene located on the long arm of chromosome 13 (13q13.3)
3. Mutations in *GRIP1*, which encodes a cytoplasmic scaffolding protein required for proper Fras1 localization at the basal membrane (Takamiya et al. 2004; Long et al. 2008), result in classical Fraser syndrome (Vogel et al. 2012; Schanze et al. 2014)
4. Genotype-phenotype correlations (van Haelst et al. 2008):
    1. Patients with an *FRAS1* mutation:
        1. More frequently skull ossification defects
        2. Low insertion of the umbilical cord
    2. Mutations were identified in only 43% of the cases suggesting that other genes syntenic to murine genes causing blebbing

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may be responsible for Fraser syndrome as well.

5. Familial cases (56%):
   1. Presence of consanguinity, estimated to be as high as 15%
   2. Multiple affected sibs born to the same parents (Slavotinek and Tifft 2002; Singh et al. 2007)
6. Three forms of cryptophthalmos, classified based on ophthalmic findings (Francois 1969):
   1. Complete (typical) cryptophthalmos:
      1. The eyelids replaced by a sheet of skin running from forehead to cheek with absence or poor development of the eyebrow
      2. Absence of the eyelashes or the gland structures
      3. The elevated skin covering the globe moves when eye movements occur
      4. The skin adherent to the underlying cornea
      5. Absence of the conjunctival sac
      6. Microphthalmia usually present
      7. Often associated with numerous congenital abnormalities, including anomalies of the head, ears, nose, and genitalia, and syndactyly. This pattern of anomalies is termed Fraser syndrome (Ferri and Harvey 1999)
   2. Incomplete (atypical) cryptophthalmos:
      1. Presence of rudimentary eyelids
      2. Lateral placement of a small conjunctival sac
      3. The palpebral aperture about one-third of normal length
      4. Usually small globe, covered almost completely by the skin
   3. Abortive form or congenital symblepharon:
      1. The upper eyelids, without a defined margin, cover and adhere to up to 75% of the upper cornea
      2. Absence of punctum in the eyelid
      3. Absence of the upper conjunctival fornix
      4. Free part of the cornea often keratinized or opaque
      5. Globes: usually normal or small size
7. Pathogenesis (Ferri and Harvey 1999):
   1. Primary failure of differentiation during embryogenesis
   2. Compression of the amniochorionic band
   3. Intrauterine inflammation
   4. Failure of lid fold development
   5. Inactivation of glutamate receptor interacting protein 1 (GRIP1), a cytoplasmic multi-PDZ scaffolding protein, leads to the formation of subepidermal hemorrhagic blisters, renal agenesis, syndactyly or polydactyly, and permanent fusion of eyelids (cryptophthalmos), Fraser syndrome-like defects in mice (Takamiya et al. 2004)

Clinical Features

1. Intrafamilial clinical heterogeneity (Chattopadhyay et al. 1993; Slavotinek and Tifft 2002)
2. Eyes:
   1. Cryptophthalmos (a developmental anomaly in which the skin is continuous over the eyeballs without any indication of the formation of eyelids): the most common feature of Fraser syndrome (84–93%) (Gattuso et al. 1987):
      1. Bilateral (more common) or unilateral
      2. Total or partial
   2. Microphthalmia
   3. Absent or malformed lacrimal ducts
   4. Ocular hypertelorism
   5. Coloboma of the upper eyelid
   6. Supernumerary eyebrows
   7. Blindness
3. Head: unusually low lateral hairline on temples extending to lateral eyebrow
4. Nose:
   1. Hypoplastic and notched nares
   2. Broad nasal bridge
   3. Midline nasal cleavage
   4. Choanal atresia

5. Mouth:
    1. Cleft lip
    2. Cleft palate
    3. High-arched palate
    4. Crowding of the teeth
6. Ears:
    1. Malformation of middle and external ears (cup shaped and low set)
    2. Microtia
    3. Low-set ears
    4. Absent pinna
    5. Skin of the upper helix contiguous with scalp
    6. Conductive hearing loss
7. Laryngeal stenosis/atresia
8. Chest: widely spaced nipples
9. Lungs:
    1. Lung hyperplasia (Stevens et al. 1994)
    2. Lung hypoplasia
10. Cardiac anomalies (Thapa and Bhattachakya 2008):
    1. Hypertrophy of the left ventricle
    2. A variant of Ebstein anomaly
    3. Coarctation of the aorta
    4. Atrial septal defect
    5. Interventricular communication
    6. Truncus arteriosus
    7. Ventricular septal defect
    8. Complex heart disease
    9. PDA
    10. Patent foramen ovale
    11. Dextrocardia
    12. Transposition of the great vessels
    13. Partial anomalous pulmonary venous connection
11. Gastrointestinal anomalies (Slavotinek and Tifft 2002):
    1. Imperforate anus
    2. Anal atresia and anal stenosis
    3. Rectal atresia
    4. Displaced anus
    5. Umbilical hernia
    6. Intestinal malrotation
    7. Colonic atresia
12. Urogenital anomalies (Codere et al. 1981; Burn and Marwood 1982; Francannet et al. 1990):
    1. Renal agenesis/hypoplasia:
        1. Unilateral
        2. Bilateral
        3. Hypoplastic bladder
    2. Male genital anomalies:
        1. Small penis
        2. Hypospadias
        3. Cryptorchidism
    3. Female urogenital anomalies:
        1. Anterior urethral atresia (Andiran et al. 1999)
        2. Bicornuate uterus
        3. Uterine hypoplasia
        4. Vaginal atresia
        5. Hypoplastic labia majora
        6. Clitoral enlargement
        7. Gonadal dysgenesis/gonadoblastoma (Greenberg et al. 1986)
13. Limbs: syndactyly of the fingers (cutaneous in 54% of cases) and toes
14. CNS involvement:
    1. Mental retardation
    2. Microcephaly
    3. Meningomyelocele
    4. Encephalocele
15. Natural history:
    1. Stillborn: 25% of affected infants
    2. Additional 20% of affected infants die before 1 year of age
    3. Survival to 96 years of age reported (Impallomeni et al. 2006)
    4. Commonest causes of death:
        1. CNS malformations
        2. Laryngeal stenosis or atresia
        3. Respiratory insufficiency
        4. Obstructive uropathy or bilateral renal agenesis
16. Diagnostic criteria (Thomas et al. 1986) requires at least two major and one minor or one major and four minor criteria for the diagnosis:
    1. Major criteria:
        1. Cryptophthalmos
        2. Syndactyly

3. Abnormal genitalia
4. Sib with Fraser syndrome

2. Minor criteria:
   1. Congenital malformation of nose
   2. Congenital malformation of ears
   3. Congenital malformation of larynx
   4. Cleft lip/palate
   5. Skeletal defects
   6. Umbilical hernia
   7. Renal agenesis
   8. Mental retardation

17. Revised diagnostic criteria for Fraser syndrome (van Haelst et al. 2007) requires either three major, or two major and two minor, or one major and three minor diagnostic criteria present in a patient:
    1. Major criteria:
       1. Syndactyly
       2. Cryptophthalmos spectrum
       3. Urinary tract abnormalities
       4. Ambiguous genitalia
       5. Laryngeal and tracheal anomalies
       6. Positive family history
    2. Minor criteria:
       1. Anorectal defects
       2. Dysplastic ears
       3. Skull ossification defects
       4. Umbilical abnormalities
       5. Nasal anomalies

Diagnostic Investigations

1. Radiography:
   1. Poor ossification of the calvarium
   2. Orbital structures
   3. Pulmonary hypoplasia
   4. Diastasis of the symphysis pubis
   5. Syndactyly
2. Renal ultrasound for renal anomalies
3. Hearing test
4. CT (De Bernardo et al. 2015):
   1. Unilateral microphthalmos
   2. Ocular globe inhomogeneous for structure and signals
   3. Thin optic nerve
   4. Presence of a malformation-like coloboma into the ocular globe with cysts
   5. A small calcification of the parietal anterior
   6. An incomplete myelination of the brain
5. MRI:
   1. Intracranial malformations: parietooccipital flattening, absent eyelids and eyelashes, and abnormal left tentorium traversing the left occipital lobe (Yesilkaya et al. 2012)
   2. Developing unilateral optic nerve and visual cortex (De Bernardo et al. 2015)
6. Molecular genetic testing (van Haelst et al. 2008; Shafeghati et al. 2008):
   1. Linkage analysis in consanguineous families indicated possible linkage to *FRAS1* and *FREM2* in 60% of the cases
   2. Mutation analysis identified 11 new mutations in *FRAS1* and one *FREM2* mutation
   3. Molecular genetic test: mutation c.[5752dup];[8544 + 1G > T] p.[(Cy51918fs)] in the *FREM2* gene (De Bernardo et al. 2015)

Genetic Counseling

1. Recurrence risk:
   1. Patient's sibs: 25%
   2. Patient's offspring: recurrence risk not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis:
   1. Prenatal diagnosis made in the follow-up of a pregnancy with a previous sibling having had the same syndrome (Feldman et al. 1985; Ramsing et al. 1990; Schauer et al. 1990; Fryns et al. 1997; Berg et al. 2001; Rousseau et al. 2002; Vijayaraghavan et al. 2005).
   2. Prenatal diagnosis made in families with a negative history (Boyd et al. 1988; Serville et al. 1989; Maruotti et al. 2004)

3. Prenatal ultrasonography:
    1. Most cases of Fraser syndrome (85%) are suspected prenatally, often due to the presence of the association of renal agenesis and cryptophthalmos (Barisic et al. 2013).
    2. Major findings:
        1. Cryptophthalmos
        2. Microphthalmia
        3. Syndactyly
        4. Ambiguous genitalia
    3. Other findings:
        1. Oligohydramnios
        2. Ear defects
        3. Renal abnormalities or agenesis
        4. Uropathy
        5. Hyperechogenic lungs
        6. Laryngeal stenosis/atresia (Balci 1999)
        7. Ascites
        8. Intrauterine growth retardation
        9. Polyhydramnios
    4. A combination of prenatal ultrasonography and fetoscopy (Gattuso et al. 1987; Kabra et al. 2000)
    5. Exome sequencing for prenatal diagnosis of fetuses with sonographic abnormalities (Drury et al. 2015)
3. Management:
    1. Immediate ocular management: frequent use of artificial tears to maintain corneal luster and clarity (Dinno et al. 1974).
    2. Intubation or tracheotomy to provide an adequate airway when laryngeal atresia/stenosis is present. Final repair of the laryngeal stenosis is deferred until about 1–2 years of age when adequate thyroid cartilage development has occurred (Karas and Respler 1995).
    3. A relatively high incidence of difficult or impossible tracheal intubation (20%) due to glottic stenosis (Mathers et al. 2014).
    4. Surgical correction of associated anomalies.
    5. Goals of reconstruction, considering the poor probability of restoring visual function (Ferri and Harvey 1999):
        1. To protect the cornea (if present) from infection and ulceration
        2. To enhance cosmetic appearance
        3. To preserve the globe
    6. Surgical treatment of congenital symblepharon variant (Brazier et al. 1986):
        1. Lid rotation flap
        2. Rotation incisions
        3. Rotation of medial end of lower lid
        4. Skin edges suture
    7. Surgical treatment at a later age (Dibben et al. 1997):
        1. Reconstruction in partial cryptophthalmos:
            1. Dissection of the eyelids from the cornea
            2. Reconstruction of the conjunctival fornices with buccal mucosa
            3. Repair the upper lid coloboma in a flap reconstruction using the inferior eyelid margin
        2. Reconstruction without grafting in complete cryptophthalmos (Ferri and Harvey 1999)
        3. Reconstruction of unilateral incomplete cryptophthalmos (Tran et al. 2015):
            1. An evisceration with orbital implant and reconstruction of the eyelids and fornices using the preexisting scleral remnant
            2. Custom ocular prosthetic fitting was performed 5 weeks postoperatively.
            3. The prosthesis was successfully retained at 4-year follow-up
    8. Surgical strategy for correction of cryptophthalmos (Saleh et al. 2009):
        1. The main indication for early surgery: presence or risk of corneal exposure in eyes with visual potential, as may occur in abortive cryptophthalmos
        2. Surgery deferred for painless eyes with no potential for vision and where there is a low risk of corneal exposure. These include:

1. Complete cryptophthalmos
2. Incomplete cryptophthalmos with completely keratinized corneas
3. Patients without corneal exposure

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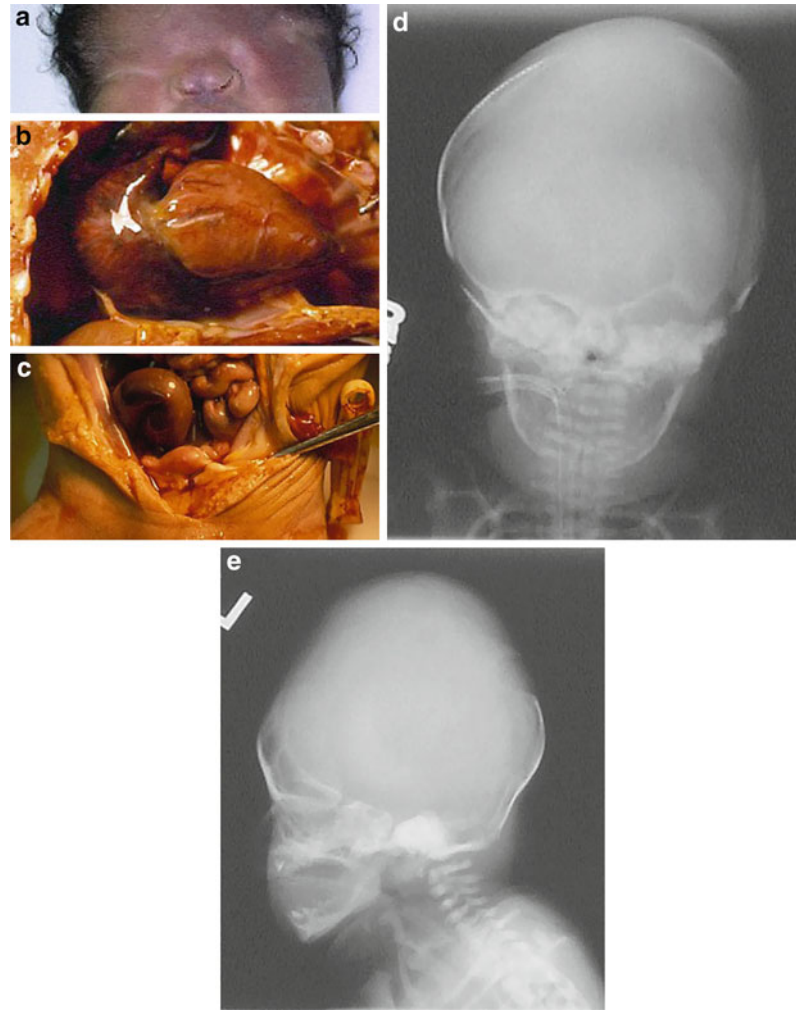

Fig. 1 (**a**–**e**) An infant with Fraser cryptophthalmos syndrome showing fused eyelids, lateral hair extending to lateral eyebrows, ocular hypertelorism, notched nares (**a**), and a tracheostomy site for management of laryngeal stenosis. Postmortem photos show lung hypoplasia (**b**), a small uterus (**c**), and clitoral hypertrophy. The skull radiographs (**d**, **e**) show poorly ossified calvarium

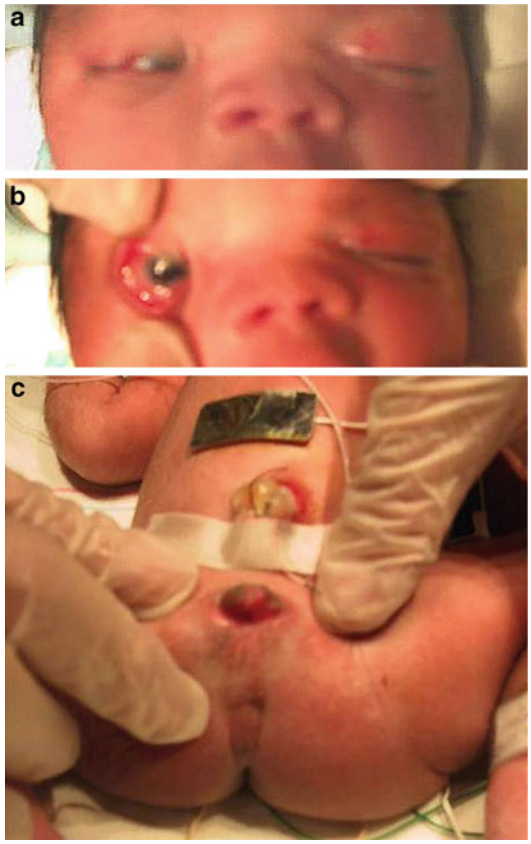

Fig. 2 (**a**–**c**) The sibling of the previous infant with Fraser syndrome showing microphthalmia, partial fusions of eyelids, ocular hypertelorism (**a**, **b**), genitourinary anomalies (**c**), and partial syndactyly of the toes. Variability of expression is illustrated in these two sibs

Freeman-Sheldon Syndrome

Contents

In 1938, Freeman and Sheldon described a syndrome characterized by a whistling face with a long philtrum, a puckered mouth, microstomia, H-shaped cutaneous dimpling on the chin, multiple joint contractures with camptodactyly, ulnar deviation of the fingers, bilateral talipes equinovarus, and kyphoscoliosis. Freeman-Sheldon syndrome (FSS) is the most severe of the distal arthrogryposes with the striking contractures of the orofacial muscles. The syndrome is also known as distal arthrogryposis (DA) type 2A, craniocarpotarsal dysplasia, or "whistling face" syndrome (Lev et al. 2000).

Synonyms and Related Disorders

Craniocarpotarsal dysplasia; "Whistling face" syndrome

Genetics/Basic Defects

1. Caused by mutations in embryonic myosin heavy chain gene (*MYH3*) (Toydemir et al. 2006). Sheldon-Hall syndrome (SHS) is known to be caused by mutations in either *MYH3*, *TNNT2* (Li et al. 2013), or *TNNT3* (Toydemir and Bamshad 2009)
2. Genetic heterogeneity (Sánchez and Kaminker 1986; Lev et al. 2000)
    1. Autosomal dominant inheritance (Malkawi and Tarawneh 1983; Marasovich et al. 1989; Gross-Kieselstein et al. 1971; Wettstein et al. 1980)
        1. Usually with normal psychomotor development, although mild motor delay attributable to joint anomalies might be present
        2. A variant of autosomal dominant inheritance, mapped to chromosome 11p15.5-pter (Krakowiak et al. 1997)
    2. Autosomal recessive inheritance (Kousseff et al. 1982; Fitzsimmons et al. 1984; Dallapiccola et al. 1989; Alves and Azevedo 1977): severe developmental retardation reported in a few patients
3. Pathogenesis
    1. Considered a form of distal arthrogryposis (Hall et al. 1982)
        1. Closely related to distal arthrogryposis type 1

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Similar limb phenotypes but distinguished only by differences in facial morphology
2. Reports of families in which different individuals were diagnosed with distal arthrogryposis type 1 or Freeman-Sheldon syndrome

2. Proposed to classify Freeman-Sheldon syndrome as distal arthrogryposis type 2 (a distinct disorder from distal arthrogryposis type 1 with overlapping phenotypes) in a revised classification of distal arthrogryposis
3. The embryonic myosin R672C mutation that underlies Freeman-Sheldon syndrome (distal arthrogryposis syndrome 2A) (DA2A) impairs crossbridge detachment and cycling in adult skeletal muscle (Racca et al. 2015)

2. Primary brain anomalies suggested to explain many manifestations of the syndrome
3. Also considered possibly a nonprogressive or slowly progressive myopathy (Vaněk et al. 1986)

4. Overlap of clinical characteristics of FSS with other DA syndromes suggests a shared etiology and/or pathogenesis (Stevenson et al. 2006)
   1. Several DAs can be caused by mutations in four genes that encode proteins of the troponin-tropomyosin complex of fast-twitch myofibers.
   2. Specifically, mutations in *TPM2*, *TNNT2* or *TNNT3*, and *MYH8* cause DA1, SHS, and trismus-pseudocamptodactyly (i.e., DA7), respectively.

Clinical Features

1. Variable clinical severity and phenotypic abnormalities (Weinstein and Gorlin 1969)
2. Normal intelligence
3. "Whistling face" appearance (Burzynski et al. 1975)
   1. Long philtrum
   2. Microstomia (Gurjar et al. 2013)
   3. Puckered mouth
   4. Pursed lips
   5. H-shaped cutaneous dimpling on the chin
4. Musculoskeletal anomalies
   1. Multiple joint contractures
   2. Camptodactyly
   3. Ulnar deviation of fingers
   4. Windmill vane hand (bilateral ulnar deviation and contracture of fingers two to five at the metacarpophalangeal joints with adduction of thumbs)
   5. Normal hands in a few reports
   6. Bilateral talipes equinovarus
   7. Kyphoscoliosis
5. Growth retardation
6. Other craniofacial features
   1. Masklike rigid face
   2. Flat midface
   3. Deep-sunken eyes with hypertelorism
   4. Antimongoloid slant of the palpebral fissures
   5. Blepharophimosis
   6. Convergent strabismus
   7. Full cheeks
   8. Small nose
   9. Coloboma alae of the nose
   10. Micrognathia
   11. Cleft palate or high-arched palate
   12. Choanal atresia
   13. Low-set and malformed ears
   14. Hearing loss (Zampino et al. 1996)
7. Other features
   1. Nasal speech
   2. Short neck
   3. Inguinal hernia
   4. Cryptorchidism
   5. Spina bifida occulta
8. Complications
   1. Difficulty in swallowing attributed to the mouth deformity
   2. Pulmonary problems due to decreased thoracic expansion
9. Diagnostic criteria of Freeman-Sheldon syndrome (Stevenson et al. 2006)
   1. Presence of ≥ 2 of the major clinical manifestations of distal arthrogryposis (DA) plus the presence of a small pinched

mouth, prominent nasolabial folds, and H-shaped dimpling of the chin
2. Major manifestations of DA of the upper limbs
    1. Ulnar deviation of the wrists and fingers
    2. Camptodactyly
    3. Hypoplastic, and/or absent flexion creases, and/or overriding fingers at birth
3. Major manifestations of DA of the lower limbs
    1. Talipes equinovarus
    2. Calcaneovalgus deformities
    3. A vertical talus
    4. Metatarsus varus

10. Genotype-phenotype correlation: phenotype severity varies significantly by genotype (Beck et al. 2014)
    1. Individuals with p.T178I were the most severely affected with both facial contractures and congenital scoliosis.
    2. Classification of individuals with DA2A into phenotypic groups of varying severity should facilitate providing families with more accurate information about natural history and suggests that individuals might benefit from personalized medical management motivated by *MYH3* genotype.
11. Differential diagnosis of Sheldon-Hall syndrome (SHS) (Stevenson et al. 2006); diagnostic criteria of SHS include:
    1. $\geq$2 of the major clinical manifestations of DA
    2. Deep nasolabial folds
    3. A small oral opening (but a larger oral opening than that of FSS)
    4. A small but protuberant chin (but lack an H-shaped dimpling of the chin)
    5. Webbing of the neck

Diagnostic Investigations

1. Radiography (O'Connell and Hall 1977)
    1. Skull
        1. Shallow anterior cranial fossa
        2. Hypoplastic mandible
        3. Small malar bones
    2. Ulnar deviation and flexion contractures of the fingers
    3. Talipes equinovarus
    4. Kyphoscoliosis
2. Polysomnography for sleep-disordered breathing
3. Muscle biopsy findings: structural changes predominantly involving type I fibers suggesting that the muscle lesion is a form of congenital fiber type disproportion (Duggar et al. 1989)
4. Biopsies of the affected facial muscles (orbicularis, masseter, buccinators, and risorius): reported to show atrophy of the muscular fibers with abundant infiltration of adipose tissue, fibrosis, central migration of the nucleus, and variation in diameter of the muscular fibers (Ferrari et al. 2008).
5. Molecular genetic testing of *MHY3* mutations

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal dominant inheritance: low unless a parent is affected
        2. Autosomal recessive inheritance: 25%
        3. Empirical risks for sibs of sporadic cases: 7%
    2. Patient's offspring
        1. Autosomal dominant inheritance: 50%
        2. Autosomal recessive inheritance: low unless the spouse is affected
        3. Empirical risk for children of sporadic case: 37%
    3. Parental gonadal mosaicism (molecularly proven somatic mosaicism in phenotypically normal parent after having an affected child) (Hague et al. 2016)
        1. A significantly increased recurrence.
        2. Parental testing is thus essential for accurate risk assessment for future pregnancies, and the use of new technologies with next generation sequencing may improve the detection rate of mosaicism.

2. Prenatal diagnosis
    1. Ultrasonography at 20 weeks of gestation in a fetus with a positive family history (Robbins-Furman et al. 1995).
        1. Bilateral equinovarus and abnormally positioned toes
        2. Clenched hands with overlapping thumbs
        3. An abnormally appearing mouth with pursing of the lips
    2. Molecular genetic diagnosis: if the family history is positive and the mutation is known in the family, prenatal molecular genetic diagnosis is possible by direct molecular testing of fetal DNA sample obtained from chorionic villus or amniotic fluid.
3. Management
    1. Tracheostomy required for severe upper airway narrowing (Robinson 1997)
    2. Management of anesthetic risks (Duggar et al. 1989; Fisher et al. 2016)
        1. Risks primarily related to severe microstomia
        2. Problems encountered: difficult intravenous access, failure to identify the subarachnoid space, and patient discomfort during surgery
        3. Combinations of myopathic and skeletal abnormalities predisposing affected patients to significant postoperative respiratory difficulty
        4. Awake endotracheal intubation or fiberoptic nasotracheal intubation in infants before induction of general anesthesia
        5. A combined spinal-epidural anesthetic approach
    3. Distraction osteogenesis for severe obstructive sleep apnea syndrome secondary to DA 2A (Toranto et al. 2014)
    4. Functional and cosmetic correction of microstomia (Neumann and Coetzee 2009)
    5. Combined surgical and non-surgical approach to extensive microstomia: bilateral commissuroplasty increases maximum mouth opening when combined with the use of a customized dynamic oral commissure retractor and was effective in the management of microstomia (Sadrimanesh et al. 2013)
    6. Functional hand reconstruction for hand deformities
    7. Orthopedic correction of clubfeet and scoliosis

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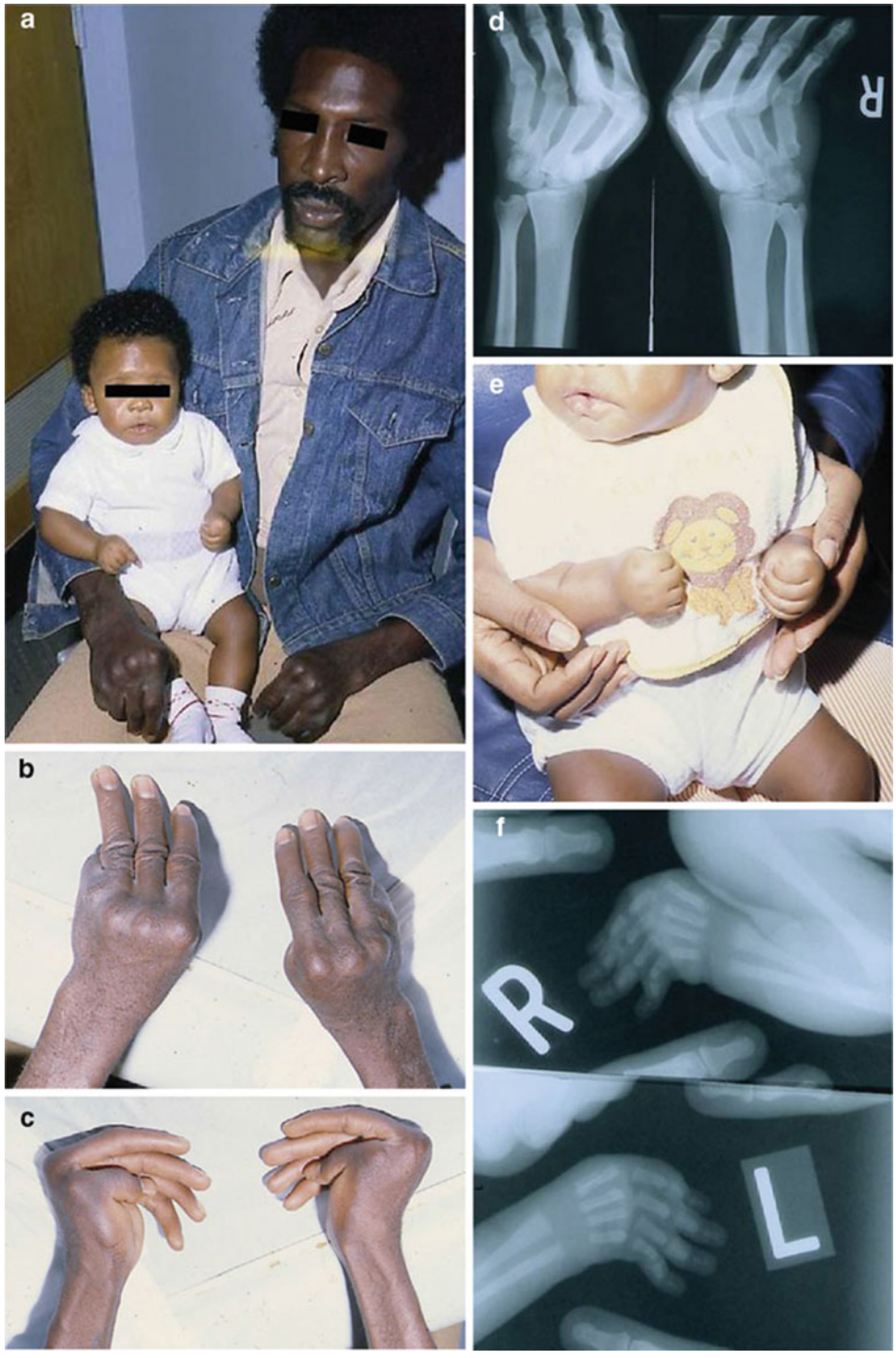

Fig. 1 (**a**–**f**) Freeman-Sheldon syndrome in a father (**a-c**) and son (**a**, **d**) showing whistling face appearance and ulnar deviation of fingers and fixed position of the thumbs. X rays of both hands and wrist AP views X-ray of the father (**d**) and the son (**a**, **e**) showed arthrogryposis, camptodactyly, and ulnar deviation of the hands and fingers

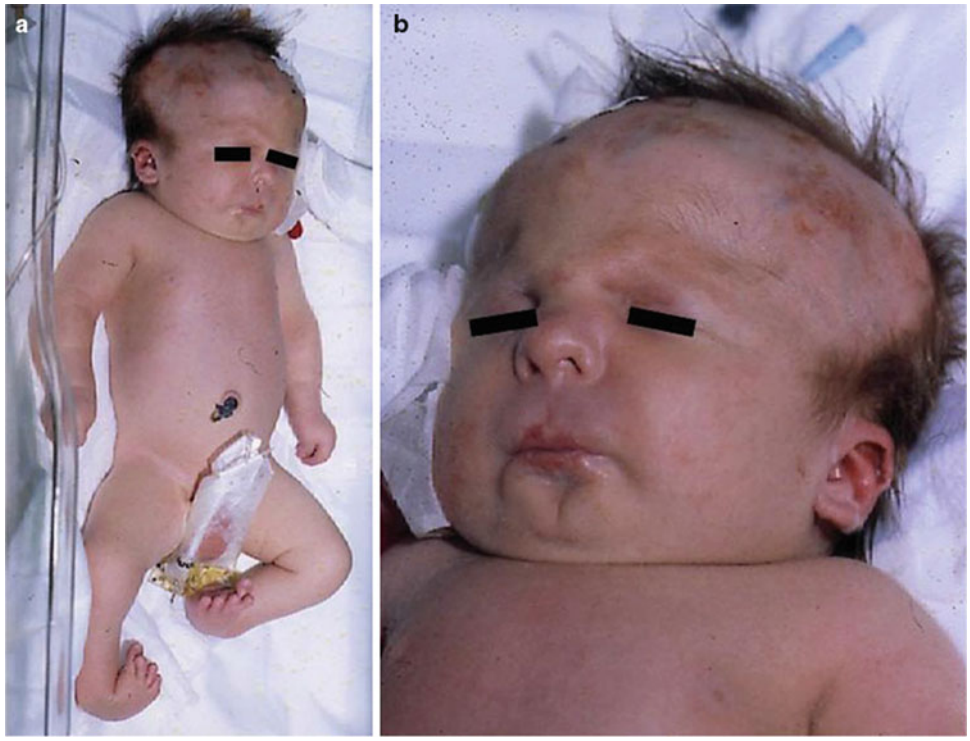

Fig. 2 (**a**, **b**) Freeman-Sheldon syndrome in a neonate showing characteristic "whistling face," ulnar deviation of the fingers with contractures, and talipes equinovarus

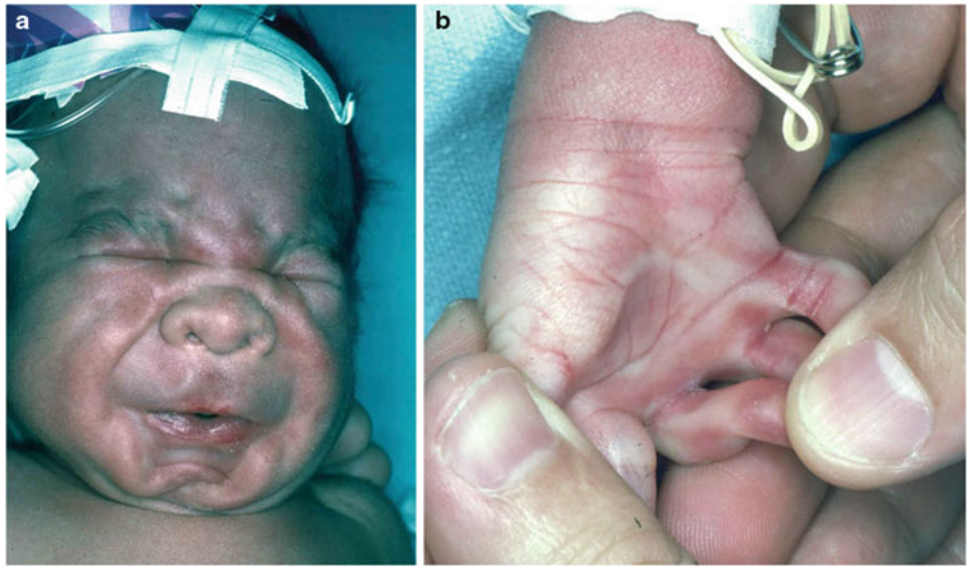

Fig. 3 (**a**, **b**) Another neonate showing characteristic "whistling face" with H-shaped cutaneous dimpling on the chin (**a**) and ulnar deviation and contractures of the fingers (**b**)

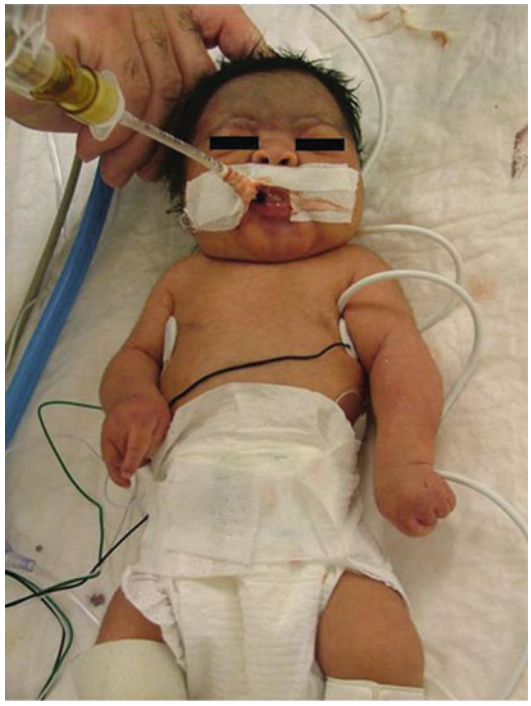

Fig. 4 A newborn with Freeman-Sheldon syndrome showing whistling appearance of the face, tight mouth opening, hypoplastic nasal alae, arthrogryposis of the hands and fingers with contractures and ulnar deviation of the wrists, and metatarsus adductus. Intrauterine growth retardation and Dandy-Walker malformation were detected prenatally by ultrasound

Friedreich Ataxia

Contents

During the period 1863–1877, Friedreich described the condition, now called Friedreich ataxia (FRDA), in nine members of three families. His initial report noted the following characteristics: age of onset around puberty and ataxia, dysarthria, sensory loss, muscle weakness, scoliosis, foot deformity, and cardiac symptoms.

FRDA is the commonest inherited ataxia (Harding 1984). Recent study based on molecular data suggests a carrier rate of 1 in 85 with a disease prevalence of 1 in 29,000 (Cossee et al. 1997).

Genetics/Basic Defects

1. Pathogenesis and molecular basis (Bidichandani and Delatycki 2014; Chawla 2015; Abrahão et al. 2015)
    1. An autosomal recessive disorder.
    2. The gene mutated in FRDA (frataxin) (FXN), mapped to 9q13-21.1, was initially called *X25* and later changed to *FRDA*.
3. *FXN* gene:
    1. Encodes a 210-amino acid mitochondrial protein called frataxin, whose biological function remains partially known.
    2. Both homozygous and heterozygous mutation mechanisms lead to a reduction of frataxin mRNA transcription and frataxin protein levels in different tissues, such as the heart, pancreas, peripheral blood cells, cerebellum, and dorsal root ganglia (Koeppen 2011).
4. The disease pathogenesis (Muthuswamy and Agarwal 2015):
    1. Fundamentally due to a lack of frataxin, which is claimed to play a role in iron-sulfur cluster synthesis.
    2. Oxidative stress builds up as a result of Fe accumulation in the mitochondria, causing degeneration of the cells (Delatycki et al. 2000), which primarily occurs in the neurons and later in the cardiac tissues, and to some extent in the pancreas.
5. Carriers of GAA expansion in one allele express near to 50% of FXN mRNA and are asymptomatic.
6. FRDA:
    1. Unique among trinucleotide repeat disorders in that it is autosomal recessive.
    2. The repeat is intronic (Campuzano et al. 1996).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. It is the only disease known to be the result of expansion of a GAA trinucleotide repeat.

7. GAA triplet repeat expansion in intron 1 of the *FXN* gene with four classes of alleles:
   1. Healthy individuals have GAA repeats between 10 and 66.
   2. Premutation (mutable normal) alleles: numbers between 35 and 66 GAA repeats.
      1. Not associated with FRDA but may expand during parental transmission, resulting in disease-causing alleles.
      2. Expansion of premutation alleles, sometimes more than tenfold the original size, has been observed in both paternal and maternal transmission.
   3. Disease-causing expanded (full penetrance) alleles (homozygous): 66–1,700 GAA repeats (Sharma et al. 2004).
   4. Borderline alleles: 44–66 uninterrupted GAA repeats.

2. Intergenerational instability, premutations, and origin of mutations
   1. GAA repeat underlying FRDA: unstable in its transmission from parent to offspring as in other trinucleotide repeat disorders (Timchenko and Caskey 1996).
   2. Maternal transmission may result in a larger or smaller allele in offspring, while paternal transmission always results in smaller allele (Monros et al. 1997; Pianese et al. 1997; Delatycki et al. 1998; De Michele et al. 1998). The size of the triplet repeat influences the direction of instability with smaller alleles more prone to increase in size and larger ones to decrease.
   3. Premutation alleles are prone to large expansion in one generation.
   4. Normal-sized alleles have a bimodal distribution:
      1. Small normal alleles (about 83%): between 6 and 12 repeats
      2. Large normal alleles (about 17%): between 14 and 34 repeats

3. Genotype-phenotype correlation: not possible to predict the specific clinical outcome in any individual based on genotype (Bidichandani and Delatycki 2014)
   1. Variability in individuals with FRDA may be caused by:
      1. Genetic background (e.g., Acadian individuals)
      2. Somatic heterogeneity of the GAA expansion
      3. Other unidentified factors
   2. GAA repeat size in homozygotes for pathogenic GAA repeat expansions:
      1. Statistically significant correlations with:
         1. Age of onset
         2. Presence of leg muscle weakness and/or wasting
         3. Duration until wheelchair use
         4. Prevalence of cardiomyopathy, pes cavus, and scoliosis
      2. Individuals with late-onset FRDA (LOFA): frequently exhibit fewer than 500 GAA repeats in at least one of the expanded alleles
      3. Individuals with very late-onset FRDA (VLOFA): usually have fewer than 300 GAA repeats in at least one of the expanded alleles
      4. Cardiomyopathy: more frequently seen with longer GAA repeat alleles
      5. Diabetes mellitus or abnormal glucose tolerance: does not show a clear-cut correlation with the size of the GAA expansion
   3. Spastic paraparesis without ataxia: may be seen in those with smaller expanded alleles or in association with the G130V missense mutation
   4. Compound heterozygotes for an expansion and a point mutation:
      1. Most compound heterozygotes are clinically indistinguishable from typical individuals with FRDA with homozygous GAA expansions.
      2. Compound heterozygotes for an expansion and a borderline “mutable” allele. Individuals with somatically unstable borderline alleles present with LOFA/

VLOFA, mild and gradually progressive disease, and normal reflexes/hyperreflexia.

4. Pathophysiology (Chawla 2015)
   1. Major pathophysiologic finding: "dying back phenomena" of axons, beginning in the periphery with ultimate loss of neurons and a secondary gliosis.
   2. Primary sites of changes in spinal cord and spinal roots resulting in loss of large myelinated axons in peripheral nerves, which increases with age and disease duration.
   3. Unmyelinated fibers in sensory roots and peripheral sensory nerves are spared.
5. Neuropathology of FRDA (Pandolfo 2009)
   1. Specific to this disorder (Koeppen 2002)
   2. Sensory neuronopathy in the dorsal root ganglia, accompanied by the loss of peripheral sensory nerve fibers and the degeneration of posterior columns of the spinal cord: a hallmark of the disease
6. Pathogenesis of cardiomyopathy (Koeppen et al. 2015)
   1. Cardiomyocyte hypertrophy
   2. Extensive endomysial fibrosis

Clinical Features

1. Diagnostic criteria for FRDA (Geoffroy et al. 1976)
   1. Primary (essential for diagnosis)
      1. Onset before the end of puberty (never after the age of 20 years)
      2. Progressive ataxia of gait
      3. Dysarthria
      4. Loss of joint position or vibration sense
      5. Absent tendon reflexes in the legs
      6. Muscle weakness
   2. Secondary
      1. Extensor plantar responses
      2. Pes cavus
      3. Scoliosis
      4. Cardiomyopathy
2. Diagnostic criteria for FRDA (Harding 1981)
   1. Primary (essential for diagnosis)
      1. Age of onset of symptoms before the age of 25 years
      2. Progressive unremitting ataxia of limbs and of gait
      3. Absence of knee and ankle jerks
   2. Secondary
      1. Dysarthria
      2. Extensor plantar responses
   3. Additional: if secondary criteria are absent, the following have to be present:
      1. An affected sib fulfilling primary and secondary criteria
      2. Median motor nerve conduction velocities of greater than 40 m/s, thus excluding cases of type I hereditary motor and sensory neuropathy
3. Typical and atypical FRDA (Harding 1981)
   1. Typical: cases meeting above criteria
   2. Atypical: cases not meeting above criteria
4. Main clinical features of FRDA patients (Abrahão et al. 2015)
   1. Neurological features in the classical phenotype of FRDA
      1. Ataxia (sensory and cerebellar)
      2. Areflexia
      3. Sensory loss
      4. Lower limb weakness
      5. Dysarthria/dysphagia
      6. Bilateral Babinski's sign
      7. Eye movements (involuntary saccades and square wave jerks)
      8. Optic neuropathy (uncommon)
      9. Auditory neuropathy (uncommon)
   2. Non-neurological features
      1. Cardiomyopathy (common)
      2. Diabetes mellitus (common)
      3. Skeletal abnormalities – pes cavus and scoliosis (common)
   3. Atypical phenotypes (Lecocq et al. 2016)
      1. Spastic ataxia, retained reflexes, lack of dysarthria, and lack of extra neurological signs
      2. Late-onset Friedreich ataxia (LOFA)
      3. Very late-onset Friedreich ataxia (VLOFA)

4. Friedreich ataxia with retained reflexes (FARR)
5. Early-onset FRDA

5. Differential diagnosis for FRDA and autosomal recessive ataxias (Jayadev and Bird 2013; Parkinson et al. 2013)
   1. Ataxia with vitamin E deficiency
   2. Ataxia with oculomotor apraxia types 1 and 2
   3. Ataxia telangiectasia (please see the chapter "► Ataxia-Telangiectasia")
   4. Charcot-Marie-Tooth disease (please see the chapter "► Charcot-Marie-Tooth Disease")
   5. Hereditary spastic paraplegia (please see the chapter "► Hereditary Spastic Paraplegia")
   6. Marinesco-Sjögren syndrome
   7. Refsum disease
   8. Autosomal recessive spastic ataxia of Charlevoix-Saguenay
   9. Hexosaminidase deficiency
   10. CoQ10 deficiency
   11. Mitochondrial mutations (mitochondrial recessive ataxia syndrome)
   12. Sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia
   13. Cerebrotendinous xanthomatosis

Diagnostic Investigations

1. Molecular genetic testing for confirmation of the disease (Muthuswamy and Agarwal 2015)
   1. Confirmatory tests for cases that are clinically unidentifiable and undifferentiable between FRDA and spinocerebellar ataxia.
   2. A triplet repeat primed polymerase chain reaction (TP PCR) for FRDA diagnosis (Ciotti et al. 2004).
      1. Validated the results with other methods such as Southern blotting, short PCR, and long PCR. However, it has its disadvantages such as the inability to discriminate between homozygosity/heterozygosity and to determine the number of GAA repeats.
      2. Further, short PCR, fluorescent PCR, and long PCR can be used to tell apart homozygosity/heterozygosity for GAA repeat expansion. Short PCR preferentially amplifies the normal allele, whereas long PCR possesses the ability to amplify expanded alleles. Thus, long and short PCR can be combined to discriminate homozygosity or heterozygosity of expansion.
   3. Southern blotting was initially used for the sizing of GAA repeats, and it is still a gold standard method for the sizing of repeats.
      1. The enzyme Eco RI was used 11 initially, and it was replaced by BsiHKA1 because of its higher resolution.
      2. Treatment of DNA with enzymes produces a 2.4-kb fragment, which is normal, and the presence of fragments above this size is considered to be positive for GAA repeat expansion.
   4. At present, long PCR is the most commonly used technique for diagnosis, followed by TP-PCR, which is being exploited for diagnostic purposes. However, accurate sizing is still possible only by Southern blot.
2. Clinical molecular laboratory testing
   1. Targeted mutation analysis
      1. Homozygous GAA expansion in *FXN* (96%)
      2. Heterozygous GAA expansion in *FXN*
   2. Sequence analysis: heterozygous point mutation in *FXN*
      1. Approximately 4% of patients are compound heterozygotes for a GAA expansion in the disease-causing range in one *FXN* allele and another inactivating *FXN* gene mutation in the other allele.
      2. No affected individuals with inactivating point mutations in both *FXN* alleles reported to date.
3. Echocardiography: reveals symmetric, concentric ventricular hypertrophy, although asymmetric septal hypertrophy may be present
4. Brainstem auditory evoked responses: typically displaying absent waves III and IV with preservation of wave I, suggestive of involvement of central auditory pathways

5. Visual evoked potentials: absent or delayed latency and reduced amplitude of the p100 wave in two thirds of patients
6. Somatosensory evoked potentials
    1. Delayed central conduction time (N13a/N20, N13b/N20)
    2. Dispersed potentials at the sensory cortex
    3. Abnormal central motor conduction
7. Magnetic resonance imaging of the brain and spinal cord: consistently shows atrophy of the cervical spinal cord and medulla with minimal evidence of cerebellar atrophy (Collins 2013)
8. Nerve conduction studies
    1. Absent sensory nerve action potentials
    2. Absent spinal somatosensory evoked potentials, although these may be reduced or even normal early in the disease course (Harding 1984)
    3. Motor nerve conduction velocities are reduced to a lesser extent than sensory nerve action potentials.
9. Histological studies
    1. Loss of myelinated fibers of the dorsal columns and the corticospinal tracts in lower cervical cord (Weil stain)
    2. Milder involvement of spinocerebellar tracts
    3. Compact fibrillary gliosis in the affected tract on hematoxylin and eosin (H&E) stain but no breakdown products or macrophages, reflecting the very slow rate of degeneration and death of fibers
    4. Shrinkage and eventual disappearance of neurons associated with proliferation of capsular cells in the dorsal spinal ganglia (H&E)
    5. Nearly devoid of large myelinated fibers in the posterior roots
    6. Degeneration and loss of cells of the Clarke column within the thoracic spinal cord

Genetic Counseling

1. Ability to diagnose FRDA by molecular means with a high sensitivity and specificity
    1. Clinically typical patients
        1. A specific and rapid diagnosis can be made in most patients and in the 4% compound heterozygous for a point mutation.
        2. The presence of one expanded allele indicates that the diagnosis is likely.
    2. Clinically atypical patients can be diagnosed to have or not to have FRDA by:
        1. GAA repeat study
        2. Mutation analysis for point mutations
    3. Carrier testing
        1. Available for relatives of affected and their partners.
        2. There is a small possibility that a point mutation may be present.
    4. For a subject with FRDA who has a carrier partner, there is a 1:2 risk of having an affected child. The a priori risk for a person with FRDA having a child with the condition is approximately 1:200 unless there is consanguinity.
    5. If the partner of a carrier does not have an expanded allele, the chance that they carry a point mutation is about 1:5,000 (taking a FRDA carrier rate of 1:100 and that 2% of mutations are point mutations). Therefore, the risk of this couple having a child with FRDA is about 1:20,000 which is only about twice the background risk of the general population.
2. Recurrence risk (Bidichandani and Delatycki 2014)
    1. Patient's sib
        1. Both parents carry a full penetrance allele, or one parent carries a full penetrance allele, and the other parent carries another deleterious *FXN* gene mutation.
            1. At conception: each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
            2. Once an at-risk sib is known to be clinically unaffected, the risk of his/her being a carrier is 2/3.

3. The wide range in age of onset and variable intergenerational instability of the GAA expansion dictate the use of caution in diagnosing an at-risk sib as unaffected.

2. One parent carries a full penetrance allele or another deleterious *FXN* gene mutation, and the other parent carries a mutable normal (premutation) allele.
   1. At conception: each sib of a proband whose parent is a carrier of a mutable normal (premutation) allele has a 25% chance of inheriting both parental mutations.
   2. Since the mutable normal (premutation) allele may remain unchanged or undergo minimal change (i.e., not expand to produce a full penetrance allele), the sibs have less than 25% chance of being affected.
   3. Each sib also has a 50% chance of being an asymptomatic carrier of one of the parental alleles and a 25% chance of being unaffected and having two normal alleles.

2. Patient's offspring
   1. All offspring inherit one mutant allele from the affected parent.
   2. Offspring have a 50% chance of being affected only if the reproductive partner of the proband is a carrier of a full penetrance allele or another deleterious *FXN* gene mutation.
   3. If the reproductive partner of the proband carries a mutable normal (premutation) allele, the risk to each offspring of developing FRDA is less than 50%.

3. Prenatal diagnosis (Bidichandani and Delatycki 2014)
   1. Possible for pregnancies at 25% risk provided both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed
      1. Amniocentesis
      2. Chorionic villus sampling
   2. Request for prenatal diagnosis of FRDA (Pandolfo and Montermini 1998)
      1. Usually prompted by a previous affected child.
      2. Most often both parents are carriers of a GAA expansion, so affected offspring have two expanded alleles.
      3. Alternatively, one of the parents carries a frataxin point mutation and the other has a GAA expansion. Affected offspring are compound heterozygotes.
      4. When the causative point mutation is known, prenatal diagnosis requires a test for this mutation along with expansion detection.
   3. Preimplantation genetic diagnosis: available for families in which the disease-causing mutations have been identified in an affected family member

4. Management
   1. Supporting measures (Bidichandani and Delatycki 2014; Collins 2013; Jayadev and Bird 2013):
      1. Prostheses, walking aids, and wheelchairs for mobility.
      2. Orthopedic interventions for scoliosis and foot deformities.
      3. Speech, occupational, and physical therapy.
      4. Hearing aids.
      5. Pharmacologic agents for spasticity.
      6. Dietary modifications and placement of a nasogastric tube or gastrostomy for dysphagia.
      7. Antiarrhythmic agents.
      8. Anticardiac failure medications.
      9. Anticoagulants and pacemaker insertion for cardiac disease.
      10. Oral hypoglycemic agents or insulin for diabetes mellitus.
      11. Antispasmodics for bladder dysfunction.
      12. Treatment for diabetes and dysphagia.
      13. Parkinsonian features may respond to L-dopa.
      14. Spasticity may respond to Baclofen or tizanidine.
      15. Psychological support.

2. Women with FRDA are capable of successful pregnancy with relatively few complications (Friedman et al. 2010).
3. Currently, no treatments have been proven to delay, prevent, or reverse the inexorable decline that occurs in this condition. However, several pharmaceutical agents are undergoing clinical assessment (Delatycki 2009; Abrahão et al. 2015).
4. Treatment with intermediate- and high-dose idebenone had beneficial effects on neurological symptoms (Schulz et al. 2009).
5. Improvement in both cardiac hypertrophy and neurological symptoms among patients with FRDA treated with a low dose of deferiprone with idebenone (Meier and Buyse 2009; Elincx-Benizri et al. 2016).

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Fig. 1 This 22-year-old man was seen for progressive muscle weakness and progressive ataxia. The patient began noticing the problem while running during football practice in high school. In the last 6 months, he has had trouble swallowing, especially liquids, and trouble speaking. At present, he walks with a cane with ataxic gait. There was a significant thigh muscle mass loss. His deep tendon reflexes are absent. Friedreich ataxia DNA test showed that the patient is homozygous for the GAA repeat expansion mutation which confirms the clinical diagnosis of Friedreich ataxia type I (FRDA1) with X25 allele 1 of 400 GAA repeats and X25 allele 2 of 400 GAA repeats

Fig. 2 The patient stands with a cane and needs to support standing with hand support on the wall

Frontonasal Dysplasia

Contents

Frontonasal dysplasia is a developmental field defect of craniofacial region characterized by hypertelorism and varying degrees of median nasal clefting. In 1967, DeMeyer first described the malformation complex "median cleft face syndrome" to emphasize the key midface defects. Since then, several terms have been introduced: frontonasal dysplasia, frontonasal syndrome, frontonasal dysostosis, and craniofrontonasal dysplasia (currently recognized as a syndrome distinct from frontonasal dysplasia) (Dubey and Garap 2000).

Synonyms and Related Disorders

Frontonasal malformation; Frontorhiny; Median facial cleft syndrome

Genetics/Basic Defects

1. Inheritance
    1. Sporadic in most cases.
    2. Rare autosomal dominant inheritance with variable expression.
    3. First human autosomal dominant frontonasal dysplasia syndrome associated with *SIX2* deletion (Hufnagel et al. 2016).
    4. Recessive mutations in the homeobox gene *ALX3* cause a recurrent pattern of frontonasal malformation (Twigg et al. 2009).
    5. Rare autosomal recessive inheritance: disruption of *ALX1* causes autosomal-recessive *ALX*-related frontonasal dysplasia (Uz et al. 2010).
    6. Rare X-linked dominant inheritance.
2. Rare association with chromosome anomalies
    1. Partial trisomy 2q and partial monosomy 7q from a balanced maternal t(2;7)(q31;q36) (Chen et al. 1992)
    2. Partial 21q22.3 deletion (Guion-Almeida et al. 2012)
    3. 22q11 microdeletion (Stratton and Payne 1997)
    4. Reciprocal translocation t(15;22)(q22;q13) (Fryns et al. 1993)
    5. Complex translocation involving chromosomes 3, 7, and 11 (Stevens and Qumsiyeh 1995)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_100

6. Either autosomal dominant or X-linked dominant inheritance (Fryburg et al. 1993; Nevin et al. 1999)
3. Rare variants of frontonasal dysplasia/malformation with variable inheritance patterns
4. Embryologically classified as a developmental field defect (Sedano and Gorlin 1986)
5. Extreme variable phenotypic expression (Cohen et al. 1971; Qureshi and Naeem-uz-Zfar 1996)
6. Pathogenesis (Twigg et al. 2009)
    1. Formation of the human face is an exquisitely orchestrated developmental process involving multiple tissue swellings (the frontonasal, medial and lateral nasal, and maxillary and mandibular prominences) derived from the neural crest (Moore and Persaud 2007).
    2. During a critical period between 4 and 8 weeks of human fetal development, these processes must undergo cell proliferation and tissue fusion to form the orbital, nasal, and oral structures (Yoon et al. 2000; Moore and Persaud 2007).
    3. Disturbance to this developmental sequence causes frontonasal malformation, a very heterogeneous group of disorders characterized by combinations of hypertelorism, abnormal nasal configuration, and oral, palatal, or facial clefting, sometimes associated with facial asymmetry, skin tags, ocular or cerebral malformations, widow's peak, and anterior cranium bifidum (DeMeyer 1967; Sedano et al. 1970; Sedano and Gorlin 1986; van der Meulen and Vaandrager 1989; Guinon-Almeida et al. 1996; Tan and Mulliken 1997; Losee et al. 2004).

Clinical Features

1. Pure frontonasal dysplasia (Dubey and Garap 2000)
    1. Variable mental retardation
    2. Inheritance pattern
        1. Sporadic in majority of cases
        2. Familial transmission in few cases
    3. Cranium bifidum occultum
    4. CNS anomalies
        1. Frontal cephalocele
        2. Meningocele/meningoencephalocele
        3. Agenesis of the corpus callosum
        4. Holoprosencephaly (Roubicek et al. 1981)
        5. Hydrocephalus
    5. Nasal anomalies
        1. Mild colobomas of the nostril
        2. Flattening of the nose with widely separated nares
        3. A broad nasal root
        4. Broad nasal tip
        5. Notching or clefting of alae nasi (cleft nose) (Fox et al. 1976)
        6. Nasal tag
    6. Ocular anomalies (Kinsey and Streeten 1977)
        1. Hypertelorism (Edwards et al. 1971)
        2. Epicanthal folds
        3. Narrowing of the palpebral fissures
        4. Ocular colobomata (Temple et al. 1990)
        5. Accessory nasal eyelid tissue with secondary displacement of inferior puncta colobomas
        6. Upper eyelid colobomas
        7. Epibulbar dermoids
        8. Microphthalmia
        9. Vitreoretinal degeneration with retinal detachment
        10. Congenital cataracts
    7. Facial anomalies
        1. Widow's peak configuration of the anterior hairline in the forehead (Smith and Cohen 1973)
        2. Median cleft of upper lip
        3. Median cleft palate
        4. Preauricular tag
        5. Absent tragus
        6. Low-set ears
    8. Other anomalies
        1. Conductive deafness
        2. Hypoplastic frontal sinuses
        3. Cardiac anomalies, especially tetralogy of Fallot

4. Limb anomalies
    1. Clinodactyly
    2. Polydactyly
    3. Syndactyly
    4. Tibial hypoplasia
5. Umbilical hernia
6. Cryptorchidism

2. Autosomal-recessive frontonasal dysplasia in two distinct families (Uz et al. 2010)
    1. Bilateral extreme microphthalmia
    2. Bilateral oblique facial cleft
    3. Complete cleft palate
    4. Hypertelorism
    5. Wide nasal bridge with hypoplasia of the ala nasi
    6. Low-set, posteriorly rotated ears
3. Other syndromes associated with frontonasal dysplasia or frontonasal malformation (Martinelli et al. 2002)
    1. Autosomal dominant form of frontonasal dysplasia with vertebral anomalies
    2. Acromelic frontonasal dysplasia (Slaney et al. 1999)
        1. Autosomal recessive disorder
        2. Similar frontonasal "dysplasia"
        3. Rare agenesis of the corpus callosum
        4. Tibial hypoplasia
        5. Polydactyly (duplicated hallux)
    3. Craniofrontonasal dysplasia (Cohen 1979; Orr et al. 1997)
        1. Possible X-linked disorder
        2. Rare mental retardation
        3. Hypertelorism
        4. Craniosynostosis
        5. Facial asymmetry
        6. Broad nasal root
        7. Bifid nasal tip
        8. Syndactyly of toes and fingers
        9. Split nails
        10. Broad first toe
    4. Acrocallosal syndrome (Nelson and Thomson 1982)
        1. Autosomal dominant or autosomal recessive disorder
        2. Severe mental retardation
        3. Hypertelorism
        4. Hypoplastic or absent corpus callosum
        5. Prominent forehead
        6. Small nose
        7. Broad nasal bridge
        8. Normal nasal tip
        9. Cardiac defects
        10. Postaxial polydactyly of hands and feet
        11. Preaxial polydactyly of feet
        12. Syndactyly of toes
        13. Clinodactyly
    5. Oral-facial-digital syndrome (Toriello 1993)
        1. X-linked disorder
        2. Variable mental retardation
        3. Agenesis of the corpus callosum
        4. Median cleft lip and palate
        5. Lobated/bifid tongue
        6. Clinodactyly
        7. Syndactyly
        8. Polydactyly
    6. Oculo-auriculo-frontonasal dysplasia (Toriello et al. 1995)
        1. Frontonasal dysplasia
        2. Ocular dermoids
        3. Eyelid colobomata
        4. Preauricular tags
    7. Fronto-facio-nasal dysplasia/dysostosis (Gollop 1981)
        1. Autosomal recessive disorder
        2. Frontonasal dysplasia
        3. Ocular dermoids
        4. Preauricular tags
        5. Cerebral lipoma
    8. Acro-fronto-facio-nasal dysplasia I
        1. Autosomal recessive disorder
        2. Frontonasal dysplasia
        3. Macrostomia
        4. Broad and notched nasal tip
        5. Fibular hypoplasia
        6. Polydactyly
        7. Short stature
    9. Acro-fronto-facio-nasal dysplasia II
        1. Autosomal recessive disorder
        2. Frontonasal dysplasia
        3. Microcephaly

4. Nasal midline groove with blind dimples
5. Broad thumbs
6. Syndactyly

10. Greig acrocephalopolysyndactyly
    1. Autosomal dominant disorder
    2. Mild mental retardation
    3. Mild features of frontonasal dysplasia
    4. Macrocephaly
    5. Broad nasal root
    6. Normal nasal tip
    7. Postaxial polydactyly of hands
    8. Preaxial polysyndactyly of feet
    9. Broad thumbs and halluces
    10. Syndactyly
11. Meinecke frontonasal dysplasia-cardiac defects
    1. Frontonasal dysplasia
    2. Microcephaly
    3. Cardiac defects, especially tetralogy of Fallot

4. Prognosis depending on severity of defects
    1. Normal intelligence in most patients
    2. Mental retardation affecting 12% of cases without CNS abnormalities
    3. Up to 50% of cases with mental retardation complicated by agenesis of the corpus callosum

Diagnostic Investigations

1. Radiology of craniofacial structures (Kurlander et al. 1967)
    1. Orbital hypertelorism
    2. Cranium bifidum occultum frontalis
    3. Primary telecanthus
    4. Median cleft nose
    5. Median cleft prolabium and premaxilla
    6. Median cleft secondary palate
    7. Some patients with frontal lipomas, dermoids, or teratomas
    8. Large cranial foramina (Vegesna et al. 2014)
2. Radiography, CT, and MRI of the brain
    1. Anterior cranium bifidum
    2. Agenesis of the corpus callosum
    3. Lipoma of the corpus callosum
    4. Arhinencephaly
    5. Hydrocephalus
    6. Occipital lobe hypoplasia (Vegesna et al. 2014)
3. Chromosome analysis for chromosome etiology
4. Molecular genetic diagnosis of *ALX1* and *ALX3* mutations: not available clinically

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal dominant disorder: not increased in de novo case unless a parent is affected
        2. Autosomal recessive disorder: 25%
        3. X-linked dominant disorder: 50% when the mother is a carrier
        4. Chromosome disorder: not increased in a de novo case; risk of unbalanced segregation from a carrier parent
    2. Patient's offspring
        1. Autosomal dominant disorder: 50%
        2. Autosomal recessive disorder: not increased unless the spouse is a carrier
        3. X-linked dominant disorder: 50%
        4. Chromosome disorder: not surviving to reproductive age
2. Prenatal diagnosis
    1. Ultrasonography (Frattarelli et al. 1996; Chervenak et al. 1984; Martinelli et al. 2002)
        1. Hypertelorism
        2. Frontonasal cephalocele
        3. Agenesis of the corpus callosum
        4. Median cleft lip
    2. 3-D ultrasonography: increasingly helpful in identifying facial features (Johnstone et al. 2008)
    3. Fetal MRI: periventricular nodular heterotopias (Recio-Rodríguez et al. 2014)
    4. Amniocentesis for associated chromosome anomaly

3. Management
    1. Speech therapy
    2. Maxillofacial surgeries for functional and cosmetic improvement
        1. Cleft lip/palate
        2. Hypertelorism
        3. A primary rhinoplasty on a bifid nose, a very mild form of FND (Núñez-Villaveirá et al. 2013)
    3. Psychosocial and/or psychiatric support

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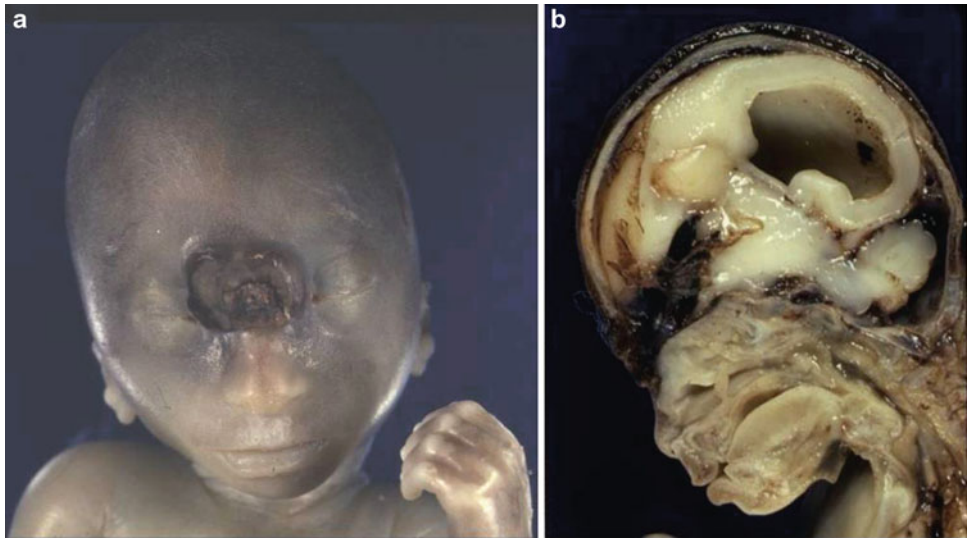

Fig. 1 (**a**, **b**) A newborn with frontonasal dysplasia showing ocular hypertelorism, cephalocele, hydrocephalus, and cranium bifidum

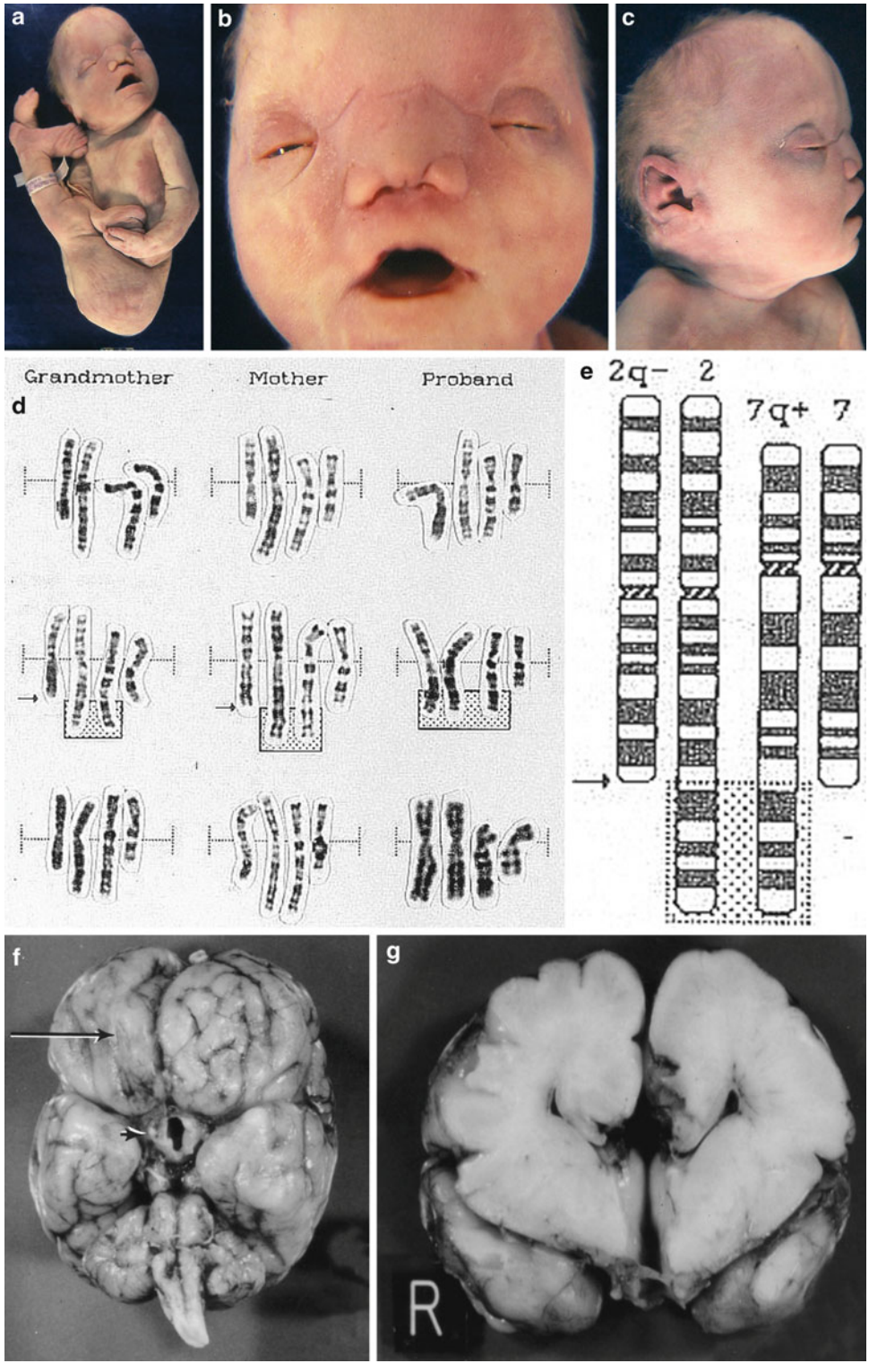

Fig. 2 (continued)

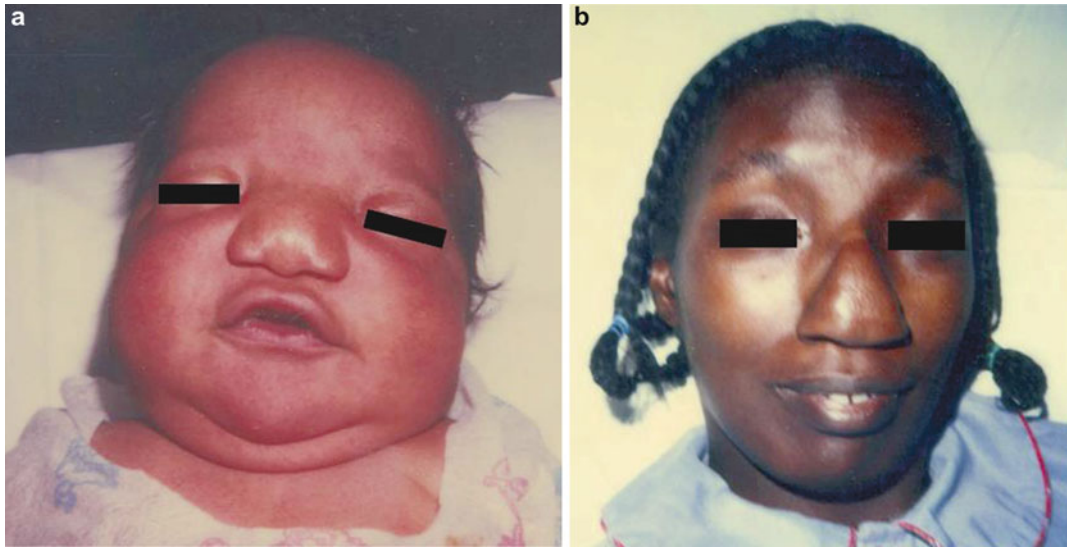

Fig. 3 (**a**, **b**) A child (**a**) and a mother (**b**) with frontonasal dysplasia showing hypertelorism and broad and notched nasal tip

Fig. 2 (**a**–**g**) A newborn with frontonasal dysplasia (**a**, **b**, **c**), iris coloboma, tetralogy of Fallot, limb anomalies (**a**), and arhinencephaly (**f**, **g**) resulting from unbalanced segregation of a maternal t(2;7)(q31;q36) (**d**). The patient had partial trisomy 2q and partial monosomy 7q (**d**) with an idiogram (**e**)

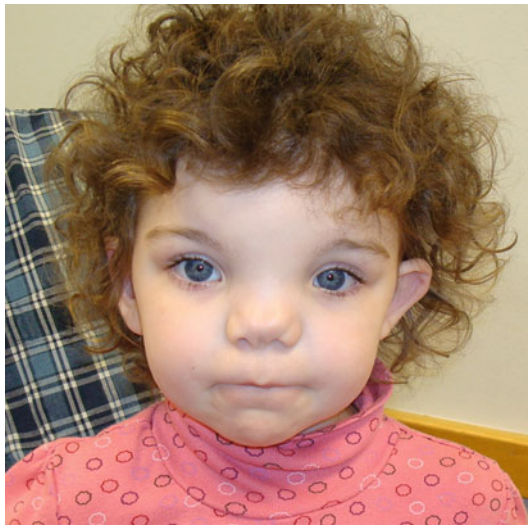

Fig. 4 A 2-year-old girl with frontonasal dysplasia

Galactosemia

Contents

Classic galactosemia (G/G) is an autosomal recessive disorder of galactose metabolism, caused by a deficiency of galactose-1-phosphate uridyl transferase. The incidence is estimated to be 1 in 30,000–1 in 60,000 births, based on the results of newborn screening programs.

Synonyms and Related Disorders

Classic galactosemia; Clinical variant galactosemia; Duarte variant; Galactokinase (GALT) deficiency; Galactose-1-phosphate uridyl transferase deficiency; Uridine diphosphate (UDP) galactose 4-epimerase (GALE) deficiency

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Leslie 2003)
2. Cause: deficiency of galactose-1-phosphate uridyl transferase (GALT)
3. Galactose metabolism (Arn 2003)
    1. D-galactose.
        1. Galactose: an important sugar in human nutrition, especially during childhood.
        2. Milk: major source of galactose, which contains lactose, a disaccharide of glucose and galactose.
        3. Liver: the primary site of galactose metabolism.
        4. Individuals have the capacity to metabolize large quantities of galactose under normal circumstances.
    2. Normal individuals.
        1. Lactase (present in the small intestine): metabolizes galactose to glucose and galactose.
        2. The resulting glucose and galactose is then absorbed via the portal system to the liver.
        3. In the liver, a series of four reactions converts galactose to glucose-1-phosphate.
        4. Glucose-1-phosphate can be metabolized to glucose, CO_2, pyruvate, or glycogen depending on prevailing metabolic conditions.
        5. Inborn errors have been described in all of the enzymes of the pathway.
    3. Affected individuals: complete deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT) causes classic galactosemia.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_101

4. Galactose-1-phosphate uridyl transferase.
    1. Causes the most common and severe form of galactosemia.
    2. The gene for GALT is mapped on chromosome 9p13.
    3. GALT is the second enzyme in the Leloir pathway, catalyzing conversion of galactose-1-phosphate and UDP glucose to UDP galactose and glucose-1-phosphate.
    4. Essential in human infants who consume lactose as their primary carbohydrate source.
    5. Near total absence of GALT activity in infants with classical galactosemia.
    6. A deficiency causes elevated levels of galactose-1-phosphate and galactitol in body tissues.
5. Galactokinase (GALK) deficiency.
    1. The first enzyme in the pathway of galactose metabolism, converting galactose to galactose-1-phospphate
    2. The only consequence of GALK deficiency: development of cataracts
6. Uridine diphosphate (UDP) galactose 4-epimerase (GALE) deficiency (Sutton 2015).
    1. UDP GALE converts UDP galactose to UDP glucose.
    2. In most patients with GALE (or epimerase) deficiency, the defect is localized to red blood cells (RBCs).
    3. These individuals typically have normal growth and development, whereas patients with generalized GALE deficiency in both RBCs and all other tissues present with symptoms similar to classic galactosemia.
7. Endogenous production of galactose may be responsible for the long-term effects, such as cognitive dysfunction and gonadal dysfunction in female patients.
8. Duarte (D) allele (Elsas et al. 1994; Beutler 1991).
    1. Very common
    2. Defined biochemically by:
        1. Reduced enzyme activity
        2. An isoform distinguishable by gel electrophoresis and isoelectric focusing
    3. Heterozygous Duarte variants (D/N)
        1. Observed in about 11% of Caucasian subjects
        2. Have about 75% of normal GALT activity
    4. Infants with a galactosemia allele and a Duarte allele (D/G)
        1. Have 1 quarter (25%) of normal enzyme activity
        2. Have reduced capacity to metabolize galactose with abnormal accumulation of galactose-1-phsphate in the red cells
        3. Phenotypically normal with no ill effect
    5. Homozygotes for the Duarte variant: patients with two Duarte alleles (D/D)
        1. Have approximately one half (50%) of normal transferase activity
        2. Mimic carriers for galactosemia
9. Genotype-phenotype correlations (Ng et al. 1994; Elsas II 2010).
    1. Q188R mutations (prevalent in 70% of Caucasians): a poorer outcome in homozygous state associated with essentially no enzyme activity (Elsas et al. 1995)
    2. Duarte variant (N314D)
        1. Homozygous state (D/D or N314D/N314D) with erythrocyte GALT enzyme activity reduced by only 50%
        2. Compound heterozygotes (D/G or N314D/Q188R)
            1. Relatively benign in most infants
            2. May or may not require dietary intervention
    3. Los Angeles (LA) variant (Langley et al. 1997) with identical N314D missense mutation but has normal erythrocyte GALT activity
    4. S135L allele (Lai et al. 1996; Lai and Elsas 2001)
        1. Prevalent in Africa
        2. The most common allele in African-Americans with classic galactosemia
        3. A good prognosis if therapy is initiated in the neonatal period without neonatal hepatotoxicity and chronic problems

5. K285N allele
    1. Prevalent in Eastern Europeans (Southern Germany, Austria, and Croatia)
    2. A poor prognosis for neurological and cognitive dysfunction in either the homozygous state or compound heterozygous state with Q188R
6. Q188R allele: the most common classic galactosemia allele in Caucasian and Hispanic Americans

Clinical Features

1. Onset of symptoms
    1. May present by the end of the first week of life
    2. May die or develop cataracts, hepatomegaly, cirrhosis, and mental retardation in late-detected cases
2. Neonatal toxicity syndrome
    1. Exposure to dietary galactose in infants with classical galactosemia results in acute deterioration of multiple organ systems, including the following (Berry 2014):
        1. Liver dysfunction
            1. Jaundice
            2. Hepatomegaly
        2. Coagulopathy
        3. Poor feeding and weight loss
        4. Vomiting and diarrhea
        5. Lethargy and hypotonia
        6. Renal tubular dysfunction
        7. Cerebral edema (encephalopathy)
        8. Vitreous hemorrhage
        9. *Escherichia coli* (or other gram-negative) sepsis: consider diagnosis of galactosemia since a high frequency of neonatal death appears to be caused by *E. coli* sepsis (Levy et al. 1977)
    2. Withdrawal of dietary galactose results in reversal of neonatal toxicity syndrome and reducing mortality and morbidity in the early weeks of life.
3. Cataracts (Burke et al. 1989)
    1. Resulting from accumulation of galactitol within the lens
    2. Seen in infants with classical GALT-deficient galactosemia (and also in galactokinase deficiency)
        1. The ocular hallmark of untreated or late-detected patients
        2. Severity of lens involvement dependent on the severity of galactosemia and the age at commencement of therapy
    3. Reoccur in older patients who have poor dietary compliance
    4. May be prevented by dietary restriction of galactose
4. Premature ovarian failure
    1. Despite the high prevalence of premature ovarian failure and subsequent infertility in galactosemic women, spontaneous pregnancies occur and may not be as rare as is generally assumed (Gubbels et al. 2008)
    2. Hypergonadotropic hypogonadism occurring almost universally (>90%) in females with classical GALT deficiency
    3. The rapidity and severity of the ovarian failure vary widely among individuals
    4. Ovarian dysfunction: most likely caused in utero (Holton 1995)
    5. Clinical manifestations
        1. Delayed puberty
        2. Primary amenorrhea
        3. Secondary amenorrhea
        4. Oligomenorrhea
5. Chronic brain effects
    1. Specific deficits
        1. Developmental speech dyspraxia and tremor
        2. Globally decreased IQ and/or learning disability
    2. Uncertainty as to:
        1. Whether these deficits are initiated in early development, perhaps even prenatally, and unmasked, as more complex brain function is required
        2. Whether these deficits represent true neurodegenerative processes compounded by dietary exposure and endogenous production of "intoxicants"
        3. Longitudinal assessment of intellectual achievement in patients with classic galactosemia (Schadewaldt et al. 2010):

1. Confirms the presence of reduced cognitive ability in classical galactosemia
2. Presents evidence for an absence of substantial galactosemia-induced aggravation of this impairment with increasing age, at least in patients from 4 to 40 years of age
3. Remains to be clarified whether a reduction of cognitive function in galactosemia may be initiated by an in utero toxicity of endogenously formed galactose and which role such a process may play in the development of intellectual deficiencies that are later maintained throughout life

6. Prognosis
   1. A life-threatening disorder if untreated.
   2. Currently, affected infants are treated before becoming ill because of newborn screening in most states.
7. Differential diagnosis (Elsas II 2010; Berry 2015)
   1. Galactokinase (GALK) deficiency
      1. An autosomal recessive disorder
      2. Considered in patients with cataracts and galactosemia but otherwise healthy
      3. Cataracts
         1. The main clinical feature
         2. Due to accumulation of galactitol
      4. Pseudotumor cerebri
         1. Described in several cases
         2. Considered to be a true consequence of the disorder
      5. These features resolve when a galactose-restricted diet is introduced
      6. Diagnosis made by detection of reduced galactokinase activity
      7. Caused by mutations in the *GALK1* gene
   2. UDP-galactose 4-epimerase (GALE) deficiency
      1. An autosomal recessive disorder
      2. Considered in patients with liver disease, sensorineural deafness, failure to thrive, and elevated galactose-1-phosphate but normal GALT activity
      3. Response to the removal of galactose from their diets
      4. Diagnosis made by detection of reduced UDP-galactose 4-epimerase activity
      5. Caused by mutations in the *GALE* gene
   3. Neonatal hepatotoxicity
      1. Infectious diseases (sepsis)
      2. Obstructive biliary disease
         1. Progressive familial intrahepatic cholestasis (Byler disease)
         2. Metabolic diseases such as Niemann-Pick disease type C and Wilson disease
   4. Fructose 1-phosphate aldolase deficiency (fructose intolerance) (Roth 2015)
   5. Neonatal hemochromatosis (Bhatia 2015)

Diagnostic Investigations

1. Newborn screening programs in most states (Leslie 2003)
   1. An almost 100% detection of affected infants in states that include testing for galactosemia in their newborn screening programs
   2. Prevention of needless deaths associated with galactosemia, resulting from limiting diagnostic measures to infants who develop symptoms
   3. A positive (i.e., abnormal) screening, followed by a quantitative erythrocyte GALT analysis
2. Liver dysfunction
   1. Bilirubin determination.
      1. Initial unconjugated hyperbilirubinemia
      2. Later conjugated hyperbilirubinemia
   2. Abnormal liver function tests.
   3. Abnormal clotting.
   4. Raised plasma amino acids, particularly phenylalanine, tyrosine, and methionine. Raised phenylalanine may result in a false positive neonatal screening test for phenylketonuria.
3. Renal tubular dysfunction
   1. Metabolic acidosis
   2. Urinalysis

1. Galactosuria
    1. The presence of reducing substances or galactose in the urine is neither sensitive nor specific.
    2. Small quantities of galactose commonly found in the urine of any patient with liver disease.
2. Albuminuria
    1. Present in the initial stage
    2. Quick disappearance of albuminuria after eliminating lactose-containing formula from the diet
3. Aminoaciduria in the later stage

4. Abnormal carbohydrate metabolism
    1. Increased plasma galactose
    2. Increased red cell galactose-1-phosphate
    3. Increased urine and blood galactitol
5. Testing for hemolytic anemia
6. Study for septicemia, especially *Escherichia coli*
7. Slit lamp examination for cataract assessment
8. Computerized tomography and magnetic resonance imaging (Nelson et al. 1992)
    1. Abnormalities on brain imaging: common in classical galactosemia
    2. Patients with late neurologic disease
        1. Abnormal white matter
        2. Ventricular enlargement
        3. Diffuse cortical atrophy with basal ganglia and brainstem involvement
        4. Cerebellar atrophy
        5. Failure of normal myelination
9. Endocrine investigations for hypergonadotropic hypogonadism
    1. Raised follicle-stimulating hormone
    2. Raised luteinizing hormone
    3. Initially normal estradiol concentration with high gonadotropin levels, indicating continued follicular development, but fall as ovarian failure progresses
10. Increased urinary galactitol excretion
11. Beutler test
    1. A fluorescent spot test for galactose-1-phosphate uridyl transferase activity
    2. Now widely used for the diagnosis of galactosemia
    3. False negative resulting from recent blood transfusions (within 3 months)
    4. False positive resulting from glucose-6-phosphate dehydrogenase deficiency
12. Red blood cell galactose-1-phosphate
    1. Concentration always raised in classical galactosemia
    2. Not significantly affected by blood transfusions
13. Biochemical confirmation of the diagnosis
    1. Red blood cell galactose-1-phosphate uridyl transferase assay
        1. A quantitative assay to confirm the diagnosis (virtual absence of the enzyme activity in classical (G/G) galactosemia)
        2. Also identifies variants with residual enzyme activity
        3. False negative results due to blood transfusion within 3 months
    2. A GALT isoelectric-focusing electrophoresis test to distinguish variant forms such as the Duarte defect
14. DNA analysis: *GALT* genotyping for providing specific molecular diagnosis
    1. Classic (G/G) galactosemia
        1. Mutation analysis for the six common *GALT* galactosemia (G) mutations
            1. Q188R mutation: the most common *GALT* allele in whites
            2. S135L: the most common allele in blacks
            3. K285N
            4. L195P
            5. Y209C
            6. F171S
        2. *GALT* sequence analysis to detect private mutations under the following two conditions:
            1. Both disease-causing mutations not detected by mutation analysis
            2. Diagnosis of galactosemia confirmed by biochemical testing
    2. Mutation analysis for Duarte variant (D/G) galactosemia identified by biochemical testing of the patient and both parents
        1. Identification of Duarte allele (N314D) by mutation analysis

2. Identification of G allele by mutation analysis or sequence analysis

15. Carrier testing
    1. Measuring GALT activity: about 50% of control values in carriers
    2. Molecular genetic testing for carriers available to family members, provided *GALT* mutation(s) has/have been identified in the proband

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. A proband with G/G galactosemia
            1. Given the parents are G/N and G/N: a 25% chance of being affected with G/G galactosemia for each sib
            2. Given the parents are D/G and G/N: a 25% chance of being affected with G/G galactosemia and a 25% chance of being affected with D/G galactosemia for each sib
        2. A proband with D/G galactosemia, given the parents are D/N and G/N: a 25% chance of being affected with D/G galactosemia for each sib
    2. Patient's offspring:
        1. Patient with G/G galactosemia and the normal spouse with N/N: All offspring are carriers.
        2. Patient with G/G galactosemia and the carrier spouse for a G allele (N/G): a 50% chance of having G/G galactosemia.
        3. Patient with G/G galactosemia and the carrier spouse for a G allele (D/G): a 50% chance of having G/G galactosemia and a 50% chance of having D/G galactosemia.
2. Prenatal diagnosis possible for fetuses at a 25% risk for classical galactosemia (Jakobs et al. 1995; Elsas 2001)
    1. Galactose-1-phosphate uridyl transferase assay in cultured amniotic fluid cells or in chorionic villus biopsies.
    2. Galactitol estimation in amniotic fluid supernatant.
    3. Mutation analysis of DNA extracted from amniocytes or chorionic villus samples if the genotype of the index case has been characterized.
    4. Prenatal diagnosis of a treatable condition, such as classic galactosemia, may be controversial if the prenatal testing is being considered for the purpose of pregnancy termination rather than early diagnosis.
    5. Preimplantation genetic diagnosis: may be available for families in which the disease-causing mutations have been identified.
3. Management (Arn 2003; Elsas II 2010)
    1. Availability of the newborn screening results within the fifth day after birth would allow the prevention of acute decompensation in classic galactosemia. A systematic diagnostic work-up in all positive newborns is essential to unravel the etiology of hypergalactosemia (Porta et al. 2015).
    2. Dietary intervention.
        1. Lactose-galactose-restricted diet
            1. Restrict milk, the principal source of lactose, and products made from milk.
            2. Breast milk and cows' milk contraindicated.
        2. Milk substitutes
            1. Use a formula free of bioavailable lactose (e.g., Isomil or Prosobee)
            2. Casein hydrolysate (Alimentum, Nutramigen, and Pregestimil): not recommended because they contain small amounts of bioavailable lactose
        3. Difficult to totally eliminate galactose since it is present in a wide variety of food, such as infant foods, fruits, and vegetables
        4. Older patients tolerating lactose much better than children, but recommend restricted milk intake throughout life

5. Calcium supplements if calcium intake does not meet the recommended daily allowance
6. May prevent cataracts, hepatomegaly, liver cirrhosis, mental retardation, and other symptoms
7. Effect of dietary restrictions during pregnancy on the long-term complications of an affected fetus: unknown
8. Individuals with homozygous Duarte variant without symptoms: do not require treatment (Ficicioglu et al. 2008)
9. Management of D/G or N344D/Q188R compound heterozygotes
    1. Decision to treat should be based on the demonstration of abnormal biochemical indices.
    2. No dietary therapy is instituted if the blood galactose and/or galactose-1-phosphate do not rise above 12 mg/dL within 4 h following such ingestion, and there are no clinical signs associated with galactosemia.
    3. Dietary therapy should probably be given if there is a greater accumulation of galactose or of galactose-1-phosphate.
    4. There is possible benefit of dietary intervention to individuals with variant forms of galactosemia with residual GALT activity in the range of 5–20: for prevention of cataracts, ataxia, dyspraxic speech, and cognitive deficits.

3. Vitamin K and fresh-frozen plasma to correct clotting abnormalities.
4. Pharmacologic treatment.
    1. An appropriate intravenous antibiotic for gram-negative sepsis.
    2. Many medications, particularly tablets, contain lactose, and this should be considered when prescribing; however, the amount of galactose is often insignificant when given over a short period.
5. Treat unconjugated hyperbilirubinemia with phototherapy or exchange transfusion to infants who may be at an increased risk of kernicterus if albumin levels are particularly low secondary to liver disease.
6. Parental feeding if the infant is too sick to tolerate enteral feeding for more than 1 or 2 days, unless there is significant liver disease or thrombocytopenia.
7. Treat the following long-term problems in older children and adults with classical galactosemia, despite early and adequate therapy.
    1. Cataracts
    2. Speech defects
    3. Poor growth
    4. Poor intellectual function
    5. Neurological deficits, predominantly extrapyramidal findings with ataxia
    6. Ovarian failure
8. Physical/speech therapy.
    1. Speech therapy for speech delay or verbal dyspraxia (Nelson 1995)
    2. Regular assessment of development and cognitive function using standardized tests recommended (Walter et al. 1999)
9. Other therapies/evaluations.
    1. Monitoring of red cell galactose-1-phosphate available for assessing dietary compliance; despite dietary adherence, these levels never decline to normal.
    2. Ophthalmologic examination for cataract assessment to be made at the time of diagnosis, every 6 months until age 3 years, and then annually (Walter et al. 1999).
    3. Referral to a pediatric endocrinologist by the time a female patient is 10 years (Walter et al. 1999).
10. Emerging therapies.
    1. None with trial data.
    2. Environment, GALT genotype, and epigenetic pathway of galactose metabolism probably all contribute to outcome.

3. In the absence of new therapies emerging from pathogenetic studies, attempts to enhance GALT activities may prove of value (Holton 1996; Elsas and Lai 1998) .

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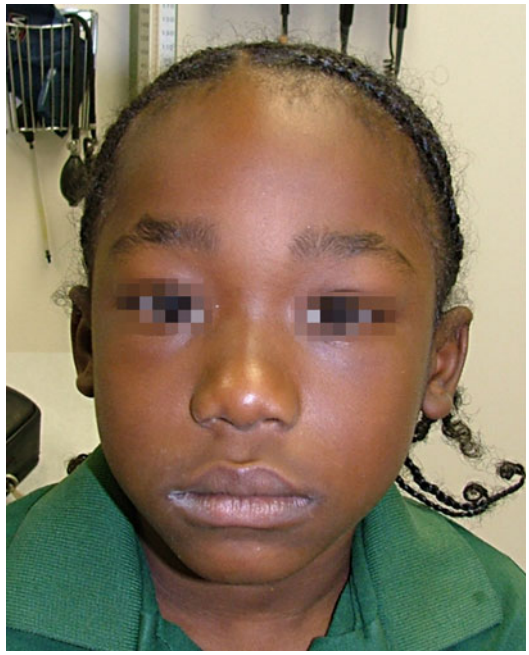

Fig. 1 A 5-year-old boy with classical galactosemia. The initial clinical presentation was at 12 days of age with unconjugated hyperbilirubinemia, presence of reducing substance in the urine, and *E. coli* sepsis. The patient was found to have posterior stellate lens opacities OU. He was found to have deficient galactose-1-phosphate uridyl transferase activity of 0.3 (normal range: 17–37 UMOL/HR/G HGB). Galactokinase was within normal limits. The patient was put on galactose-free diet and has been growing well

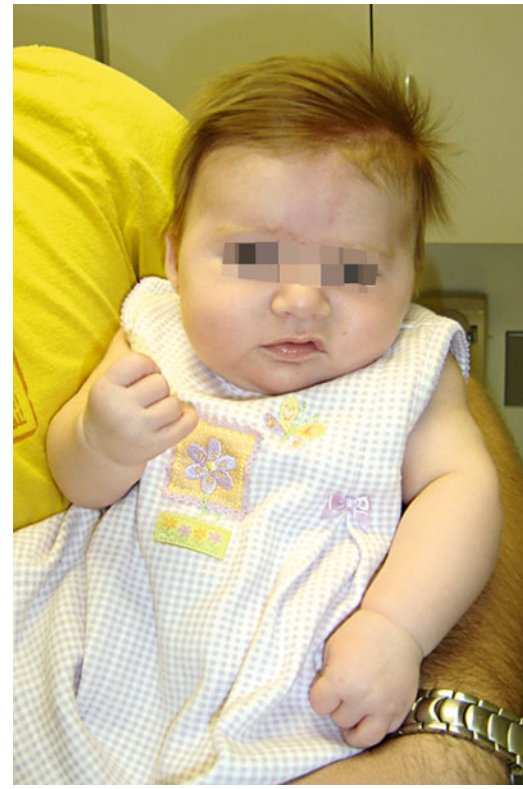

Fig. 2 A 2-month-old girl with D/G compound heterozygote. The newborn screening revealed total blood galactose (Gal + Gal-1-phosphate) level of 33.4 mg/dL (normal, <15.0) and blood galactose (without Gal-1-phosphate) level of 3.7 mg/dL. Enzyme assay for uridyl transferase was 41.3 μm (normal, >40.0). DNA analysis showed one copy of the N314D (Duarte galactosemia) variant and one copy of the Q188R (classical galactosemia) mutation. The patient is currently on Isomil and growing well

Gastroschisis

Contents

Gastroschisis (Greek for belly cleft) is a congenital paraumbilical wall defect characterized by the protrusion of the intestines uncovered by the peritoneum. It represents one of the most common congenital malformations requiring multidisciplinary neonatal intensive care, with an incidence of approximately 1 in 3300 births that seems to be increasing (Alvarez and Burd 2007).

Synonyms and Related Disorders

Anterior abdominal wall defects (Bladder exstrophy; Cloacal exstrophy; Limb–body wall and body-wall complex; Omphalocele)

Genetics/Basic Defects

1. Precise etiology unknown
2. Inheritance
    1. Isolated occurrence in most cases (Calzolari et al. 1995)
    2. Rare autosomal dominant inheritance
3. Pathogenesis and risk factors Sharp et al. (2000); Fillingham and Rankin 2008; Lammer et al. 2008; Rasmussen and Frias 2008)
    1. Pathogenesis
        1. Most commonly quoted: Hoyme's vascular disruption theory with disruption occurring in the omphalomesenteric artery (Hoyme et al. 1983)
        2. More recent proposed pathogenesis
            1. Consequence of abnormal folding of the body wall (Feldkamp et al. 2007).
            2. Disruption of endothelial oxide synthase pathway (its relationship to vasculogenesis) by environmental exposures or by genetic variation may represent one pathogenetic model for gastroschisis (Lammer et al. 2008).
    2. Risk factors (Torfs et al. 1994)
        1. Vascular insult
            1. Association of maternal smoking and maternal cocaine use with an increased incidence of gastroschisis
            2. The association of intestinal atresia and gastroschisis (Luck et al. 1985)
        2. Premature atrophy or abnormal persistence of the right umbilical vein
        3. In utero rupture of a hernia of the umbilical cord

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Young maternal age (<20 years of age) (Baer et al. 2015): the most striking epidemiological association with gastroschisis (20–25%)
5. Primiparous mothers
6. Socially disadvantaged mothers
7. Use of vasoactive drugs (e.g., decongestant pseudoephedrine) early in pregnancy
8. Use of aspirin and decongestants
9. Recreational (illicit) drug use (particularly the use of more than one drug)
10. Low socioeconomic status
11. Maternal nutrition
12. Living in close proximity to landfill sites
13. Other novel risk factors
    1. Prior history of gynecological infection/disease
    2. Change of paternity
    3. Paternal age

4. Rare syndrome association
   1. Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS)
   2. Amniotic band syndrome
   3. Limb–body wall complex
5. Rare association with chromosome abnormalities
   1. Trisomy 21
   2. Trisomy 13

Clinical Features

1. Herniation of abdominal contents
   1. Through a small abdominal wall defect
      1. Lateral to the insertion of the umbilical cord
      2. Most often to the right side of the umbilical cord
   2. Without covering sac
   3. The herniated viscera floating freely in the amniotic cavity
   4. Rare extrusion of the liver
   5. Dilatation of bowel loops due to partial lymphatic and venous obstruction when they are mechanically compressed against the sidewall of the defect
   6. Massive dilatation of the bowel secondary to volvulus, atresia, and ischemia
2. The incidence of associated anomalies relatively infrequent except associated gastrointestinal anomalies (10–20%)
   1. Intestinal stenosis/atresia, often related to:
      1. Intrauterine volvulus
      2. Strangulation of the blood supply to the extruded segment of intestine at the extremely tight abdominal wall defect
   2. Adhesions
   3. Malabsorption
   4. Meckel diverticulum
   5. Protein-losing enteropathy
   6. Midgut volvulus
   7. Necrosis
   8. Severe short gut syndrome
   9. Hypoperistalsis
3. Prognosis and complications
   1. Oligohydramnios
      1. Associated with a high incidence of intrauterine growth retardation which occurs in up to 60% of affected fetuses
      2. Possible secondary effects of severe oligohydramnios
         1. Pulmonary hypoplasia
         2. Limb compression
         3. Cord compression
   2. Polyhydramnios probably associated with reduced bowel motility or bowel obstruction
   3. Fetal distress during labor
   4. IUGR (Fries et al. 1993)
   5. Small for gestational age (Chescheir et al. 1991)
   6. Prematurity
   7. Sepsis
   8. Bowel damage
   9. Cardiac anomalies
   10. Nongastrointestinal-associated anomalies including occasional occurrence of amyoplasia and arthrogryposis
   11. Problems with absorptive and motility functions
   12. Intraoperative complications

13. Greater than 90% survival rate (Baerg et al. 2003)
14. Higher mortality rate (50%) associated with herniation of the liver
15. Rare reports of spontaneous resolution of gastroschisis and closure of the anterior abdominal wall defect (Tawil et al. 2001)

4. Intrauterine fetal death rate: 10–15% (Brantberg et al. 2004)
5. Outcomes in neonates with gastroschisis in US children's hospitals (Lao et al. 2010)
    1. Critical comorbidities and procedures
        1. Cardiovascular defects (15%)
        2. Pulmonary conditions (5%)
        3. Intestinal atresia (11%)
        4. Intestinal resection (12.5%)
        5. Ostomy formation (8.3%)
    2. Factors associated with mortality
        1. Large bowel resection (odds ratio 8.26)
        2. Congenital circulatory disease (odds ratio 5.62)
        3. Pulmonary disease (odds ratio 8.22)
        4. Sepsis (odds ratio 3.87)
    3. Factors associated with sepsis
        1. Intestinal ostomy (odds ratio 2.94)
        2. Respiratory failure (odds ratio 2.48)
        3. Congenital circulatory anomalies (odds ratio 1.58)
        4. Necrotizing enterocolitis (odds ratio 4.38)
6. Differential diagnosis (Nichol et al. 2008)
    1. Omphalocele
        1. Characterized by its involvement of the cord insertion and surrounding membrane.
        2. The distinction is important given the higher risk for chromosomal and other anomalies in omphalocele.
        3. The rare finding of a ruptured omphalocele may be very difficult to distinguish from a gastroschisis in utero (Bair et al. 1986).
        4. Characteristics of omphalocele (Christison-Lagay et al. 2011)
            1. Sac: present
            2. Associated anomalies: common
            3. Location of defect: umbilicus
            4. Maternal age: average
            5. Mode of delivery: cesarean/vaginal
            6. Surgical management: not urgent
            7. Prognostic factors: associated anomalies
        5. Characteristics of gastroschisis (Christison-Lagay et al. 2011)
            1. Sac: absent
            2. Associated anomalies: uncommon
            3. Location of defect: right of the umbilicus
            4. Maternal age: younger
            5. Mode of delivery: vaginal
            6. Surgical management: urgent
            7. Prognostic factors: condition of the bowel
    2. Limb–body wall and body-wall complex
        1. Both may involve defects of the ventral body wall, often large and asymmetric, and often involving multiple organs including the liver.
        2. The lack of a free-floating umbilical cord and scoliosis, with or without limb defects, will suggest this diagnosis.
    3. Amniotic band syndrome
        1. Amniotic band syndrome is often difficult to distinguish from body-wall complex.
        2. Frequently, will also involve severe anomalies of the craniofacial area.
        3. Like limb–body wall complex, may involve adhesion to the placenta.
    4. Bladder exstrophy (Glasser 2015; Khan 2015)
        1. May present as an external, well-defined, solid or complex mass immediately superior to the fetal genitalia sonographically
        2. Prolonged and repeated scans fail to reveal the fetal bladder.
        3. The renal collecting system and ureters need not be dilated and unilateral or horseshoe kidneys may be found.
        4. Uterine and adnexal anomalies are relatively frequent.
        5. The pubis is abnormally wide.
        6. Umbilical cord insertion may be abnormal.

5. Cloacal exstrophy (Glasser 2015; Khan 2015)
    1. Consists of a low omphalocele, bladder or cloacal exstrophy, and, frequently, other caudal anomalies, including meningomyelocele anal atresia and lower limb anomalies
    2. A single umbilical artery in most affected fetuses
    3. Sonographic findings include a low anterior abdominal mass below the umbilical cord that is associated with an absent urinary bladder.

Diagnostic Investigations

1. Routine blood work
2. Chromosome analysis rarely indicated (incidence of chromosomal anomalies <5%)
3. Abdominal radiography
4. Abdominal ultrasound
5. Gastrointestinal investigations to rule out gastroesophageal reflux, abnormal intestinal absorption and motility, and Hirschsprung disease
6. Echocardiography

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: The sibling recurrence risk is estimated to be 3.5% (familial occurrence of gastroschisis has been reported) (Torfs and Curry 1993) unless a parent is affected with an autosomal dominant disorder.
    2. Patient's offspring: The offspring recurrence risk is not increased unless the patient is affected with an autosomal dominant disorder.
2. Prenatal diagnosis
    1. Elevated maternal serum alpha-fetoprotein (MSAFP): MSAFP levels are greater in gastroschisis than in omphalocele (Palomski et al. 1988)
    2. Prenatal ultrasonography
        1. 2D ultrasonography followed by 3D ultrasonography can be useful for more-efficient counseling and postnatal therapeutic planning (Bonilla-Musoles et al. 2001)
        2. Demonstration of a mass adjacent to the anterior ventral wall representing the herniated viscera
        3. Herniation almost always exits through the right rather than the left lower quadrant.
        4. Cord vessels observed to the left of the exiting bowel
        5. Dilated bowel loops within or outside the abdomen observed when the abdominal wall defect is small
        6. Possible evisceration of stomach
        7. Possible evisceration of the urinary bladder with secondary hydronephrosis
        8. Polyhydramnios associated with bowel obstruction
        9. Gastroschisis can be prenatally diagnosed at 1st trimester (Cerekja et al. 2012)
    3. Amniocentesis
        1. Elevated amniotic fluid alpha-fetoprotein
        2. Positive acetylcholinesterase in gastroschisis but not omphalocele (Saleh et al. 1993)
        3. Chromosome analysis
3. Management (Langer et al. 1987)
    1. Counseling of parents (Hunter and Soothill 2002)
        1. Inform 5–10% incidence of fetal or neonatal death
        2. Inform long-term digestion problems associated with short gut syndrome
    2. No clear evidence indicating early cesarean section improves the outcome (Kirk and Wah 1983; Stringer et al. 1994; Segel et al. 2001)
    3. Requires multidisciplinary NICU care (Mills et al. 2010)
        1. Despite a high probability of survival (long-term survival rate over 85%) (Weber et al. 2002), gastroschisis babies and their families face a

prolonged hospitalization with the potential for significant long-term morbidity, especially that related to impaired capacity for enteral nutrition leading to cholestatic liver disease
    2. Potential need for organ transplantation
4. Endotracheal intubation for respiratory distress in neonates
5. Avoid hypothermia, hypovolemia, and sepsis
6. Fluid and electrolyte balance to prevent metabolic acidosis commonly observed as a result of poor perfusion related to hypovolemia
7. Insertion of an orogastric tube
    1. To prevent air swallowing
    2. To aspirate intestinal contents
8. Parenteral antibiotics
9. Surgical repair: primary repair versus staged repair with silastic silo
10. Total parenteral nutritional support for prolonged adynamic ileus (Baerg et al. 2003)
11. Potential need for organ transplantation (Mian et al. 2008)
12. Risks of prematurity must be weighed against the potential advantages of preterm delivery for infants with gastroschisis (Langer et al. 1993)
13. Early delivery is associated with prolonged enteral feeds/length of hospital stay, suggesting elective delivery at <37 weeks is not beneficial (Carnaghan et al. 2014).
14. Prenatal repair of gastroschisis (Luo et al. 2015)
    1. The ex utero intrapartum treatment procedure: performed to ensure fetal oxygen supply, which was likely to be compromised by the deep fetal anesthesia.
    2. The gastroschisis can be successfully repaired before the neonate is delivered.
    3. Maternal hemodynamics can be kept stable during this surgical procedure.
    4. The prenatal repair of abdominal wall defect is safe for the mother and the fetus, which could potentially improve the neonatal outcomes.

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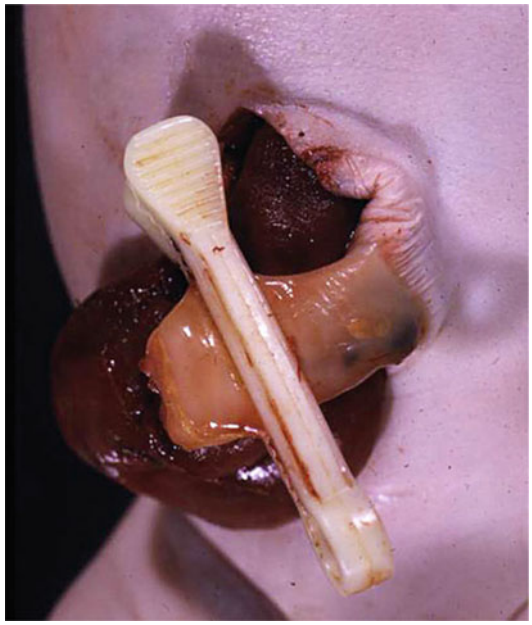

Fig. 1 A premature neonate had herniation of gastric antrum, small intestine, and colon through the gastroschisis, right of intact umbilicus. There was malrotation of the intestine

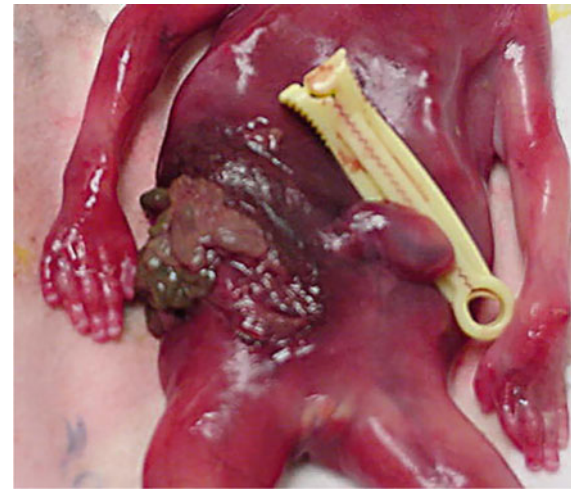

Fig. 2 A stillborn with gastroschisis showing herniation of abdominal contents

Gaucher Disease

Contents

Gaucher disease is the most common lysosomal storage disease and the most common genetic disorder among Ashkenazi Jews (Desnick 1982a, b). The disease incidence in the Ashkenazi population in Israel is 1 in 7750 to 1 in 10,000. The disease frequency in the Caucasian population is approximately 1 in 50,000 live births (Grabowski 2000).

Synonyms and Related Disorders

Acid beta-glucocerebrosidase deficiency; Gaucher disease type 1 (nonneuropathic type); Gaucher disease type 2 (acute neuropathic type); Gaucher disease type 3 (chronic neuropathic type); Gaucher disease type 4 (cardiovascular type); Glucocerebrosidase deficiency; Perinatal lethal Gaucher disease (collodion type)

Genetics/Basic Defects

1. Inheritance
   1. Autosomal recessive
   2. The gene encoding β-glucocerebrosidase (acid β-glucosidase) mapped to 1q21
2. Caused by mutation in the glucocerebrosidase (*GBA*) gene that results in deficiency of β-glucocerebrosidase activity
   1. Over 200 different mutations reported
   2. Four common mutations (N370S, L444P, 84GG, IVS2 + 1) (Grabowski 1997; Sibille et al. 1993; Charrow et al. 2000)
      1. Account for about 90% of the disease-causing alleles in the Ashkenazi Jewish population
      2. Account for 50–60% of the disease-causing alleles in the non-Jewish population
      3. Presence of the common N370S precludes neuronopathic involvement, also in combination with severe L444P.
   3. Other rare mutations and unique mutations: worldwide differences in genetic mutations.
   4. Genetic heterogeneity results in phenotypic heterogeneity: phenotypic presentation of the same mutation may vary in a wide spectrum: this difference is most possibly related with ethnicity, genetic background, and environmental and nutritional factors (Harmanci and Bayraktar 2008).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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5. Gaucher disease: a prototype of molecular medicine (Grabowski et al. 1996)

3. Consequences of deficient β-glucocerebrosidase activity (Charrow et al. 1998)
   1. Accumulation of glucocerebroside in the lysosomes of monocyte-derived macrophages in the reticuloendothelial system.
   2. Resulting hypersplenism produces progressive anemia and thrombocytopenia.
   3. Accumulation of glucocerebroside in bone marrow resulting in:
      1. Osteopenia
      2. Lytic bone lesions
      3. Pathologic fractures
      4. Chronic bone pain
      5. Acute episodes of excruciating "bone crisis"
      6. Bone infarct
      7. Osteonecrosis

Clinical Features

1. Notable for marked phenotypic variability/heterogeneity (Balicki and Beutler 1995; Mistry et al. 2015)
2. Type 1 (nonneuronopathic type) (GD1) (Nagral 2014; Thomas et al. 2014; Dandana et al. 2016)
   1. Absence of neurologic involvement
   2. Young adults/adults or chronic form: the most common form
   3. Representing about 85% of cases with Gaucher disease
   4. Most common in Ashkenazi Jewish population (1 in 450)
   5. 1 in 100,000 in general population
   6. Glucocerebrosidase activity: some activity but much less than normal
   7. Wide range of age of onset and rate of progression
      1. Ranging from disability in toddlers to asymptomatic disease in octogenarians
      2. The mean age at diagnosis: 21 years
   8. Skeletal involvement (Charrow et al. 1998)
      1. Clinical or radiographic evidence of bone disease in 70–100% of patients with type 1 Gaucher disease.
      2. May be the most debilitating and disabling aspect of type 1 Gaucher disease, leading to:
         1. Bone marrow infiltration by Gaucher cells
         2. Failure of remodeling
         3. Osteopenia
         4. Focal lytic or sclerotic lesions
         5. Osteonecrosis (Pastores et al. 2000)
         6. Osteomyelitis and bone crisis
         7. Chronic bone pain
         8. Pathologic fractures
   9. Hepatosplenomegaly
      1. Enlarged spleen with resultant hypersplenism associated with pancytopenia.
      2. Infarction of the spleen resulting in acute abdominal pain.
      3. Rare acute surgical emergencies because of splenic rupture.
      4. Hepatomegaly common but cirrhosis and hepatic failure rare.
   10. Pancytopenia
      1. Anemia secondary to the following cause:
         1. Hemolysis secondary to hypersplenism
         2. Hemodilution such as pregnancy
         3. Splenic sequestration
         4. Depressed erythropoiesis due to bone marrow failure from Gaucher cell infiltration or medullary infarction (in advanced cases, particularly postsplenectomy)
      2. Leukopenia
         1. Commonly noted
         2. Rarely severe enough to contribute to recurrent infections
         3. Risk of infection compounded by chemotactic defects in leukopenic patients
      3. Thrombocytopenia
         1. Resulting from hypersplenism, splenic pooling of platelets, or

marrow infiltration of Gaucher cells or infarction.
2. Associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy.
3. The risk of bleeding increases when there are concomitant clotting abnormalities.

11. Pulmonary disease
    1. Interstitial lung disease
    2. Alveolar/lobar consolidation
    3. Pulmonary hypertension
    4. Hepatopulmonary syndrome
        1. Dyspnea
        2. Cyanosis with digital clubbing
        3. Liver dysfunction
12. Cholelithiasis in adult patients (32%)
13. Cardiac and renal complications rarely encountered
14. Neurological complications secondary to bone disease
    1. Severe osteopenia with vertebral compression
    2. Emboli following long bone fracture
    3. Coagulopathy secondary to hematomyelia
    4. Parkinsonian features in a few patients: uncertain cause-and-effect relationship or just a coincidence
15. Absence of primary central nervous system disease
16. Ocular signs: absent
17. Increased risk of myeloma
18. Life span with or without therapy: early childhood to late adulthood
19. Therapeutic options
    1. Respond to ERT: good
    2. Substrate reduction therapy
    3. Orthopedic interventions
    4. Consider bisphosphonates for osteopenia

3. Type 2 (acute neuronopathic type) (GD2) (Sidransky et al. 1996; Sidransky 1997; Tayebi et al. 1999; Nagral 2014; Thomas et al. 2014; Weiss et al. 2015; Dandana et al. 2016)
    1. Infantile form: the rarest and most severe form of the disease
    2. No particular ethnicity
    3. Incidence: 1 in 100,000 live births
    4. Representing about 10% of cases with Gaucher disease
    5. Glucocerebrosidase activity: very little activity
    6. Early nervous system problems
    7. Onset before age 2 years, mostly symptomatic by age 6 months
    8. Normal at birth
    9. Development of hepatosplenomegaly
    10. Regression of developmental milestones
    11. Arrest of growth
    12. Brainstem abnormalities
        1. Bulbar signs
            1. Stridor
            2. Squint
            3. Swallowing difficulty
        2. Pyramidal signs
            1. Opisthotonus
            2. Head retroflexion
            3. Spasticity
            4. Trismus
    13. Oculomotor abnormalities
        1. Oculomotor apraxia
        2. Saccadic initiation failure
        3. Opticokinetic nystagmus
        4. Strabismus
    14. Other organ involvement:
        1. Nonimmune hydrops fetalis
        2. Congenital ichthyosis
        3. Life span with or without therapy: less than 2 years
    15. Therapeutic options
        1. Response to ERT: poor, not indicated
        2. No disease-specific therapy
        3. Palliative
    16. Collodion baby phenotype (congenital ichthyosis) in some neonates (Tayebi et al. 1999; Stone et al. 2000)
    17. Perinatal lethal Gaucher disease: a subset of type 2 or a specific clinical entity (Tayebi et al. 1999; Mignot et al. 2003)
        1. Lethality of a homozygous null mutation reported (Tayebi et al. 1999;
        2. Nonneurological involvement
            1. Nonimmune hydrops fetalis
            2. Prematurity

3. Fetal demise or death usually occurring within 2 days to 3 months
4. Hepatosplenomegaly (92%)
5. Thrombocytopenia (38%) associated with purpura (22%)
6. Anemia (10%)
7. Neonatal ichthyosis/collodion baby phenotype (41%)
8. Bone marrow invasion by Gaucher cells, a constant finding at autopsy

3. Neurological involvement
   1. Neurologic signs overlapping with classical type 2 Gaucher disease.
   2. Hypokinesia (43%) with facial dysmorphology.
   3. Contractures of distal joints (club foot, camptodactyly) (30%).

18. Universally progressive and fatal, succumb to apnea or aspiration by age 2–4 years

4. Type 3 (chronic neuronopathic type) (GD3) (Nagral 2014; Thomas et al. 2014; Dandana et al. 2016)
   1. Juvenile form: presenting in childhood or early adulthood
   2. No particular ethnicity: observed primarily in a cluster of cases from Sweden (Norrbottenian type) but may occur in other ethnic groups
   3. Glucocerebrosidase activity: little activity
   4. Hepatosplenomegaly
   5. Anemia
   6. Thrombocytopenia
   7. Bony involvement
   8. Kyphosis (Gibbus)
   9. Growth retardation
   10. Pulmonary infiltrates and esophageal varices associated with liver cirrhosis
   11. Neurologic disease (later onset): neurologic manifestation less severe compared to type 2
      1. Oculomotor apraxia: frequently the only neurologic finding (Bohlega et al. 2000))
      2. Supranuclear (horizontal) gaze palsy
      3. Seizures in some patients
         1. Generalized tonic-clonic seizures
         2. Progressive myoclonic epilepsy
      4. Advanced stage
         1. Dementia
         2. Ataxia
   12. Extensive vascular and valvular involvement (calcifications): reported in type 3 Gaucher disease (Altunbas et al. 2015)
   13. Lifespan extending into the third to fourth decade
   14. Therapeutic options
      1. Response to ERT: variable
      2. Bone marrow transplantation (considered in some patients)

5. Type 4 (cardiovascular type) (GD4)
   1. Calcification of the aortic and mitral valves
   2. Mild splenomegaly
   3. Corneal opacities
   4. Supranuclear ophthalmoplegia

6. B-cell neoplasia (including multiple myeloma) and Parkinson's disease: divergent but true comorbidities of Gaucher disease (Cox et al. 2015; Huang et al. 2015)

Diagnostic Investigations

1. General clinical laboratory blood tests (Charrow et al. 1998)
   1. Hemoglobin concentration for anemia.
   2. Platelet count for thrombocytopenia.
   3. Liver enzymes for liver disease.
   4. Iron, ferritin, and total iron-binding capacity for coexistent iron deficiency or iron overload.
   5. Prothrombin time and activated partial thromboplastin time for:
      1. Clotting defects associated with liver disease
      2. Factors IX and Factor X deficiency with Gaucher disease
      3. Factor XI deficiency that may cosegregate with Gaucher disease among Ashkenazi Jewish population
   6. Alkaline phosphatase, serum calcium, phosphorous, and 24-h urinary calcium for markers of bone involvement and defects in calcium absorption and metabolism.
   7. Total and direct bilirubin, and total protein and albumin for monitoring liver function.

8. Serum protein electrophoresis and serum immunoelectrophoresis for detecting monoclonal gammopathies that may be more common in adult patients with Gaucher disease than in the general population.
9. Plasma chitotriosidase (markedly elevated in plasma).

2. Abdominal ultrasound
   1. Assessing organ volume and parenchymal abnormalities
   2. Gallstone detection
3. Brainstem auditory evoked response (BAER) for abnormal wave form in type 2 and type 3
4. Bone densitometry for quantitative assessment of osteopenia
5. Radiography (Grabowski et al. 1998; Wenstrup et al. 2002; Marcucci et al. 2014; Simpson et al. 2014; Masi and Brandi 2015)
   1. Erlenmeyer flask deformity
      1. Common but not pathognomonic finding.
      2. Deformity resulting from the impairment of remodeling of the metaphyseal region of tubular bones.
      3. Manifesting as a flaring of the distal lateral aspects of the femur and proximal tibia.
   2. Bone crises
      1. Most common in childhood and adolescence presenting as episodes of severe bone pain associated with fever and leucocytosis.
      2. The signs and symptoms are indistinguishable from osteomyelitis; however, no infection exists.
      3. The terms "pseudo-osteomyelitis" and "aseptic osteomyelitis" have been historically used to characterize this condition.
   3. Lytic bone lesions
   4. Osteosclerosis due to aberrant remodeling after bone infarction with deposition of calcium
   5. Generalized osteopenia: decreased bone density
      1. Nearly universal in children and adults with Gaucher disease
      2. Associated with increased risk of bone fractures
   6. Osteonecrosis (avascular necrosis)
      1. Believed to be secondary to chronic infarction.
      2. Affecting primarily the femoral head, proximal humerus, and vertebral bodies.
      3. Resulting in fracture and joint collapse.
   7. Cortical thinning
   8. Fractures
   9. Bone marrow infiltration
   10. Rarely acute osteomyelitis
   11. Growth retardation
6. MRI
   1. Extent of marrow involvement (Maas et al. 2002)
   2. Fibrosis and/or infarction
   3. Cerebral atrophy
7. Proton magnet resonance spectroscopy of the brain in children (Khalek et al. 2013): a noninvasive technique (Pastores 2010) that can be used to detect brain abnormalities in neuronopathic Gaucher disease (NGD), and the choline/creatine ratio can be considered a biomarker of NGD as it is well correlated with clinical types, modified severity scoring tool and genotyping
8. Bone marrow aspiration (Pastores and Hughes 2015)
   1. Presence of lipid-engorged macrophages ("Gaucher cells").
      1. Fibrillary, "crumpled silk" appearance to the cytoplasm.
      2. Eccentrically placed nucleus.
      3. Stained positively with periodic acid-Schiff (PAS) reagent.
   2. Not a mandatory test since the bone marrow findings are nonspecific changes and not reliable.
9. Assay of acid β-glucocerebrosidase enzyme activity in peripheral blood leukocytes, lymphoblasts, cultured fibroblasts, amniocytes, and chorionic villi samples (Pastores and Hughes 2015)
   1. The most efficient and confirmatory diagnostic test
   2. Affected individuals: 0–15% of normal activity

3. Individuals with type 1 Gaucher disease: 10–15% of normal activity
4. Individuals with type 2 Gaucher disease: ≤10% of normal value
5. Unreliable for carrier detection since the values overlap in carriers and noncarriers

10. Molecular diagnosis (Nagral 2014)
    1. Mutation analysis confirms the diagnosis and can prognosticate the natural course of the disease.
    2. Patients with mutations secondary to N370S substitution do not develop neurological disease15 and those with homozygosity or compound heterozygosity for L444P or D409H mutation are usually associated with neurological disease.
    3. The D409H allele is also associated with cardiovascular and corneal involvement.
11. Molecular genetic testing to identify two disease-causing alleles providing additional confirmation of the diagnosis (Pastores and Hughes 2015)
    1. Targeted mutation analysis
    2. Sequence analysis

Genetic Counseling

1. Recurrence risk (Pastores and Hughes 2015)
    1. Patient's parents
        1. Heterozygotes (carrying a single copy of a disease-causing mutation in the *GBA* gene) in most instances
        2. Asymptomatic
        3. A homozygous parent possible.
            1. High carrier frequency in certain population (approximately 1 in 18 in Ashkenazi Jews population)
            2. Variable phenotype with the N370S/N370S genotype
    2. Patient's sib
        1. 25% affected, given the parents are carriers.
        2. 50% affected when one of the parents is a homozygote and the other a heterozygote.
    3. Patient's offspring
        1. When the spouse is not a carrier: all offspring obligate heterozygotes.
        2. When the spouse is a carrier: 50% of offspring affected and 50% of offspring carriers.
    4. GD carrier screening (Falcone et al. 2012)
        1. Offered at a high rate within the scope of Jewish ancestry-based carrier screening
        2. Genetic counseling dilemma
            1. Possible difficulty of having to make a decision on whether to pursue prenatal diagnosis and possible termination for a condition with reduced penetrance, variable severity, and effective treatment
            2. Carrier screening for GD may reveal that an individual has a mild or asymptomatic form of GD.
    5. Genetic counseling (Weiss et al. 2015)
        1. Families need to be educated about risks and alternatives relevant to future family planning, including prenatal diagnosis, preimplantation diagnosis, sperm or egg donation, as well as adoption.
        2. Unusual mechanisms including uniparental disomy for chromosome 1 and germline or de novo mutations have been described in patients with GD (Saranjam et al. 2013; Benko et al. 2008). Thus, the recurrence risk is not always obvious.
2. Prenatal diagnosis
    1. Prenatal ultrasound findings in perinatal lethal Gaucher disease (Rowlands and Murray 1997; Beaujot et al. 2013)
        1. Perinatal lethal GD: phenotypic heterogeneity (Mignot et al. 2003, 2006; Plakkal et al. 2011)
        2. Nonimmune hydrops fetalis
        3. Hepatosplenomegaly
        4. Abnormal fetal movements, posture, and tone
        5. Gaucher's disease should be considered in all fetuses with hydrops and arthrogryposis (Rowlands and Murray 1997)

2. Available to pregnancies at increased risk
    1. Highly useful to predict nonneuronopathic disease with assurance.
    2. Overall difficulty in predicting disease progression adding complexity.
    3. If the disease is controlled, with proper therapy and monitoring, mothers are more likely to experience uncomplicated pregnancies and deliveries (Giannubilo et al. 2015).
3. Analysis of β-glucocerebrosidase enzymatic activity (0–15% of normal), performed on fetal cells obtained by:
    1. CVS cells
    2. Amniocytes
4. Mutation analysis of the *GBA* gene when the disease-causing *GBA* mutations have been identified in both parents or a prior affected sibling, performed on fetal cells obtained by:
    1. CVS cells
    2. Amniocytes
5. Preimplantation genetic diagnosis (PGD) (Altarescu et al. 2010)
    1. In the case of type 1 Gaucher disease, PGD might be considered because it obviates the ethical dilemma of pregnancy termination should the fetus be affected.
    2. PGD is possible for at-risk pregnancies provided the disease-causing mutations have been previously identified in the family.

3. Management (Vellodi et al. 2001; Pastores and Barnett 2003)
    1. Symptomatic care
        1. Partial or total splenectomy
            1. For patients who have massive splenomegaly with significant infarction and persistent severe thrombocytopenia with high risk of bleeding.
            2. Enzyme replacement therapy alleviates hypersplenism and eliminates the need for splenectomy.
        2. Transfusion of blood products for severe anemia and bleeding
        3. Analgesics for bone pain
        4. Joint replacement surgery to relieve bone pain and restore joint function
        5. Oral bisphosphonates suggested in patients with Gaucher disease and low bone density
    2. Therapy to reduce glucosylceramide accumulation
        1. Bone marrow transplantation
        2. Enzyme replacement therapy
        3. Substrate reduction therapy
        4. Gene therapy
    3. Bone marrow transplantation (Ringden et al. 1995)
        1. Corrects metabolic defect
        2. Improves blood counts
        3. Reduces increased liver volume
        4. Stabilizes bone disease and neurologic disease in a few patients
        5. Limited use in patients with type 1 and type 3 Gaucher disease because of the morbidity and mortality associated with the bone marrow transplantation
        6. Useful concomitant therapy for patients with chronic neurological Gaucher disease and progressive disease on enzyme replacement therapy
    4. Enzyme replacement therapy (ERT) (Barranger and O'Rourke 2001; Charrow 2009)
        1. Efficacy using alglucerase and imiglucerase (Bembi et al. 2002).
            1. For treating the visceral and hematological aspects of Gaucher disease: improvement in hematologic parameters, normalization of bone marrow fat content, and improved bone mineral content and quality of life.
            2. Treatment responses seen within months.
            3. Effective for halting or reversing the skeletal pathology of Gaucher disease.
            4. The optimal dosage and the response time of ERT for treating the skeletal system, particularly for pediatric patients, are not well defined.

2. Intravenous infusions of purified macrophage-targeted human β-glucocerebrosidase.
    1. Alglucerase (Ceredase, Genzyme Corporation), derived from human placenta
    2. Imiglucerase (Cerezyme, Genzyme Corporation), derived from recombinant DNA production methods
3. Treatment results (visceral aspects of type 1 and type 3 Gaucher disease) (Pastores et al. 1993; Weinreb et al. 2002)
    1. Breakdown of stored glucocerebroside.
    2. Reduction in liver and spleen size.
    3. Amelioration or resolution of anemia and thrombocytopenia.
    4. Decreased bone pain (Poll et al. 2002)
    5. Increased bone mineralization.
    6. Remodeling over a period of several years.
    7. Improved health-related quality of life.
    8. IgG antibodies to alglucerase reported to develop in approximately 13% of patients (Rosenberg et al. 1999). These antibodies have little clinical effect and diminish with continued therapy in most circumstances. However, the presence of antibodies could be associated with an increased risk of hypersensitivity reactions (Charrow et al. 1998).
    9. Prolonged treatment over 3 1/2 years with macrophage-targeted glucocerebrosidase produces objective reversal of disease in both the axial and appendicular skeleton in patients with type 1 Gaucher disease. Marked improvement occurs in marrow composition and bone mass in both children and adults (Rosenthal et al. 1995)
4. Four treatments available for GD1: 3 ERTs (enzyme replacement therapies) and 1 SRT (substrate reduction therapy) (Bennett and Mohan 2013)
    1. Miglustat, an SRT: approved for mild to moderate GD1
    2. ERTs are available for moderate to severe GD1 and can improve quality of life within the first year of treatment.
    3. The newest ERT, taliglucerase alfa, is plant-cell derived that can be produced on a large scale at lower cost.
    4. Eliglustat tartrate (Balwani et al. 2016; Sechi et al. 2016)
    1. A newly developed SRT for GD, which is created to specifically inhibit GCS, with the aim to reduce substrate accumulation with limited side effects
    2. Recommendations for the use of eliglustat in the treatment of adults with Gaucher disease type 1 in the United States
    5. No drugs have been approved for GD2 or GD3.
5. Management of bone disease in GD1 (Giuffrida et al. 2014)
    1. The severity of skeletal involvement in type 1 GD is variable, but associated with significant pain, disability, and reduced quality of life; thus, all patients should be monitored regularly for the onset and progression of skeletal pathology.
    2. Dual energy X-ray absorptiometry is the method of choice for measuring bone mineral density, whereas MRI is the method of choice for evaluating bone marrow infiltration.
    3. Correct performance and interpretation of these methods are paramount to obtaining clinically useful information.
6. Long-term treatment outcomes in type 1 Gaucher disease (Charrow and Scott 2015): ERT has dramatically improved the outlook for patients with Gaucher disease. The future holds promise of new therapies, which may help address as yet unmet needs. These include

pharmacologic chaperones, and the potential development of molecules able to cross the blood–brain barrier that might lead to effective treatment for neuronopathic disease.

7. Treatment in patients with type 2 Gaucher disease (Charrow et al. 1998).
    1. Enzyme therapy may slow but does not prevent the development of lethal CNS disease in Gaucher disease type 2, even when initiated presymptomatically (Bove et al. 1995)
    2. Limited and disappointing: unaltered ultimate fatal course.
    3. Therapy at birth given to an infant, identified prenatally, failed to alter the inevitable neurologic outcome.
    4. Currently not recommended to treat patients with type 2 Gaucher disease.
8. Currently, no hard data available to show the efficacy of enzyme therapy for reversing existing or rapidly progressing CNS disease in type 3 patients with Gaucher disease.
9. Effect of enzyme therapy on the cardiac, valvular, and hydrocephalic manifestations of type 4 patients remains unknown.
10. ERT is a lifelong treatment since withdrawal of therapy inevitably leads to progression of Gaucher disease and the (sometimes rapid) loss of the progress made with ERT.

5. Substrate reduction therapy
    1. Miglustat, a formulation aimed at restoring metabolic homeostasis by limiting the amount of substrate precursor synthesized to a level that can be effectively cleared by the mutant enzyme with residual hydrolytic activity.
    2. Additional controlled longitudinal studies needed to be undertaken with a larger number of patients not only to determine the biochemical but also clinical long-term outcomes of patients with type 1 Gaucher disease on miglustat therapy (Ficicioglu 2008).
6. The future of Gaucher disease therapy (Harmanci and Bayraktar 2008)
    1. Gene therapy
        1. Neither ERT nor SRT has achieved excellent results in terms of neurological and pulmonary involvement due to problems such as inability to pass through the blood–brain barrier.
        2. Possibility of administration and incorporation of a healthy genome replacing a deficient genome.
        3. In early animal models of gene therapy, the vectors responsible for "infecting" a healthy genome were viruses (adeno-associated virus, lentivirus, and retrovirus). These studies showed promising results for the future (Kim et al. 2004; Enquist et al. 2006; McEachern et al. 2006).
        4. The advantage of gene therapy: its widespread infection of specific targeted cells in the body substantially increasing the enzyme levels to a considerable level.
    2. Chaperone treatment
        1. Imino sugars: ability to increase the strength of the target enzyme (glucocerebrosidase) (Sawkar et al. 2002).
        2. These chemicals increase the half-life of the enzyme by inhibiting its degradation and by providing stabilization.
        3. Although this option currently does not seem to offer a monotherapy option, chaperones might be an option for combination treatment strategies.

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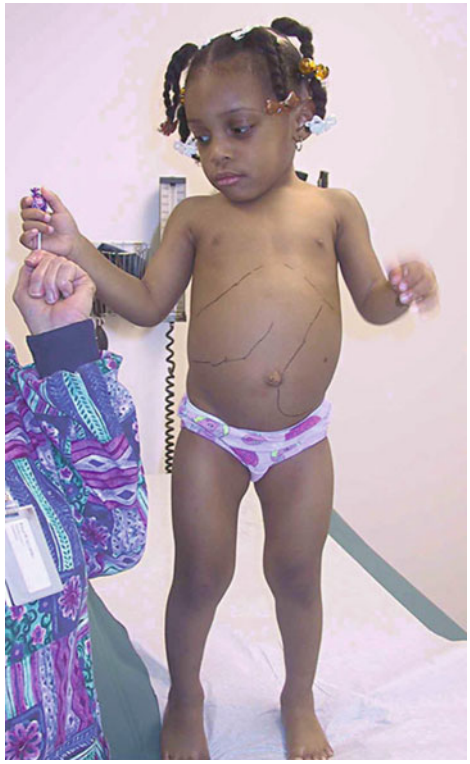

Fig. 1 A 3-year-old African-American female child with Gaucher disease showing hepatosplenomegaly. She had history of "large belly" since she was 6–12 months of age, anemia (hemoglobin of 8.7 g%), and thrombocytopenia (73,000). She had an elevated total acid phosphatase of 29 U/L (2.3–5.0), a very low leukocyte beta-glucocerebrosidase of 0.01 U (0.08–0.35), and "Gaucher cells" in the bone marrow

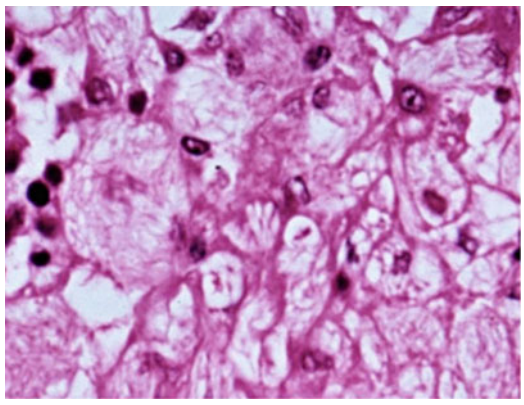

Fig. 2 Bone marrow smear from another patient with Gaucher disease showing extensive infiltration by Gaucher cells (H&E stain)

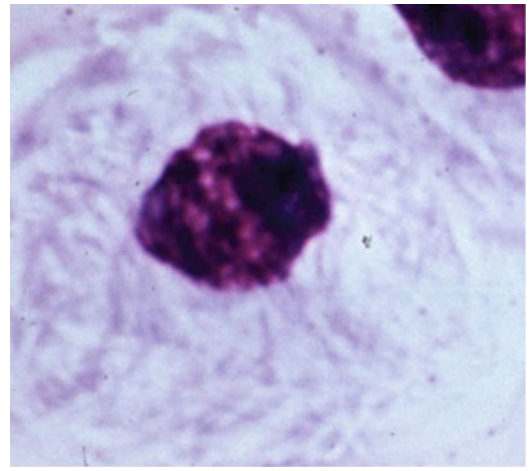

Fig. 3 Higher magnification of bone marrow smear showing a Gaucher cell (Wright-Giemsa stains)

Generalized Arterial Calcification of Infancy

Contents

General arterial calcification of infancy is a rare and usually fatal disease. The condition is also called idiopathic arterial calcification of infancy.

Synonyms and Related Disorders

Idiopathic infantile arterial calcification; Infantile occlusive arteriopathy

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Moran and Becker 1959; Stanley et al. 1988).
2. Cause (Rutsch et al. 2008).
    1. Loss-of-function mutations in *ENPP1* gene (located on chromosome 6q22-q23) that inactivate ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*).
        1. This cell-surface enzyme generates inorganic pyrophosphate, a solute that regulates cell differentiation and serves as an essential physiologic inhibitor of calcification (Rutsch et al. 2003)
        2. *ENPP1* coding region mutations are associated with generalized arterial calcification of infancy in ≈75% of subjects.
        3. This mutation was recently found to also cause autosomal-recessive hypophosphatemic rickets (Lorenz-Depiereux et al. 2010).
    2. Plasma cell membrane glycoprotein-1 (PC-1) nucleoside triphosphate pyrophosphohydrolase deficiency (Rutsch et al. 2001).
        1. Associated with human infantile arterial calcification, especially with periarticular calcification.
        2. May explain the sharing of certain phenotypic features between some infantile arterial calcification patients and PC-1-deficient mice.
3. Basic defects.
    1. Possibly a defect of elastic fiber.
        1. Occurrence of calcification particularly in the internal elastic lamina.
        2. Material with the staining properties of mucopolysaccharide accumulates around the elastic fibers.
    2. Fundamental lesions.
        1. A remarkable predilection for mineralization around the internal elastica laminae of medium- to large-sized arteries.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Narrowing of the arterial lumen due to a marked intimal proliferation.
3. Pathogenesis.
   1. Incompletely understood.
   2. Involves calcification (calcium hydroxyapatite deposition) in the internal elastic lamina of large- and medium-sized arteries, associated with a stenosing, fibroproliferative medial smooth muscle cell-mediated process, maximal in the area of the internal elastic lamina.
   3. Relates to decreased levels of plasma and urinary inorganic pyrophosphate whose role is to inhibit hydroxyapatite crystal deposition in bone and cartilage.

Clinical Features

1. Stormy clinical course.
2. Infant usually thrive normally right after birth.
3. Thereafter, following symptoms develop rapidly.
   1. Poor feeding.
   2. Vomiting.
   3. Respiratory distress.
      1. Tachypnea.
      2. Tachycardia.
      3. Cyanosis.
   4. Hypertension (Van Dyck et al. 1989).
   5. Myocardial infarctions.
   6. Progressive congestive cardiac failure.
4. Prognosis.
   1. Death (sudden death or unexpected infant death).
      1. Usually occurring during early infancy secondary to coronary insufficiency.
      2. 85% of cases dying before 6 months of age (Byard 1996).
      3. Causes of death.
         1. Vascular occlusion due to extensive calcification of the arterial media associated with intimal proliferation.
         2. Other complications of obstructive arteriopathy including renal artery stenosis (Thiaville et al. 1994).
         3. Ischemic myocardial ischemia/cardiomyopathy resulting in refractory heart failure.
   2. Rare regression of calcification and prolonged survival (Marrott et al. 1984; Thomas et al. 1990; Ciana et al. 2006): Once the severe circulatory problems of infancy are overcome, disease prognosis may be better than previously thought.

Diagnostic Investigations

1. Blood workup.
   1. Normal calcium levels.
   2. Normal phosphate levels.
   3. Relative deficiency of plasma pyrophosphate (Stuart et al. 1990)
2. Urinalysis: Low levels of urinary inorganic pyrophosphate indicating systemic pyrophosphate deficiency (Rutsch et al. 2000)
3. Radiography Calcifications of major arteries and particularly ligaments are pathognomonic radiologic signs of this disorder (Meradji et al. 1978; Chen et al. 1982; Maayan et al. 1984)
   1. Demonstration of the calcified arteries, leading to possible diagnosis of the condition during life.
   2. Extensive vascular calcification.
      1. Upper and lower limbs.
      2. Neck.
      3. Subclavicular fossae.
      4. Axillae.
   3. Periarticular calcification and stippled calcification of the epiphyseal cartilage.
   4. Cardiac enlargement.
4. ECG changes suggesting.
   1. Coronary occlusion.
   2. Myocardial infarct.
5. Ultrasonography (Whitehall et al. 2003):
   1. Marked calcification in the aorta/arteries.
   2. Calcified plaques in the lumen of the aorta.
   3. Dropper studies: reduced arterial blood flow.

6. Echocardiography to demonstrate coronary calcification.
7. Aortogram showing striking obliterations of the peripheral vessels.
8. Biopsies of peripheral arteries showing extensive intimal mineralization.
9. Postmortem gross pathological findings usually limited to the cardiovascular system
    1. An enlarged heart.
    2. Focal calcifications of coronary arteries and other peripheral arteries.
    3. Pale or mottled areas of the myocardium or other viscera indicative of infarction.
10. Histopathology (Bird 1974; Moran 1975; Anderson et al. 1985)
    1. Extensive mineralization (calcium hydroxyapatite deposition) of arteries.
        1. Usually noted around the internal elastic lamina of the medium-sized arteries.
        2. Often accompanied by a marked intimal hyperplasia causing luminal narrowing.
        3. Tends to be most severe in the coronary arteries.
            1. Resulting in myocardial ischemia and infarction.
            2. Death usually attributable to myocardial infarction or heart failure.
    2. Involvement of a variety of arteries.
        1. Aorta.
        2. Pulmonary arteries.
        3. Carotid arteries.
        4. Iliac arteries.
        5. Femoral arteries.
        6. Visceral arteries.
        7. Limb arteries.
        8. Vessels of the brain usually not affected.
    3. Cardiac abnormalities.
        1. Left or biventricular hypertrophy.
        2. Fibrointimal thickening.
        3. Calcification of the coronary arteries.
        4. Endocardial fibroelastosis (Sholler et al. 1984)
        5. Widespread ischemic myocardial damage.
        6. Coronary artery occlusion (Lussier-Lazaroff and Fletcher 1973)
    4. Generalized arterial calcification of infancy generally indistinguishable from the following conditions.
        1. Metastatic calcification of arteries secondary to advanced renal disease.
        2. Arterial lesions in hypervitaminosis D or secondary to other toxic agents.
        3. Hyperparathyroidism of pregnancy.
11. Molecular genetic diagnosis: not yet available clinically (only available in a few research laboratories) (Cheng et al. 2005; Dlamini et al. 2009).

Genetic Counseling

1. Recurrence risk.
    1. Patient's sib: 25%.
    2. Patient's offspring.
        1. Not surviving to reproductive age in majority of patients.
        2. Low recurrence risk for those who survive.
2. Prenatal diagnosis.
    1. Fetal ultrasonography and radiography to detect calcium hydroxyapatite deposits (echogenic walls of arterial vessels).
        1. Presence of mitralic echogenic foci in the 14th week of gestation (Ciana et al. 2006).
        2. Echogenic great arteries at 29 weeks of gestation (Reitter et al. 2009).
    2. Fetal echocardiography (Nagar et al. 2003).
        1. Fetal nonimmune hydrops.
        2. Increased echo (calcific type) density of walls of the fetal aorta, pulmonary arteries, coronary arteries, within the lumen of the heart, and other arterial walls.
        3. Poor focal contraction of the heart, as a result of the expected accompanying cardiac ischemia due to coronary artery narrowing.
        4. Dilated cardiac chambers.
        5. Pericardial effusion.
        6. Hypertrophic cardiomyopathy.

3. Fetal ultrasonography, radiography, and CT scan (Spear et al. 1990)
    1. Ultrasonography: hyperechogenic artery walls
    2. Radiography: calcified aorta, celiac axis and superior mesenteric artery
    3. CT: calcified aorta, fetal ascites and maternal hydramnios
    4. Prenatal diagnosis.
        1. Reference ranges for the disease-related enzymes in amniocytes or fibroblast cultures from CVS have not been established.
        2. Molecular genetic diagnosis: Prenatal diagnosis may be possible in at-risk families, provided disease-causing mutations have been identified previously.
3. Management (Stuart 1993).
    1. Therapy with diphosphonates (nonhydrolyzable analogs of inorganic pyrophosphate) (Van Dyck et al. 1989).
        1. Function of diphosphonates.
            1. Simple chemical compounds containing phosphate-carbon-phosphate bonds.
            2. Inhibit the precipitation of several calcium salts in vitro.
            3. Block the conversion of amorphous calcium phosphate into crystalline hydroxyapatite.
            4. Partially converting apatite crystals into a colloidal state with treatment of large amounts of certain diphosphonates.
        2. Effective in some patients.
            1. Some apparent reduction of calcification.
            2. Usually with persistence of ischemic effects of intimal fibroproliferation.
            3. Except for the p.P305T mutation, which was universally lethal when present on both alleles, the identified *ENPP1* mutations per se have no discernable effect on survival. However, survival seems to be associated with hypophosphatemia linked with hyperphosphaturia and also with bisphosphonate treatment (Rutsch et al. 2008).
            4. Case report by Ramjan et al. 2009: Low-dose disodium pamidronate (0.1 mg/kg per week for 4 weeks), which commenced on the seventh day after birth and was changed to oral risedronate sodium (1 mg/kg per week as a single dose) at 4 weeks of age. Complete resolution of arterial calcification was seen by 3 months of age. Treatment with bisphosphonates is ongoing but is planned to be discontinued at 3 years of age. The child has remained healthy and developmentally normal.
    2. Management of arterial hypertension.
        1. May be refractory to conventional medical therapy.
        2. Prostaglandin E_1 infusion.
    3. Management of myocardial infarctions.
    4. Treatment with bisphosphonates (Ranjan et al. 2009).
    5. In utero diphosphonate etidronate therapy (Stuart et al. 1990; Bellah et al. 1992).
        1. Apparent radiographic and ultrasonographic improvement in the degree of vascular calcification.
        2. Unable to prevent the lethal progression of intimal vascular occlusive disease.

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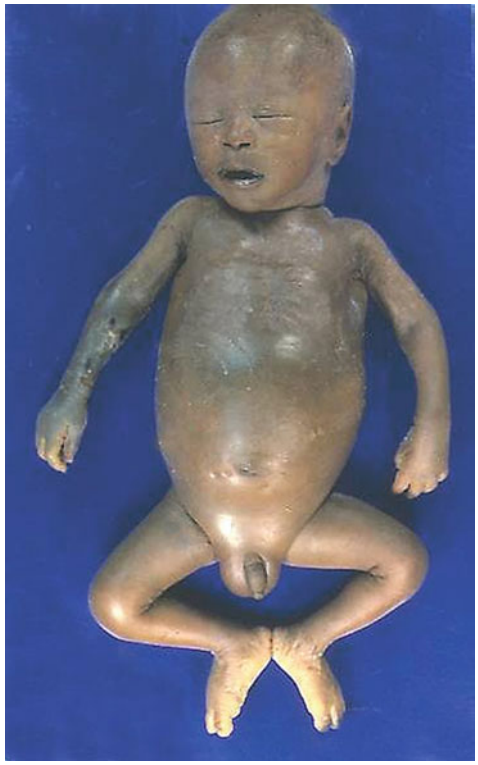

Fig. 1 Postmortem picture of a neonate (twin B) with generalized arterial calcification showing ischemic changes of the right arm. The pregnancy was complicated by polyhydramnios. At 2 weeks of age, he was noted to have intercostal retraction and tachypnea with distended abdomen and hepatomegaly

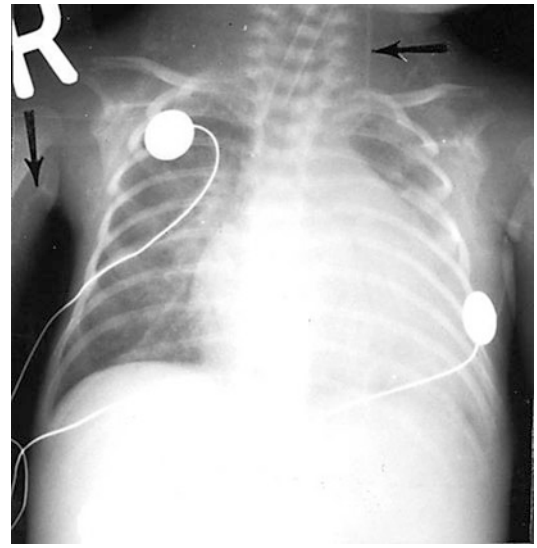

Fig. 2 Radiograph examinations showed extensive vascular calcification extending down the upper and lower limbs, neck, supraclavicular fossae, and axillae. Radiograph here shows an enlarged heart and linear calcification (*arrows*) of the carotid and brachial arteries

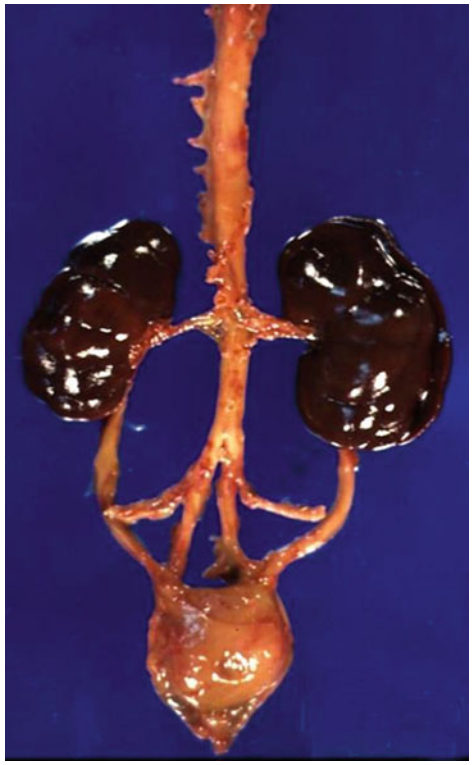

Fig. 3 Gross view of vessels, especially the renal arteries, intercostalis, and iliacs, which were hard with mineralization of vessel walls

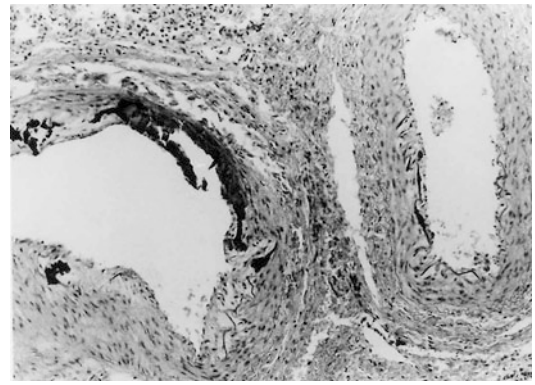

Fig. 4 Artery on the right shows the earliest type of lesion with mild intimal hyperplasia, mild fragmentation, and early mineralization of internal elastic lamina. Artery on the left shows a more advanced lesion with moderate intimal proliferation, moderate fragmentation of internal elastica lamina, and heavy mineralization in and around elastic fibers

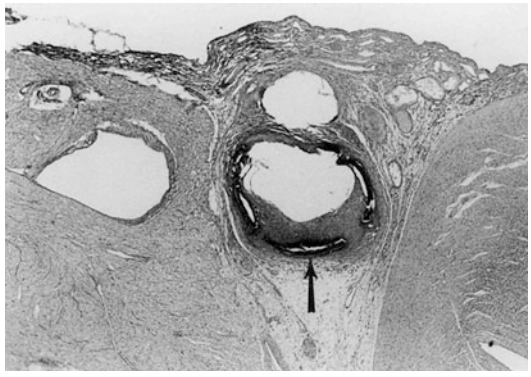

Fig. 5 Advanced mineralization in and around internal elastica lamina (coronary artery)

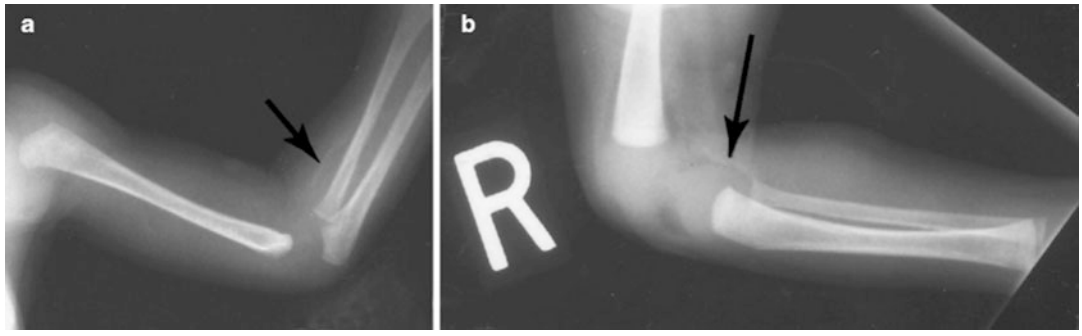

Fig. 6 (**a,b**) Radiographs of twin B show linear calcification (*arrow*) of the radial artery (*upper*) and popliteal artery (*lower*). At 35 days of age, the twin suffered a cardiac arrest and expired shortly thereafter. No autopsy was performed

Genitopatellar Syndrome

Contents

In 1988, Goldblatt et al. (1988) first reported a 4-year-old boy with hypoplastic patellae, mental retardation, scrotal hypoplasia, skeletal deformities, renal anomalies, flattened nasal bridge, and short stature. Later in 2000, Cormier-Daire et al. (2000) reported seven patients with genital anomalies (scrotal hypoplasia and cryptorchidism in the boys and clitoral hypertrophy in the girls), facial dysmorphism, renal anomalies, absent patella, and severe mental retardation in the two survivors. The condition is now known as genitopatellar syndrome (GPS).

Synonyms and Related Disorders

Absent patellar, facial dysmorphism, mental retardation, renal anomalies, and scrotal hypoplasia; Ohdo syndrome; Say-Barber-Biesecker variant of Ohdo syndrome; Say-Barber-Biesecker/Young-Simpson syndrome (SBBYSS)

Genetics/Basic Defects

1. An autosomal recessive inheritance of this condition was proposed (Cormier-Daire et al. 2000; Reardon 2002).
2. KAT6B-related disorders are inherited in an autosomal dominant manner (Campeau and Lee 2013).
3. Normal karyotypes and normal array-based comparative genome hybridization (aCGH) in all except one case of ovotestes and XY sex reversal in a female with an interstitial 9q33.3-q34.1 deletion encompassing *NR5A1* and *LMX1B* causing features of genitopatellar syndrome (Schlaubitz et al. 2007).
4. Mutations of *LMX1B*, *TBX4*, *WNT4*, and *WNT7A* genes, consistent with nail-patella syndrome, small patella syndrome, and defects in Müllerian ducts and limb development, respectively, were excluded (Abdul-Rahman et al. 2006; Schlaubitz et al. 2007).
5. GPS (Campeau et al. 2012; Gannon et al. 2015).
    1. Recently been shown to be caused by distinct mutations in the histone acetyltransferase *KAT6B* (Simpson et al. 2012).
    2. All variants are de novo dominant mutations that lead to protein truncation.
    3. Mutations leading to GPS occur in the proximal portion of the last exon and lead to the expression of a protein without an activation domain.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_105

4. Report of a deletion of the *KAT6B* gene to further delineate the haploinsufficiency phenotype
6. SBBYSS (Campeau et al. 2012; Gannon et al. 2015)
   1. Features: present only in SBBYSS including long thumbs and long great toes and lacrimal duct abnormalities
   2. Typically, patients have a distinctive mask-like face with severe blepharophimosis and ptosis, a broad nasal bridge, bulbous nasal tip, small mouth, thin upper lip, and small, low set ears.
   3. Also recently been shown to be caused by distinct mutations in the *KAT6B*
   4. Mutations leading to SBBYSS occur either throughout the gene, leading to nonsense-mediated decay, or more distally in the last exon.
   5. Synonymous variant c.3147G > A as a splice site mutation and a mutational hot spot in Say-Barber-Biesecker/Young-Simpson (SBBYS) type of blepharophimosis, "mental retardation" syndromes and the more severe genitopatellar syndrome (Yilmaz et al. 2015).

Clinical Features

1. Genital anomalies
   1. Males (Sankararaman et al. 2012)
      1. Scrotal hypoplasia
      2. Cryptorchidism
      3. Small penis
   2. Females (Lammer and Abrams 2002)
      1. Prominent clitoris and labia minora
      2. Hypoplastic clitoris and labia minora
2. Absent/hypoplastic patella (Armstrong and Clarke 2002)
3. Arthrogryposis
   1. Knees
      1. Flexion contractures
      2. Skin dimples at the knee
   2. Flexion contractures or dislocation/subluxation of the hips
4. Other skeletal anomalies
   1. Brachydactyly of the upper limbs
   2. Clubfeet
   3. Hypoplasia of pelvic bones
5. Distinctive craniofacial features
   1. Microcephaly
   2. Abnormal skull shape
   3. Hypertelorism
   4. Midfacial hypoplasia
   5. A large, broad nose with a high nasal bridge
   6. Micrognathia
6. CNS anomalies
   1. Severe psychomotor retardation
   2. Hypotonia
   3. Swallowing and feeding difficulties during neonatal period
   4. Absence of corpus callosum
   5. Colpocephaly
7. Congenital heart defects (Lifchez et al. 2003)
   1. VSD
   2. ASD
   3. PDA
   4. PFO
   5. Abnormal aortic arch
8. Renal anomalies
   1. Multicystic kidneys
   2. Hydronephrosis
   3. Large fused kidney
   4. Vesicoureteral reflux
9. Anal atresia or ventral displacement of the anus (Penttinen et al. 2009)
10. Mild manifestations of ectodermal dysplasia
    1. Sparse scalp hair
    2. Delayed tooth eruption
11. Severe respiratory problems
    1. Apnea
    2. Pulmonary hypoplasia
12. Hearing loss (Bergman et al. 2011)
13. Differential diagnosis (Bongers et al. 2005; Lam et al. 2009)
    1. Nail-patella syndrome
       1. Caused by *LMX1B* mutations
       2. Nail dysplasia
       3. Absent/hypoplastic patella
       4. Elbow synostosis
       5. Presence of iliac horns
       6. Nephropathy (glomerular basement membrane)
       7. Open-angle glaucoma

2. Small patella syndrome
    1. Caused by *TBX4* gene mutations
    2. Absent/hypoplastic patella
    3. Knee contractures
3. Isolated patella aplasia/hypoplasia
    1. A rare autosomal dominant disorder
    2. Congenital aplasia or hypoplasia of the patellae: the only clinical and radiographic feature
4. Meier-Gorlin syndrome (ear-patella-short stature syndrome)
    1. An autosomal recessive pleiotropic condition
    2. Classical triad: bilateral microtia, patellar aplasia or hypoplasia, and severe pre- and postnatal growth retardation
5. RAPADILINO syndrome (Kääriäinen et al. 1989)
    1. Autosomal recessive disorder in which patellar malformations are accompanied by short stature and external ear malformations
    2. The acronym RAPADILINO stands for the characteristic main features: RA dial and PAtellar aplasia or hypoplasia, cleft or highly arched PAlate, infantile DIarrhea and DIslocated joints, LIttle size and LImb malformation, and long slender NOse and NOrmal intelligence (Kääriäinen et al. 1989)
    3. Additional frequent findings comprise absent thumbs, micrognathia, dysmorphic auricles including dysmorphic ear lobes and partial unfolded ear helices, a high-pitched voice, and metatarsus varus.
6. Subtelomeric 1q deletion syndrome causing patellar hypoplasia and limb deformities, features overlapping with genitopatellar syndrome.

Diagnostic Investigations

1. Cranial ultrasound and MRI to detect CNS malformations
2. Radiography for skeletal anomalies and absent patella (for older child)
3. Renal ultrasound for renal anomalies
4. MRI of the patella to ascertain absence of the patella (Sankararaman et al. 2012)

Genetic Counseling

1. Recurrence risk (Campeau and Lee 2013)
    1. Patient's sib
        1. The risk to the sibs of the proband depends on the genetic status of the proband's parents.
        2. If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.
        3. If a parent of the proband has germline mosaicism for a *KAT6B* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant may be as high as 50%.
    2. Patient's offspring: To date, individuals with *KAT6B*-related disorders rarely reproduce.
2. Prenatal diagnosis/preimplantation genetic diagnosis: Possible for families in which the pathogenic variant has been identified (Campeau and Lee 2013)
3. Management: supportive

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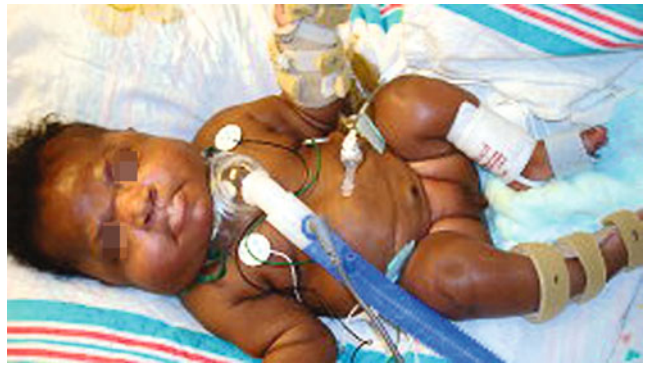

Fig. 1 The neonate was a twin A of dizygotic twins, delivered at 29 weeks via emergency C section secondary to suspected chorioamnionitis. The baby was noted to have no scrotal sac with nonpalpable testes. He was noted to have abnormal positioning of the legs with contractures of the hips and the knees and clubfeet. He was also noted to have an imperforate anus with intestinal malrotation which were repaired. Renal ultrasound showed bilateral hydronephrosis (Sankararaman et al. 2012)

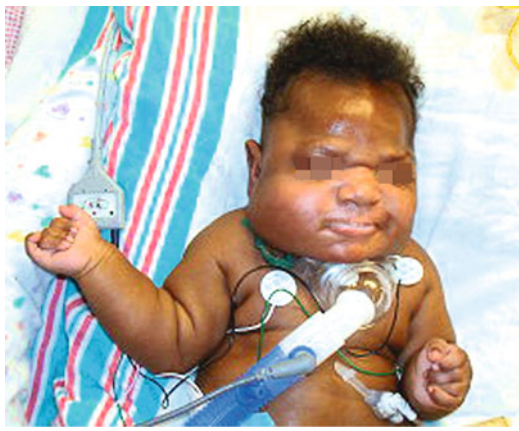

Fig. 2 Craniofacial features were characterized by coarse face, flat occiput, bitemporal narrowing, and a deep crease across the nasal bridge. The neck was short. There were proximal interphalangeal contractures of the digits two to four on both hands, a single flexion crease on the fifth digit. Transverse palmar creases were present bilaterally. MRI of the brain showed absence of the corpus callosum with delayed myelination, prominent DSF spaces in the frontal region, and mega cisterna magna. Chromosome analysis and microarray analysis were normal

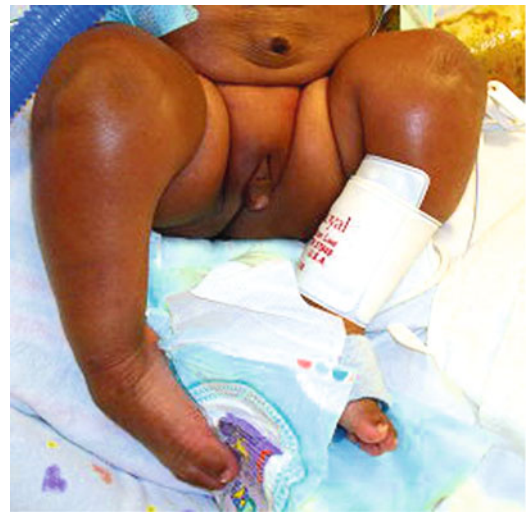

Fig. 3 Showed knee dimples with flexion contractures, popliteal webbing, and talipes equinovarus

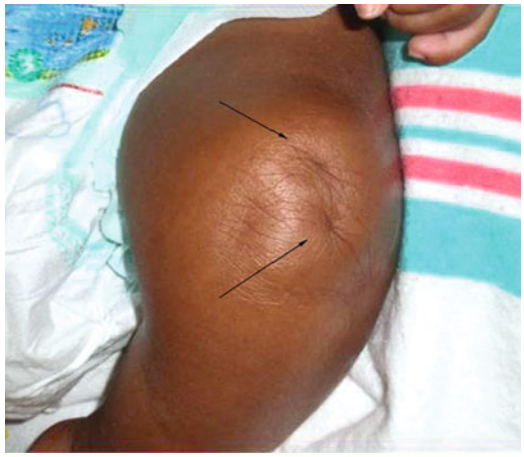

Fig. 4 Dimples on both knees shown by *black arrows*

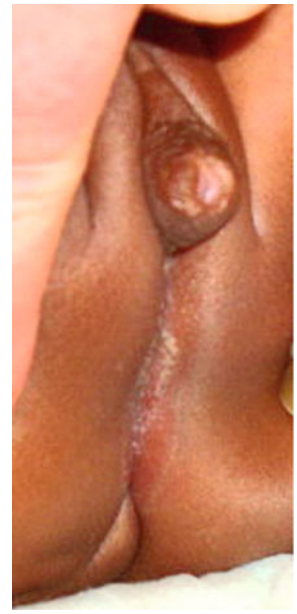

Fig. 6 This photo showed scrotal hypoplasia and imperforate anus

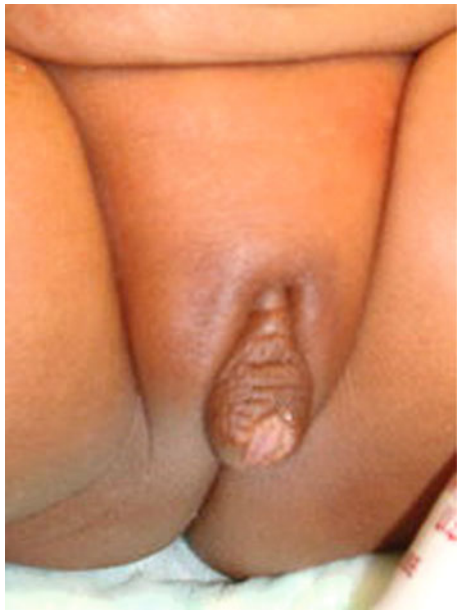

Fig. 5 External genitalia showed scrotal hypoplasia and bilateral cryptorchidism

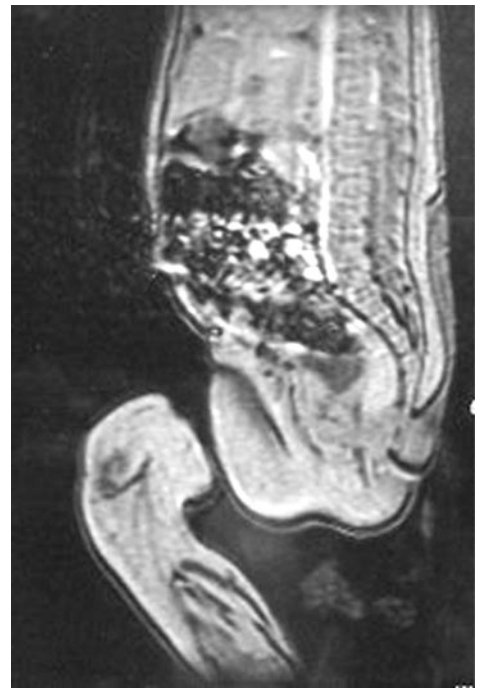

Fig. 7 MRI of the knee showed absence of the patella

Giant Congenital Melanocytic Nevi

Contents

Giant congenital melanocytic nevi (GCMN) or giant congenital nevi are rare, congenital, disfiguring lesions present at birth with a risk of degeneration to malignant melanoma (Watt et al. 2004) and may be associated with neurocutaneous melanosis (NCM) (Hale et al. 2005; Ka et al. 2005). The incidence of giant-sized congenital melanocytic nevi greater than 20 cm in diameter was estimated at approximately one in 20,000 live births. The larger bathing trunk variety occurs approximately one in 500,000 live births (Castilla et al. 1981).

Synonyms and Related Disorders

Congenital melanocytic nevi (CMN); Garment or bathing trunk nevi; Giant congenital nevi

Genetics/Basic Defects

1. GCMN generally occurs in isolation, but rare familial occurrence (Voigtländer and Jung 1974; Hecht et al. 1981; De Wijn et al. 2009) points to a genetic background.
2. Genetic basis of giant nevi:
    1. Concept of paradominant inheritance (Danarti et al. 2003):
        1. Heterozygous individuals carrying the mutation are phenotypically normal, and the trait would only manifest itself when heterozygosity was lost at an early developmental stage.
        2. Would explain why lesions occur in a mosaic pattern, occur sporadically, and do not show any consistent pattern of Mendelian inheritance.
        3. Discordance for giant pigmented nevi in monozygotic twins was reported (Cantu et al. 1972).
    2. Nevi harboring the BRAFE600 mutation undergo cell cycle arrest and senescence, thus preventing the development of malignancy in these lesions (Michaloglou et al. 2005).
    3. Using single-strand conformational polymorphism and sequencing analysis, BRAF

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and N-ras oncogene mutations were found to be extremely common in individuals with congenital nevi, which could explain the higher risk of developing cutaneous melanoma (Papp et al. 2005).

4. Reports on chromosome abnormalities in GCMNs – infrequent:
   1. Two balanced translocations involving the BRAF gene and one deletion of the long arm of chromosome 6 out of 27 GCMNs (Dessars et al. 2008).
   2. 22% of mitoses with polyploid and 4% with chromosome rearrangements involving 1p, 12q, and 19p from a single GCMN (Heimann et al. 1993).
5. *NRAS* mutation – the sole recurrent somatic event found in large congenital melanocytic nevi (Charbel et al. 2014):
   1. The genetic profile of small–medium CMNs: significantly different, with 70% of cases bearing NRAS mutations and 30% showing BRAF mutations.
   2. These findings strongly suggest that NRAS mutations are sufficient to drive melanocytic benign proliferations in utero.
6. Clinical variability in large CMN may be due to the many potential modifiers of a mosaic *NRAS* or *BRAF* gain-of-function genotype (Etchevers 2014).
7. *BRAF* mutations are also associated with neurocutaneous melanocytosis and large/giant congenital melanocytic nevi (Salgada et al. 2015).
8. The pattern of inheritance (De Wijn et al. 2009):
   1. Likely not Mendelian.
   2. Discordance in identical twins (Morganroth et al. 1991) and the segmental distribution of lesions suggest a postzygotic mutation.
   3. A polygenic paradominant inheritance best explains the clinically observed transmission pattern.
   4. Candidate genes include those influencing neural crest development and melanocyte proliferation.
3. Embryological origin of congenital melanocytic nevus:
   1. Not well understood
   2. Hypothesis:
      1. Giant congenital nevi develop between the 5th and 25th weeks of gestation.
      2. Dysregulated growth of melanoblasts occurs secondary to morphogenic errors in neuroectodermal development, resulting in dysregulated migration of melanoblasts from the neural crest to the skin and leptomeninges.

Clinical Features

1. Congenital melanocytic nevi (Zaal et al. 2004; Tannous et al. 2005):
   1. Definition: benign proliferation of cutaneous melanocytes, clinically apparent at birth or becoming so within the first postnatal weeks
   2. Incidence: affects approximately 1% of all newborns
   3. Characteristics: vary in size, macroscopic appearance, and histology as a group
   4. Classification of congenital melanocytic nevi based on final size of the nevi:
      1. Small: less than 1.5 cm in diameter
      2. Intermediate: 1.5–20 cm in diameter
      3. Giant or large (also called garment or bathing trunk nevi: measuring more than 20 cm in diameter) (Ruiz-Maldonado et al. 1992; West et al. 2007)
2. Giant congenital nevi: classified based on the percentage of body area affected (a congenital nevi covering 1% of body surface area in the face and neck and 2% elsewhere on the body)
3. Clinical manifestations of giant congenital nevi:
   1. Onset: flat, brown, or brownish-black patches but with increasing age may become elevated and develop a mottled appearance and nodular surface.
   2. Appear darker at birth than a few weeks later.

3. Found most commonly on the trunk, followed by the limbs and the head (Madaree et al. 1997).
4. Giant nevi: almost always confined to the skin but, rarely, invade the underlying fascia and muscle.
5. Most giant CMN involves the trunk and has a predominant bathing suit distribution.
6. Innumerable nevi with giant congenital melanocytic nevus clinically mimicking neurofibromatosis: a diagnostic challenge (Boyers et al. 2015).
7. Associated abnormalities (De Wijn et al. 2009):
    1. Neurocutaneous melanosis (Arneja and Gosain 2005; Araújo et al. 2015):
        1. Incidence of NCM in children with GCMN: 29.2% (Bekiesinska-Figatowska et al. 2014).
        2. Characterized by the presence of benign or malignant melanocytic proliferations in the CNS in association with a giant CMN or three or more smaller melanocytic nevi (Kadonaga and Frieden 1991).
        3. Signs and symptoms of symptomatic neurocutaneous melanosis (hydrocephalus, seizures, developmental delay, cranial nerve palsies, or a tethered spinal cord) (Foster et al. 2001).
        4. Almost all children with neurocutaneous melanosis have giant nevi on the head, neck, or dorsal spine.
    2. Structural brain abnormalities:
        1. Dandy–Walker malformation
        2. Hemimegalencephalopathy
        3. Meningohydroencephalocele
        4. Lissencephaly
        5. Microcephaly
        6. Spina bifida occulta
    3. Polydactyly
    4. Linear epidermal nevus syndrome
    5. Segmental neurofibromatosis
    6. Encephalocraniocutaneous lipomatosis
    7. General lipomatosis
    8. Placental nevomelanocytosis
    9. Hirschsprung disease
    10. Hypotrophy of the underlying bone or subcutaneous fat (limb hypoplasia)
    11. Ear deformities
    12. Angiomas
    13. Malignant melanoma (Marghoob et al. 1996; DeDavid et al. 1997)
4. Prognosis
    1. Usually disfiguring.
    2. The lifetime risk for the development of malignant melanoma in giant congenital nevi: approximately 4–42% (about a 14-fold increased risk of developing cutaneous and extracutaneous melanoma) (Trozak et al. 1975; Baader et al. 1992).
    3. Giant nevi on the scalp in a posterior axial location and those with surrounding satellite nevi are at greatest risk of malignant transformation.
5. The most frequently encountered clinically important vascular and pigmented birthmarks (Dohil et al. 2000): congenital nevi, hypopigmented lesions, vascular malformations and hemangiomas
6. Neonatal malignant melanoma (Dargeon et al. 1950; Leech et al. 2004)
    1. Extremely rare
    2. Develops within a giant congenital nevus or preexisting nevus
    3. Can occur de novo on apparently normal skin
    4. Arises from maternal malignant melanoma via placental metastases (Holland 1949; Brodsky et al. 1965)
    5. May metastasize or spread locally
    6. Notoriously difficult to diagnose in children, especially neonates:
        1. Clinical indicators such as changes in color, size, shape, rapid growth rate, nodularity, and even ulceration may occur in benignly evolving GCNs.
        2. Histologic features accepted as evidence of malignancy in an adult, such as mitotic activity, nuclear pleomorphism, and pagetoid melanocytic proliferation, may also be present in benign lesions in infants.

3. Morphologic findings of melanocytic lesions from frozen tissue specimen cannot be confidently interpreted.

Diagnostic Investigations

1. Twenty-four-hour urine: high concentration in children with giant melanocytic nevi, especially in those with neurocutaneous melanosis, helps in predicting patients with more serious neurological course of the disease (Sawicka et al. 2015).
2. Biopsies:
   1. Probably only useful in clarifying the nature of pathological changes that occur in discrete areas of these nevi
   2. Sampling of multiple areas required when there is a question of malignant change
3. Magnetic resonance imaging (MRI) (Kinsler et al. 2001):
   1. Highly sensitive in detecting melanin, which produces short T1 (Frieden et al. 1994) and T2 relaxation times due to interactions of unpaired electrons in the stable free radicals of melanin with the protons of free water.
   2. Can delineate the extent of underlying soft tissue involvement and assist in preoperative planning.
   3. Neither the location nor the size of the nevus appears to correlate completely with the presence or absence of MRI abnormalities suggestive of CNS melanosis.
   4. Foci of melanosis generally became more difficult to detect on follow-up images, which may be related to changes in the signal intensity of the brain that accompany myelination.
   5. Recommend MR imaging in addition to ongoing developmental and neurological evaluations to help identify individuals who are at greater risk for CNS disease, as well as encourage MR imaging for those with giant nevi in the lumbosacral region.
   6. MR findings in asymptomatic GCMN group were similar to the ones of parenchymal NCM. T1 shortening in parenchymal NCM does not cause a significant clinical significance, unless there is subsequent occurrence of leptomeningeal involvement (Kim et al. 2014).
   7. MRI of the brain is necessary in each child with giant congenital melanocytic nevi to confirm or rule out neurocutaneous melanosis, especially its most severe and lethal form, with leptomeningeal contrast enhancement (Sawicka et al. 2015).
4. Positron emission tomography (Makosz et al. 2004):
   1. To detect occult primary melanoma as well as melanoma metastases within the nevi
   2. May play an important role in long-term monitoring and management of these patients
5. Dermoscopy (episcopy, dermatoscopy, skin surface microscopy, epiluminescence microscopy): allows in vivo visualization of anatomical pigmented structures in the epidermis, dermoepidermal junction, and superficial papillary dermis not usually seen by the naked eye (Lodha et al. 2003).
6. Whole-exome sequencing for somatic mutation detection (*NRAS*, *BRAF*) (Charbel et al. 2014).

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib: increased but exact risk not known
   2. Patient's offspring: increased but exact risk not known
2. Prenatal diagnosis: not reported but possible by fetoscopy (an invasive procedure)
3. Management
   1. Early and complete surgical excision is recommended because of an increased lifetime risk of malignancy (4–10%) (Warner et al. 2008).
   2. The surgical and reconstructive options for congenital melanocytic nevus are varied depending on the size and location of the nevus (Pearson et al. 2005):

1. Laser treatment: the results for congenital nevus have been unsuccessful because the deeper portions of the nevi are unaffected by the laser.
2. Dermabrasion:
    1. Plagued by recurrence if performed too superficially and hypertrophic scar if performed too deep.
    2. Produces uneven changes in the pigmentation of the skin because the melanocytic cells are found at varying depths in the dermis; dermabrasion produces uneven changes in the pigmentation of the skin.
    3. Dermabrasion has been abandoned for the treatment of nevi.
3. Curettage (Rasmussen et al. 2015):
    1. A gentle/less-invasive alternative with a lower complication rate, fewer operations needed, and good cosmetic outcome.
    2. Moreover, it is suitable for larger nevi and nevi in difficult locations.
    3. In case of repigmentation or severe morbidity after curettage, excision can always be performed at a later stage.
4. Excision:
    1. Excision followed by primary closure: a frequently used technique.
    2. Caution not to distort important structures such as oral commissure, eyelids, and eyebrows.
    3. Early excision with detailed histological examination of excised parts can speed up diagnosis of melanoma (Sawicka et al. 2015).
5. Stage excision:
    1. Consider when the resultant wound is too large to close or places excessive tension along the closure, increasing the risk of wound dehiscence
    2. An outpatient procedure involving less postoperative care and expense
6. Serial excision (Hassanein et al. 2015):
    1. CMN amenable to serial excision can be removed effectively and safely.
    2. Children are left with a single linear scar, do not have donor or recipient site morbidity from skin grafting, and are not subjected to potential tissue expander complications and injections required for expansion.
7. Skin grafting.
    1. A useful tool in the management of medium to large congenital nevi.
    2. Avoid split-thickness skin grafting because of the potential for an unsightly donor site and a greater need for inpatient care or a more complicated outpatient experience.
    3. Consider full-thickness grafts to allow for an acceptable donor site and less postoperative care.
    4. Considered in areas of the body of lesser esthetic importance.
8. Tissue expansion:
    1. Commonly used when a nevus is too large for primary closure: serial excision will produce residual deformity on the adjacent structures, or skin grafting will produce an undesirable esthetic result.
    2. The ability to replace tissue with like tissue, such as hair-bearing scalp with hair-bearing scalp, typically allows an acceptable esthetic result.
    3. The drawbacks include multiple operations (placement followed by removal and advancement), difficulty in expanding axial portions of the body, the weekly clinical visits for expansion, discomfort for the child during the expansion process, and the esthetic deformity produced during the expansion process.
9. Cultured epithelial autograft:
    1. Represents another reconstructive option
    2. Requires a tissue sample from the patient, several weeks for cellular production, and final placement
    3. Cultured epithelia autograft's application to giant congenital nevi:

natural as in the burn treatment of large total body surface area burn
4. Can be used for giant nevi that preclude the use of tissue expansion or skin grafting secondary to lack of donor site availability
5. Definite shortcomings: including expense, time required for manufacturing of the graft (less of a limiting factor in children with nevi), and durability
6. Preferred procedure to split-thickness skin grafting because no donor site morbidity exists, decreased blood loss occurs, a greater area of excision with resultant faster removal of a nevus can be accomplished, and the durability of the cultured epithelia autograft compares favorably with a split-thickness graft

10. Enzymatically separated epidermal grafting (Kishi et al. 2009):
    1. A useful method for the treatment of GCMN
    2. Easy to perform
    3. Cosmetically satisfactory results
11. A successful surgical approach to the immense surface area of lesions encountered in adulthood GCMN (Su et al. 2015):
    1. Massive en bloc excision of GCMN.
    2. Staged reconstructive process involved the use of Integra (covering the skin defect with Integra dermal regeneration template (Tønseth et al. 2015)) followed by split-thickness skin grafting.
    3. This case provides a scenario in which early treatment may have reduced the need for a more morbid operation including partial resection of muscles with localized spread even without malignant transformation. Early surgical excision should be considered not only for presence of high-risk phenotypical features concerning for development of malignant transformation but also for likelihood of improved outcomes including morbidity of delayed excision, improved cosmetic result, and quality of life.
12. Psychosocial ramifications of congenital melanocytic nevi in children (Schaffer 2015):
    1. Especially in patients with larger nevi and those located in visible sites such as the face.
    2. Children with large or giant CMN are more likely to suffer from anxiety, depression, and social problems.
    3. Patients and families facing psychological and medical issues related to congenital melanocytic nevi may benefit from counseling and internet support groups such as Nevus Network (www.nevusnetwork.org) and Nevus Outreach, Inc. (www.nevus.org).

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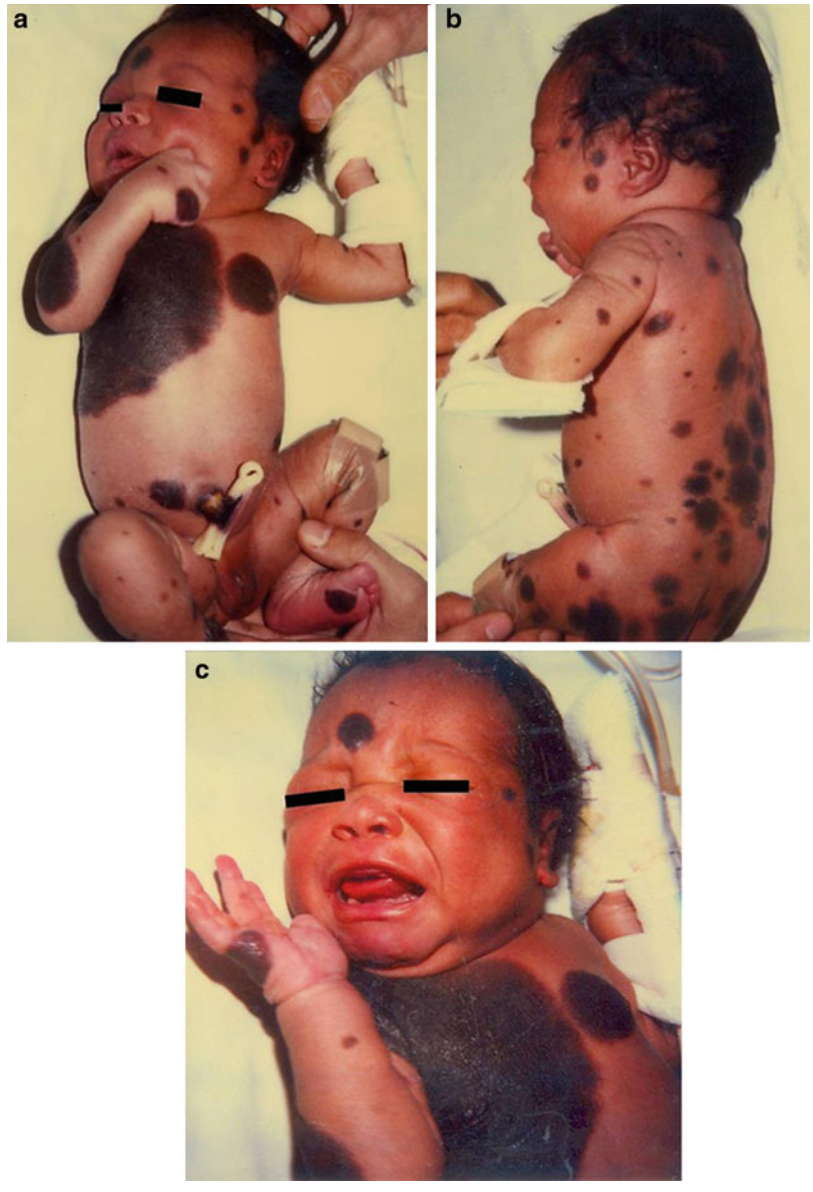

Fig. 1 (**a**–**c**) A newborn with multiple congenital nevi scattered throughout the body including a giant one on the right anterior chest

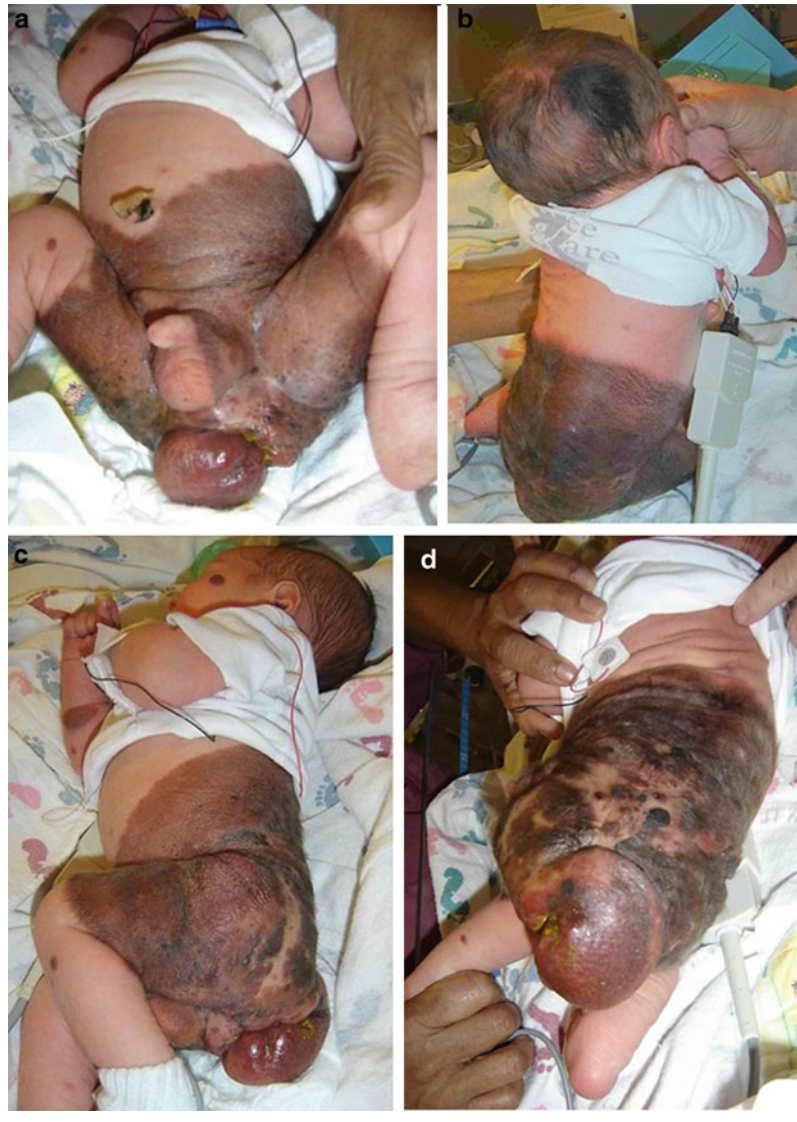

Fig. 2 (**a**–**d**) A neonate with a bathing trunk nevus, extending from the mid-trunk to the knees, with a large unevenly pigmented lesion of the back, buttocks, and upper extremities as well as several nodules and a large hypertrophic area over the sacrum

Gilbert Syndrome

Contents

Gilbert syndrome is a benign hereditary condition of mildly (about 40–60%) impaired bilirubin glucuronidation, characterized by intermittent unconjugated hyperbilirubinemia in the absence of hepatocellular disease or hemolysis (Fretzayas et al. 2012). It is the most common inherited disorder of bilirubin glucuronidation.

Synonyms and Related Disorders

Constitutional hepatic dysfunction; Familial nonhemolytic jaundice; Hyperbilirubinemia I; Hyperbilirubinemia, Gilbert type; Meulengracht disease

Genetics/Basic Defects

1. Generally considered as an autosomal recessive disorder (Chowdhury et al. 2001).
2. Earlier reports suggested autosomal dominant inheritance (Foulk et al. 1959; Powell et al. 1967; Sleisenger et al. 1967).
3. The number of TA repeats within the promoter region of the *UGT1A1* (uridine diphosphoglucuronate-glucuronosyltransferase 1A1) gene (located at 2q37.1) ultimately influences the serum unconjugated bilirubin concentration, by reducing inducibility of the *UGT1A1* gene and therefore hepatic bilirubin conjugation and excretion (Bulmer et al. 2013).
4. Individuals with an increased number of TA repeats in the gene promoter for *UGT1A1* (usually >7 in both alleles) are often diagnosed with Gilbert's syndrome, which is defined by an individual having an unconjugated bilirubin concentration >1 mg/dL (>17.1 μM) (Strassburg 2008).
5. A number of polymorphisms in the promoter region of *UGT1A1* exist, including the UGT1A1⁄28 (7/7 TA repeats in each allele) that clearly elevate unconjugated bilirubin concentrations (Bosma et al. 1995).
6. The majority of studies confirm lowered circulating lipid concentrations in persons with higher bilirubin concentrations (Bulmer et al. 2013).

Clinical Features

1. Typically present during adolescence and more commonly diagnosed in males (Muraca and Fevery 1984).
2. Characterized by intermittent episodes of jaundice: may be triggered by dehydration, fasting,

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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intercurrent febrile illnesses, menstruation, physical exertion, stress, and overexertion (Fretzayas et al. 2012).
3. Hyperbilirubinemia: predominantly unconjugated.
4. Other than jaundice, most patients are typically asymptomatic.
5. Normal physical examination findings.
6. Differential diagnosis.
    1. Crigler-Najjar syndrome type I: total bilirubin levels from 20 to 45 mg/dL
    2. Crigler-Najjar syndrome type II: total bilirubin levels from 1 to 6 mg/dL

Diagnostic Investigations

1. Laboratory tests (Roy-Chowdhury et al. 2014)
    1. Unconjugated hyperbilirubinemia: total bilirubin levels usually <3 mg/dL
        1. Higher bilirubin concentration: triggering factors (fasting, hemolysis, intercurrent febrile illnesses, physical exertion, stress, and menses)
        2. Reduced bilirubin concentration (Ohkubo et al. 1981; Black and Sherlock 1970; Kutz et al. 1984)
            1. Administration of corticosteroids
            2. Administration of hepatic enzyme inducers such as phenobarbital and clofibrate
    2. A normal complete blood count, blood smear, and reticulocyte count
    3. Normal plasma aminotransferases and alkaline phosphatase concentrations
2. Molecular genetic analysis: demonstration of mutation in the *UGT1A1* gene

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive: 25% risk
        2. Autosomal dominant: 50% risk if one parent is affected
    2. Patient's offspring
        1. Autosomal recessive: not increased unless the spouse is a carrier
        2. Autosomal dominant: 50% risk
2. Management
    1. No specific therapy required
    2. Most important aspect of the care of patients: recognition of the disorder and its benign nature

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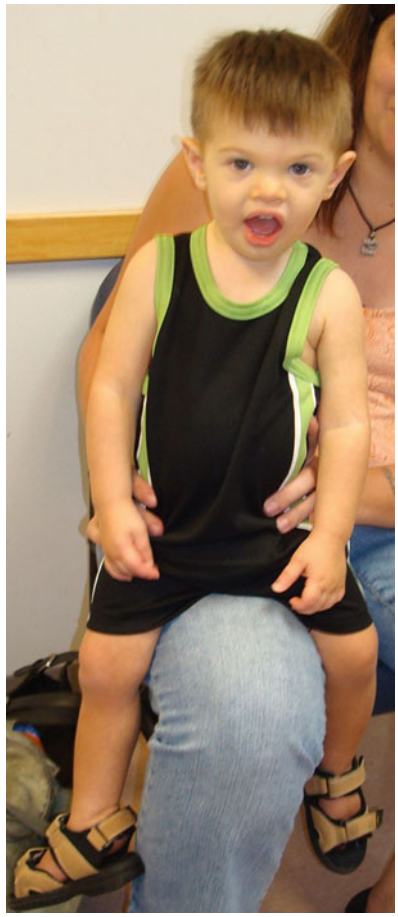

Fig. 1 The patient was evaluated for elevated unconjugated bilirubin levels and developmental delay. He had a history of neonatal jaundice which was getting worse. He was found to be homozygous for the A $(TA)_7TAA$ allele of *UGT1A1* gene and has the genotype known to be associated with Gilbert syndrome. The presence of elevated unconjugated bilirubin levels with this genotype in this patient suggests the diagnosis of Gilbert syndrome (Courtesy of Dr. Susanne Ursin)

Glucose-6-Phosphate Dehydrogenase Deficiency

Contents

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect, affecting more than 400 million people worldwide, especially in tropical Africa, the Middle East, tropical and subtropical Asia, some areas of the Mediterranean, and Papua New Guinea. The gene frequencies are estimated to be as high as 5–25% in these areas (Luzzatto et al. 2001).

Genetics/Basic Defects

1. Caused by mutations in the G6PD gene (mapped to Xq28 region) (Pai et al. 1980; Luzzatto 2006):
    1. About 140 mutations have been described.
    2. Most mutations are single missense point mutations, entailing single amino acid replacements in the G6PD protein.
    3. Few exceptions:
        1. Small deletions (of one to eight amino acids)
        2. Presence of two mutations (rather than one)
2. Inheritance:
    1. X-linked recessive in terms of clinical expression:
        1. Not truly recessive since heterozygous females can even develop severe hemolytic attacks
        2. Coexistence in female heterozygotes of two-cell populations, G6PD(+) and G6PD(−), secondary to X-chromosome inactivation (Davidson et al. 1963)
        3. Homozygous females not rare in many populations with high frequency of G6PD deficiency
    2. Codominant in terms of biochemical characteristics of electrophoretic variants segregating in a pedigree
3. Genetic heterogeneity (Beutler et al. 1991; Calabro et al. 1993; Luzzatto et al. 2001):
    1. Diverse biochemical characteristics:
        1. Presence of over 400 genetically distinct variants of G6PD
        2. Many allelic mutations in the G6PD gene causing these variants
        3. Presence of several structural mutants without enzyme deficiency
    2. Heterogeneous molecular characteristics (Beutler 1990, 1993):
        1. Some variants with different names proved to be identical.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Some variants thought to be homogeneous proved to be heterogeneous.
3. Different mutations responsible for:
   1. Chronic hemolytic anemia: less common
   2. Episodic hemolysis: more frequently seen
4. Diverse clinical manifestations, to a large extent, explainable by the genetic heterogeneity (Beutler 1991).
5. Variants that are associated with nonspherocytic anemia are located either near the glucose-6-phosphate or the nicotinamide adenine dinucleotide phosphate (NADP) binding sites. Variants more distant from these sites are not associated with chronic hemolysis (Beutler et al. 1992).

4. Pathogenesis:
   1. G6PD:
      1. A central enzyme in the pentose phosphate shunt of glucose metabolism
      2. Catalyzes glucose-6-phosphate (G6P) to 6-phosphogluconic acid (6PG)
      3. Reduces nicotinamide adenine dinucleotide phosphate (NADP) to the reduced form of NADP (NADPH)
   2. NADPH: converts glutathione disulfide (GSSG) to reduced glutathione (GSH)
   3. Reduced glutathione GSH
      1. Inactivates hydrogen peroxides (H_2O_2)
      2. Protects protein sulfhydryl groups from oxidation
      3. Neutralizes agents that threaten to oxidize either hemoglobin or components of the red cell membrane
   4. In the absence of G6PD:
      1. Red cell membrane and hemoglobin damaged by oxidant exposure
      2. Leading to rapid hemolysis
5. Hemolysis secondary to inability of G6PD-deficient red cells to withstand the oxidative damage produced, directly or indirectly, by the triggering agents (Beutler 1991, 1994; Luzzatto et al. 2001):
   1. Drugs
   2. Infections
   3. Ingestion of fava beans with life-threatening manifestations especially favism in children (Luisada 1941; Kattamis et al. 1969)
6. G6PD deficiency conferring resistance against *Plasmodium falciparum* malaria based on (Luzzatto et al. 2001):
   1. Prevalence of G6PD deficiency and the past and present endemicity of *Plasmodium falciparum* malaria
   2. The high prevalence in malaria-endemic areas of G6PD mutants
   3. Heterozygote advantage

Clinical Features

1. History:
   1. Asymptomatic in the vast majority of G6PD-deficient individuals without being aware of their genetic abnormality
   2. No positive history of acute intravascular hemolytic crises without exposure to oxidant stress
   3. Neonatal jaundice/hyperbilirubinemia (Lopez and Cooperman 1971; Valaes 1994; Kaplan and Hammerman 1998; Kaplan et al. 1999)
   4. Chronic hemolytic anemia:
      1. An insidious decrease in hemoglobin
      2. Observed in certain variant enzymes
   5. Required a careful investigation to establish the history of exposure to inciting agents
2. Common clinical manifestations (Luzzatto et al. 2016):
   1. Neonatal jaundice: may cause permanent neurologic damage or death in some severe cases
   2. Episodes of acute hemolytic anemia:
      1. Drug-induced hemolysis
      2. Infection-induced hemolysis
      3. Favism: occurrence of acute hemolysis after ingestion of broad beans (*Vicia faba*)
      4. Chronic nonspherocytic hemolytic anemia

5. Associated with hemoglobinuria since red cell destruction in these acute hemolytic events is largely intravascular
6. Kernicterus (Carpentieri et al. 1974; Washington et al. 1995; De Gurrola et al. 2008)
7. Concomitance with a variety of clinical situations, including diabetic ketoacidosis, hypoglycemia, myocardial infarction with pericardial tamponade, and strenuous exercise

3. Symptoms and signs of acute hemolytic crisis:
   1. Headache
   2. Lethargy
   3. Pallor
   4. Jaundice
   5. Red, clear urine

3. Symptoms and signs of chronic hemolytic crisis:
   1. Pallor
   2. Jaundice
   3. Severe chronic hemolysis observed in a rare subset of G6PD-deficient patients

4. Drugs to be avoided by G6PD-deficient patients (Beutler 1996, 2008; Cappellini and Fiorelli 2008; Youngster et al. 2010; Luzzatto and Seneca 2014; Bubp et al. 2015):
   1. Diaminodiphenyl sulfone (dapsone)
   2. Flutamide (Eulexin)
   3. Furazolidone (Furoxone)
   4. Isobutyl nitrite
   5. Methylene blue
   6. Niridazole (Ambilhar)
   7. Nitrofurantoin (Furadantin)
   8. Phenazopyridine (Pyridium)
   9. Primaquine
   10. Rasburicase (Elitek)
   11. Sulfacetamide
   12. Sulfanilamide
   13. Sulfapyridine

5. Drugs to be used with caution in therapeutic doses for patients with G6PD deficiency (without nonspherocytic hemolytic anemia) (Beutler 1996, 2008; Cappellini and Fiorelli 2008; Youngster et al. 2010; Luzzatto and Seneca 2014; Bubp et al. 2015):
   1. Acetaminophen (Tylenol)
   2. Acetylsalicylic acid (aspirin)
   3. Antazoline (Antistine)
   4. Antipyrine
   5. Ascorbic acid (vitamin C): intravenous doses only reported
   6. Benzhexol (Artane)
   7. Chloramphenicol
   8. Chlorguanidine (proguanil, Paludrine)
   9. Chloroquine
   10. Colchicine
   11. Diphenhydramine (Benadryl)
   12. Glyburide (glibenclamide, DiaBeta, Glynase)
   13. Isoniazid
   14. L-Dopa
   15. Quinine
   16. Streptomycin
   17. Sulfacytine
   18. Sulfadiazine
   19. Sulfaguanidine
   20. Sulfamethoxazole (Gantanol)
   21. Sulfisoxazole (Gantrisin)
   22. Trimethoprim
   23. Tripelennamine (Pyribenzamine)
   24. Vitamin K

6. Types of G6PD deficiency (Segel et al. 2002):
   1. X-minus variety:
      1. Most common type seen in the USA
      2. An X-linked condition primarily affecting African-American males
      3. Females affected if homozygous for G6PD deficiency or if there's unfavorable random X-chromosome inactivation resulting in a large proportion of deficient red cells
   2. Mediterranean variety:
      1. Develops severe hemolysis when exposed to oxidant drugs
      2. Characterized by enzyme deficiency in red cells of all ages, including reticulocytes, and shows no evidence of spontaneous recovery
   3. Other varieties:
      1. Develops chronic hemolytic anemia without external oxidant exposure

2. Susceptible to develop cholelithiasis because of heightened bilirubin turnover
3. Complaints of abdominal pain or fatty food intolerance

Diagnostic Investigations

1. Newborn screening (Bernardo and Nock 2014):
   1. Useful to providers in providing excellent care for newborns.
   2. Dangerous complications of neonatal hyperbilirubinemia are preventable, and evidence supports the use of newborn G6PD screening programs in reducing such complications as hospital readmissions and kernicterus.
2. Acute hemolysis (Segel et al. 2002):
   1. Precipitous anemia:
      1. A fall in hemoglobin
      2. A fall in hematocrit
      3. Subsequent rise in reticulocyte percentage
   2. Elevated bilirubin, particularly the indirect fraction
   3. Reduced haptoglobin as it binds free hemoglobin and is removed from the circulation
   4. Hemoglobinemia +/− hemoglobinuria
3. Diagnosis of G6PD deficiency (Frank 2005; Kaplan and Hammerman 2010):
   1. Rapid fluorescent screening spot test detecting the generation of NADPH (reduced NADP) from NADP:
      1. The test is positive if the blood spot fails to fluoresce under ultraviolet light (NADPH fluoresces intensely when activated by long-wave UV light; fluorescence under UV light source is normal and indicates G6PD activity).
      2. Useful in identifying totally deficient individuals with <20% residual activity.
      3. Could erroneously classify as normal males and females with partial deficiency (20–60% residual enzyme activity).
      4. Not helpful in identifying most heterozygotes with intermediate levels of G6PD activity.
   2. Quantitative analysis of G6PD activity by assessing NADPH formation spectrophotometrically:
      1. G6PD-deficient male hemizygotes and female homozygotes: usually <50% normal activity, frequently <20%, and often undetectable (Luzzatto 2006).
      2. Heterozygous females may have intermediate activity, but this may range from normal to deficient, and many female heterozygotes with partial enzyme activity will not be detected.
      3. Falsely obtaining normal test results during or immediately after an acute hemolytic event.
   3. In field research, where quick screening of a large number of patients is needed, other tests have been used; however, they require definitive testing to confirm an abnormal result (Iwai et al. 2003; Jalloh et al. 2004).
   4. Tests based on polymerase chain reaction detect specific mutations and are used for:
      1. Population screening
      2. Family studies
      3. Prenatal diagnosis
4. Direct DNA analysis
   1. Sequence analysis (analysis of the entire coding region)
   2. Targeted mutation analysis

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib (if the mother is a carrier)
      1. 50% of male siblings affected
      2. 50% of female siblings carriers (some female heterozygotes may be affected)
   2. Patient's offspring
      1. 100% of female offspring carriers (some female heterozygotes may be affected)
      2. 50% of female offspring affected (homozygotes) if the spouse is a carrier
      3. Male offspring not affected unless the spouse is a carrier

2. Prenatal diagnosis: may be possible in at-risk families, provided disease-causing mutations have been identified previously
3. Management (Luzzatto et al. 2016):
    1. Prevent or remove precipitating agents.
    2. Control infection.
    3. Phototherapy for neonatal hyperbilirubinemia.
    4. Supportive transfusion.
    5. Exchange transfusion to prevent kernicterus.
    6. Hemodialysis may be necessary if there is acute renal failure.
    7. In adults, the most important measure is to provide fluids to prevent hemodynamic shock that entails the threat of acute renal failure.
    8. In children, more often than in adults, blood transfusion may be indicated; in a child with favism, it may be lifesaving.
    9. Fortunately, once acute hemolytic anemia is overcome, full recovery without sequelae is the rule rather than the exception.

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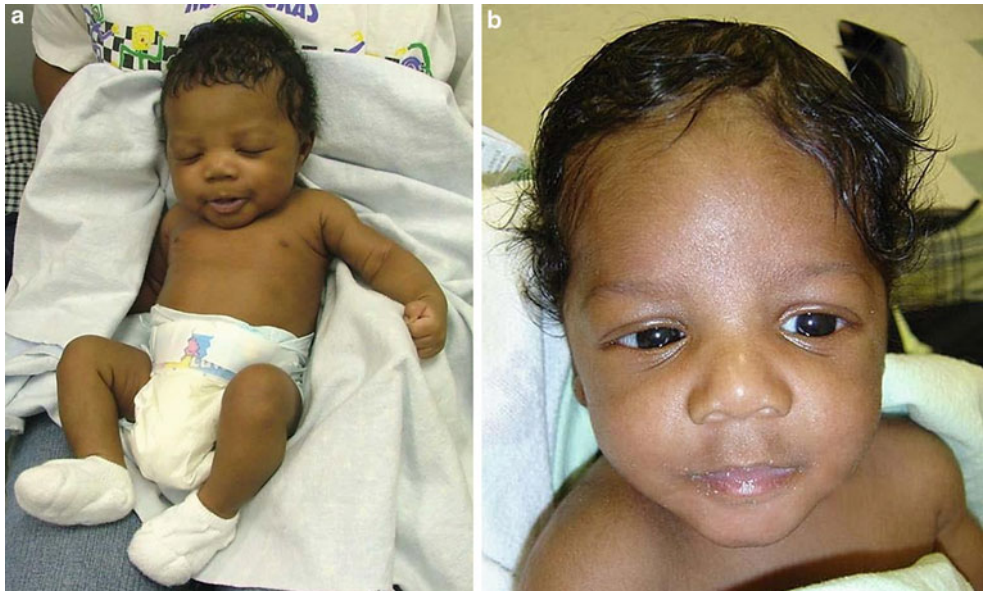

Fig. 1 (**a**, **b**) 1-month-old and 2-month-old boys with G6PD deficiency who are asymptomatic. The newborn screenings of both boys identified one (hemizygous) copy of the double mutations (G202A; A376G)

Fig. 2 An 8-week-old girl with G6PD deficiency who is asymptomatic. The newborn screening identified compound heterozygote consisting of one copy of the double mutation (G202A; A376G) and one copy of the A378G mutation. This phenotype is seen only in females since this is an X-linked disorder

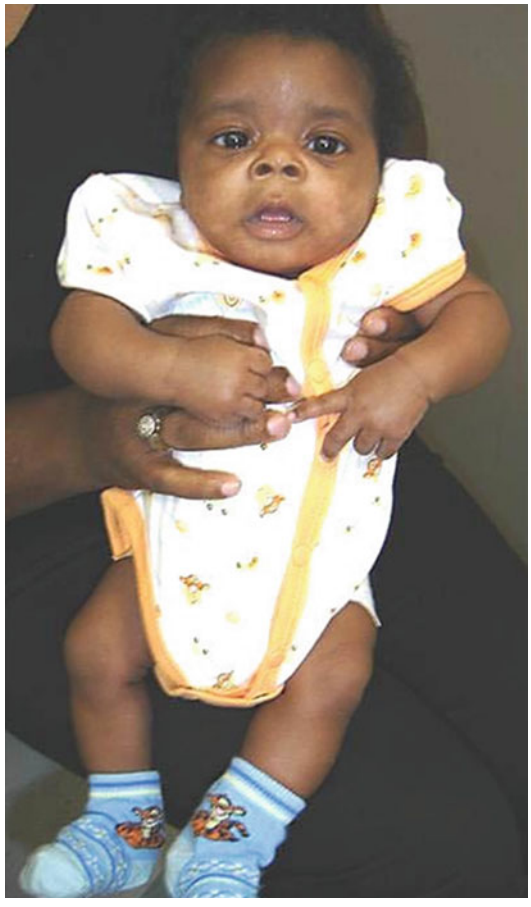

Fig. 3 A 1-month-old boy with G6PD deficiency who is asymptomatic. The newborn screening revealed G6PD of 3.8 (10.8–16.2 U/g Hb). Molecular analysis showed one copy of A376G mutation

Fig. 4 A patient of Mediterranean ancestry with G6PD deficiency. He has had a history of hemolytic anemia crisis after ingestion of fava bean

Fig. 5 Fava beans

Glycogen Storage Disease, Type 2

Contents

Type II glycogen storage disease (GSD), also known as Pompe disease, is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase (acid maltase). Incidence is estimated at 1 in 50,000 in most populations, implying a carrier frequency of 1 in 100 (Kleijer et al. 1995).

Synonyms and Related Disorders

Acid maltase deficiency; Glycogenosis type II; Pompe disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Kleijer et al. 1995)
2. Caused by deficiency of acid maltase (acid α-glucosidase), leading to the pathological accumulation of glycogen in lysosomes, predominantly in the skeletal muscle, heart, and liver
    1. Virtual absence of α-glucosidase activity in infantile form (Pompe disease)
    2. Considerable residual enzyme activity in the great majority of patients with the adolescent or adult form (Mehler and DiMauro 1977)
3. Identification of various mutations in the α-glucosidase (*GAA*) gene (mapped on 17q23-25), leading to the disease
    1. Types of mutations
        1. Point mutations
        2. Deletions
        3. Insertions
    2. Compound heterozygotes in most patients
    3. Relatively common mutations among European patients
        1. The single base pair deletion ΔT525 causing premature termination at nucleotide 658–660
        2. Deletion of exon 18
4. Genotype-phenotype correlation
    1. The nature of the mutation is generally considered a good predictor of a clinical phenotype.
    2. Homozygosity for either exon 18 or ΔT525 mutation or compound heterozygosity for these two mutations results in a severe infantile form of GSDII (Ausems et al. 1996)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_108

3. Combination of either of these mutations with leaky IVS1t-13 g mutation results in the majority of cases in the adult phenotype
4. A splicing defect (IVS6 t-22 g) results in a removal of exon 6, and insertion of 21 nucleotides of the intronic sequence defined the juvenile phenotype in a compound heterozygote patient who carries a silent second allele. Homozygosity for the same splicing defect resulted in a milder adult phenotype
5. Growing number of cases in recent years where the genotype does not match the phenotype (Laforêt et al. 2000)

5. Pathophysiology (American Association of Neuromuscular and Electrodiagnostic Medicine 2009)
   1. Mutations in both copies of the GAA gene lead to varying degrees of GAA deficiency (Kishnani and Howell 2004)
      1. Infantile-onset form: either totally or virtually absent acid α-glucosidase enzyme activity in skin fibroblasts
      2. Late-onset form: some residual enzyme activity (1 ~ 40%) in skin fibroblasts in most affected children and adults
   2. Primary defect
      1. Progressive intralysosomal storage of glycogen
      2. Recognition of the role of dysfunctional autophagy in the disease process

Clinical Features

1. Infantile form (Slonim et al. 2000; Raben et al. 2002).
   1. Classical infantile form
      1. Onset within first weeks or months of life or even at birth
      2. Characterized by complete or near complete deficiency of α-glucosidase
      3. Poor feeding (difficulty sucking and swallowing) and failure to thrive, early complaints
      4. Cyanosis and attacks of dyspnea beginning early
      5. Frequent respiratory infections
      6. Delayed motor milestones
      7. Cardiomyopathy (hypertrophic) (~95%): the important finding suggesting diagnosis (Noori et al. 2002)
         1. Marked cardiomegaly
         2. Congestive heart failure
      8. Striking hypotonia
         1. Increasing generalized weakness
         2. Affecting bulbar musculature
         3. Without muscle atrophy
      9. Macroglossia (~62%)
      10. Moderate hepatomegaly (~82%)
      11. Calf hypertrophy
      12. Depressed or absent reflexes due to glycogen accumulation in spinal motor neurons
      13. Impaired alertness
      14. Accumulation of glycogen in the lysosomes rapidly disrupts cellular function in the most severe form
          1. Rapidly disrupts cellular function
          2. Leading to intractable cardiorespiratory failure
          3. Most patients die by 1 year of age
   2. Nonclassical infantile form
      1. Onset in infancy
      2. Slower progression
      3. Involving primarily skeletal muscle with minimal or no cardiac involvement (without cardiomegaly)
      4. May present with delayed motor milestones if onset is in early preschool age
      5. May present with a decrease in motor skills if onset is later in childhood
      6. Usually demonstrates progressive proximal weakness with different degrees of respiratory muscle involvement
      7. Presence of respiratory complications often contributing to early death
2. Juvenile form
   1. Juvenile onset (first decade)
   2. Characterized by presence of reduced but residual α-glucosidase activity
   3. Clinical boundaries between juvenile and adult forms not precisely defined
   4. Clinical manifestations

1. Predominantly skeletal muscle weakness with respiratory muscle involvement and mild hepatomegaly
2. Cardiac involvement: absent or mild
    1. Arrhythmia
    2. Mild ventricular dysfunction
3. Death results from respiratory failure after a course lasting several years

3. Adult form
    1. Onset: second to sixth decades
    2. Characterized by higher levels of residual α-glucosidase activity
    3. Slower progression of the skeletal muscle weakness
        1. Upper arms
        2. Pectoral muscles
        3. Asymmetry of affected muscle groups
        4. Limb-girdle weakness, a prominent finding
        5. Respiratory muscle involvement (weakness of the diaphragm) (about 33%): a hallmark of the disease
        6. Little or no cardiac abnormality
    4. Acute respiratory failure
4. Differential diagnosis of infantile-onset Pompe disease (with respect to shared signs and symptoms) (ACMG Work Group on Management of Pompe Disease et al. 2006; Kishnani et al. 2006)
    1. Acute Werdnig-Hoffman disease (spinal muscular atrophy I)
        1. Hypotonia
        2. Progressive proximal myopathy
        3. Absent reflexes
    2. Hypothyroidism
        1. Hypotonia
        2. Macroglossia
    3. Endocardial fibroelastosis
        1. Breathlessness
        2. Feeding difficulties
        3. Cardiomegaly
        4. Heart failure
    4. Myocarditis: cardiomegaly
    5. Congenital muscular dystrophy
        1. Severe hypotonia
        2. Severe muscle weakness
    6. Glycogen storage diseases: IIIa (Debrancher deficiency/Cori or Forbes disease) and IV (branching enzyme deficiency/Anderson disease)
        1. Cardiomegaly
        2. Myopathy
        3. Elevated creatine kinase (CK)
    7. Mitochondrial/respiratory chain disorders
        1. Hepatomegaly
        2. Muscle weakness
        3. Cardiomegaly
        4. Elevated creatine kinase (CK)
    8. Danon disease
        1. Cardiomegaly
        2. Cardiomyopathy
        3. Myopathy
        4. Vacuolar glycogen storage
    9. Idiopathic hypertrophic cardiomyopathy: biventricular hypertrophy
    10. Peroxisomal disorders
        1. Hypotonia
        2. Hepatomegaly
5. Differential diagnosis of late-onset Pompe disease (ACMG Work Group on Management of Pompe Disease et al. 2006; Kishnani et al. 2006; Katzin and Amato 2008; American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) 2009; Dubrovsky et al. 2013): Heterogeneity of presentation can mimic other neuromuscular disorders, and the differential diagnosis includes a broad range of myopathies as well as motor neuron and neuromuscular junction disorders
    1. Dystrophies
        1. Limb-girdle muscular dystrophy: progressive muscle weakness in the pelvis, legs, and shoulders (shared signs and symptoms)
        2. Dystrophinopathies (Duchenne and Becker muscular dystrophy): progressive proximal muscle weakness, respiratory impairment, difficulty walking, and elevated creatine kinase (CK) (shared signs and symptoms)
        3. Myofibrillar myopathy
        4. Myotonic dystrophy type 2
        5. Scapuloperoneal syndromes: progressive muscle weakness behind the knees and around the shoulder blades (shared signs and symptoms)

6. Danon disease: hypertrophic cardiomyopathy, skeletal muscle myopathy, and vacuolar glycogen storage (shared signs and symptoms)
7. X-linked myopathy with excessive autophagy
8. Facioscapulohumeral muscular dystrophy
9. Rigid spine syndrome: spinal rigidity and lower back pain (shared signs and symptoms)

2. Inflammatory myopathies
   1. Polymyositis: unexplained muscle weakness (shared signs and symptoms)
   2. Inclusion body myositis
3. Congenital myopathies
   1. Nemaline rod myopathy
   2. Central core and multiminicore myopathy
   3. Centronuclear myopathy
   4. Hyaline body myopathy
   5. Other congenital myopathies
4. Other metabolic myopathies
   1. Glycogen storage diseases (debranching enzyme deficiency (IIIa), branching enzyme deficiency (IV), McArdle disease (V), and muscle phosphofructokinase deficiency (VII)): hypotonia, hepatomegaly, muscle weakness, and elevated creatine kinase (CK)
   2. Mitochondrial myopathy: hypotonia, hyperreflexia, hepatomegaly, and some forms with hypertrophic cardiomyopathy, muscle weakness, and elevated creatine kinase (CK)
   3. Lipid disorder myopathies
5. Motor neuron disorders
   1. Spinal muscular atrophy types II and III: asymmetrical muscle weakness and atrophy of voluntary muscles (shared signs and symptoms)
   2. Kennedy disease
   3. Amyotrophic lateral sclerosis
6. Neuromuscular junction disorders
   1. Myasthenia gravis: generalized muscle weakness (shared signs and symptoms)
   2. Congenital myasthenic syndromes
   3. Lambert-Eaton syndrome
7. Peripheral neuropathy
   1. Hereditary neuropathies
   2. Chronic inflammatory demyelinating polyneuropathy
   3. Amyloid neuropathy
8. Rheumatoid arthritis: stiffness/pain upon exertion (shared signs and symptoms)

Diagnostic Investigations

1. Elevated serum creatine kinase in most patients (Ausems et al. 1999)
2. Elevated serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH)
3. Radiography: tremendous cardiomegaly
4. EKG: can readily observe the signs of cardiac glycogenosis (indicators of relative myocardial ischemia)
   1. Very large QRS complex in all leads
   2. Short P-R interval: pathognomonic of infantile Pompe disease
   3. Left axis deviation or absence of the normal right axis deviation (presence of biventricular hypertrophy)
   4. Inverted T wave
   5. ST segment depression
5. Echocardiography (De Dominicis et al. 1991): biventricular hypertrophy without outflow obstruction
6. EMG
   1. Infantile form: nonspecific myopathic changes or normal finding
   2. Adult form
      1. Pseudomyotonia
      2. High-frequency discharges
      3. Fibrillations
7. Muscle biopsy
   1. Presence of vacuoles that stain positive for glycogen (PAS) as well as for the lysosomal enzyme acid phosphatase
   2. A typical lacework appearance of histologic sections from the myocardium resulting from deposition of stored material in the cardiac fibrils
   3. Electron microscopy

1. Membrane-bound glycogen
2. Glycogen accumulation within the lysosome

4. The muscle biopsy, in spite of its shortcomings, allowed us to recognize an underreported, ERT-resistant pathology in late-onset Pompe disease (LOPD). Numerous lysosomes and autolysosomes loaded with lipofuscin appear to be a hallmark of LOPD skeletal muscle. Lipofuscin accumulation – a result of inefficient lysosomal degradation – may in turn exacerbate both lysosomal and autophagic abnormalities (Feeney et al. 2014)

8. Histology: glycogen accumulation
   1. Infantile form
      1. Muscle
      2. Liver
      3. Motor nuclei in the brain stem
      4. Anterior horn cells of the spinal cord
      5. Placenta (Bendon and Hug 1985)
         1. Amniotic storage cells identified and shown histochemically to contain glycogen
         2. Pathognomonic accumulation of lysosomal glycogen in the placenta by electron microscopy in the second trimester
         3. Confirmation of the prenatal diagnosis made by enzyme assay
      6. Other tissues
         1. Endothelial cells
         2. Kidneys
         3. Skin
   2. Adult form: not seen in the heart, liver, or brain
9. Lung MRI (Wens et al. 2015)
   1. An innovative tool to visualize diaphragmatic dynamics in Pompe patients and to study chest wall and diaphragmatic movements
   2. Diaphragmatic displacement may be severely disturbed in patients with Pompe disease
10. Cardiac MR imaging: hypertrophy of right and left ventricles and the interventricular septum with an irregular inhomogeneous appearance of the myocardium (Boxer et al. 1986)
11. Brain MR imaging
    1. T1-weighted MR images of the brain revealed multifocal dural thickening that enhanced after intravenous gadolinium administration. Open opercula and focal pachygyria over bilateral perisylvian regions also were noted (Lee et al. 1996)
    2. Bright tongue sign (Karam 2016)
       1. Abnormal diffuse T1 hyperintensity of the tongue musculature in an adult patient with Pompe disease
       2. Bright tongue sign is well known in patients with bulbar amyotrophic lateral sclerosis but also can be seen in other neuropathies or myopathies that can affect the tongue muscle
12. A CT angiography or an MR angiography: recommended, in late-onset Pompe disease patients, for early detection of cerebrovascular malformations as they could lead to life-threatening events such as subarachnoid hemorrhage or brainstem compression (Montagnese et al. 2016)
13. Diagnostic enzymatic test: deficient acid maltase in leukocytes, muscle, and skin fibroblasts
14. DNA analysis by targeted mutation analysis
15. Newborn screening by determining the total α-glucosidase in plasma or dried blood spots (Umapathysivam et al. 2001; Chien et al. 2009)
16. Heterozygote detection
    1. Reduced α-glucosidase activity: not reliable
    2. DNA-based detection more appropriate and definitive within families
17. Western blot analysis of cultured skin fibroblast (Bali et al. 2015)
    1. Gold standard for determining cross-reactive immunological material (CRIM) status
    2. CRIM status: an important prognostic factor in patients with infantile Pompe disease (IPD) being treated with enzyme replacement therapy

18. Next-generation sequencing: used as a first-tier test in patients with suspected muscle disorders of undetermined etiology, which could further increase overall diagnosis of muscle conditions and potentially reduce diagnostic delay (Lévesque et al. 2016)
19. Recommendations for diagnostic tests in Pompe disease in adults (Pompe Disease Diagnostic Working Group et al. 2008; Llerena Junior et al. 2016)
    1. Screening test: DBS ("dried blood spot") on filter paper to perform enzymatic activity analysis of acid α-glucosidase (GAA)
    2. "Gold standard" diagnostic test: in fibroblasts or muscle tissue for acid α-glucosidase (GAA) enzymatic assay
    3. Diagnostic test: molecular analysis of the *GAA* gene
    4. Diagnostic test in DBS: GAA activity in lymphocytes and/or leucocytes

Genetic Counseling

1. Recurrence risk (Llerena Junior et al. 2016)
    1. Parents of individuals with Pompe disease (PD): healthy obligatory heterozygotes
    2. The diagnosis of an individual with PD justifies the active search of the disease among his/her siblings. Asymptomatic or mildly symptomatic cases are often identified due to the intrafamilial clinical variability observed between two siblings with PD
    3. Patient's sib: 25%
    4. Patient's offspring: not increased unless the spouse is a carrier in which cases 50% of offspring will be affected and 50% will be carriers
2. Prenatal diagnosis (Phupong et al. 2005)
    1. Rapid prenatal diagnosis by electron microscopy of uncultured amniocytes (Hug et al. 1984)
    2. Deficient activity of lysosomal acid α-glucosidase in cultured amniocytes or CVS
    3. Electron microscopic study of chorionic villus biopsies for the pregnancy at risk: fibrocytes with typical vacuoles filled with glycogen
    4. Mutation analysis on amniocytes or CVS: 100% reliable prediction of the genetic status of the fetus, including heterozygosity (Kleijer et al. 1995)
3. Management
    1. Supportive therapy to manage symptoms and minimize complications whenever possible
        1. Respiratory therapy
        2. Physical therapy (Case and Kishnani 2006)
        3. Dietary therapy: L-alanine supplementation (Bodamer et al. 2000, 2002)
        4. Infection prevention
        5. A high-protein diet to improve muscle function
        6. Ventilator support
    2. Administration of purified α-glucosidase not effective
    3. Bone marrow transplantation (Hug 1986; Watson et al. 1986) presumably to provide enzyme secreted by the normal cells continuously
        1. Results not promising
        2. Transitory engraftment of the haploidentical transplant
        3. No enzyme detected in muscle cells
        4. Patient died of complications of the transplant
    4. Enzyme replacement therapy (Kikuchi et al. 1998; Amalfitano et al. 1999; Chen and Amalfitano 2000)
        1. ERT with recombinant human α-glucosidase from rabbit milk in Pompe patients (Van den Hout et al. 2000, 2001)
            1. Intended to directly address the underlying metabolic defect via intravenous infusions of rhGAA enzyme
            2. The enzyme generally well tolerated
            3. Normalization of muscle α-glucosidase activity
            4. Improved tissue morphology and motor and cardiac function
            5. Significantly decreased left ventricular mass index

6. Recommend early treatment (before irreversible damage) and follow-up of long-term effects
7. Anti-rhGAA antibody may limit the efficacy of the treatment
8. Extensive muscle damage may be unrefractive to therapy

2. Infantile-onset Pompe disease (Amalfitano et al. 2001; Klinge et al. 2005; Kishnani et al. 2006, 2007)
   1. Significantly prolongs survival, decreases cardiomegaly, and improves cardiac and skeletal muscle function
   2. An emerging phenotype characterized by progressive weakness and decreased motor function has been identified in patients with infantile-onset Pompe disease that initially responded well to enzyme replacement therapy with alglucosidase alfa (Case et al. 2012, 2015; Prater et al. 2012)
   3. Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated with rhGAA since birth (Chien et al. 2015): experienced long-term survival without requiring ventilation and nearly normal development but presented with residual myopathy and other manifestations such as ptosis and speech disorders
3. Late-onset Pompe disease (Bernstein et al. 2010): Gastrointestinal symptoms resolved within the first 6 months of ERT with rhGAA. Patients gained weight and remain symptom free, two for over 4 years

5. Gene therapy aiming at providing a permanent endogenous source of enzyme for the affected tissues: not available currently (Poenaru 2000)

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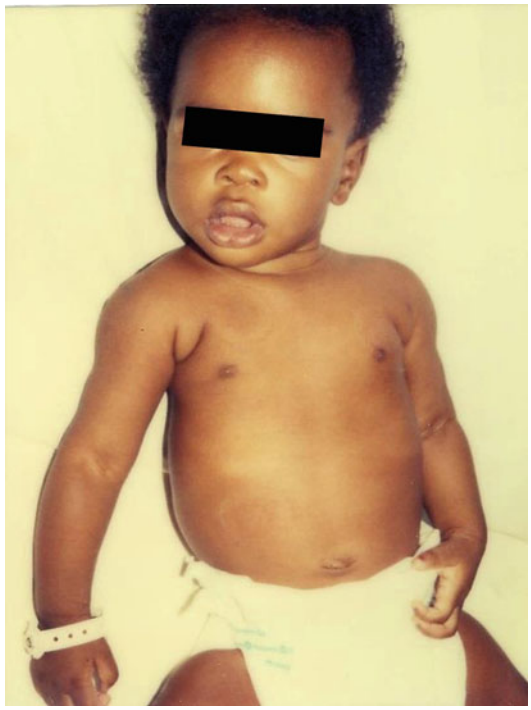

Fig. 1 An infant with massive cardiomegaly and hypotonia. Diagnosis of Pompe disease was confirmed by deficient acid maltase in the leukocytes

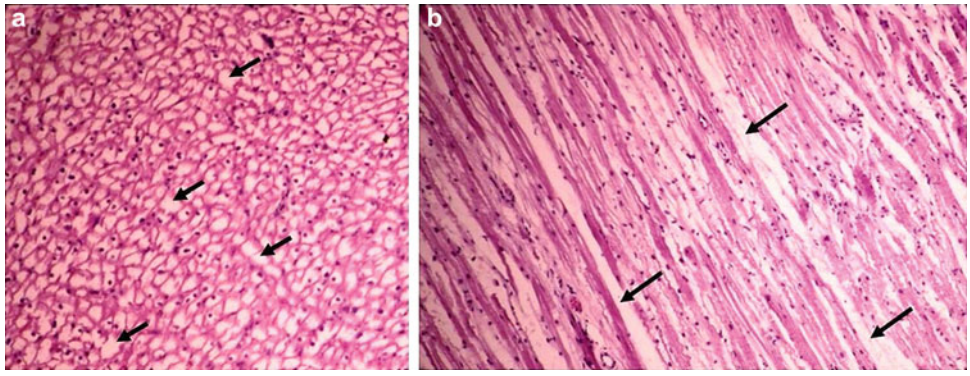

Fig. 2 (**a**, **b**) Different patient with Pompe disease. (**a**) Myocardium. Note numerous vacuolated fibers (*arrows*) due to glycogen accumulation. HE, ×40. (**b**) Smooth muscle from GI tract. Note clear areas represent glycogen deposition (*arrows*)

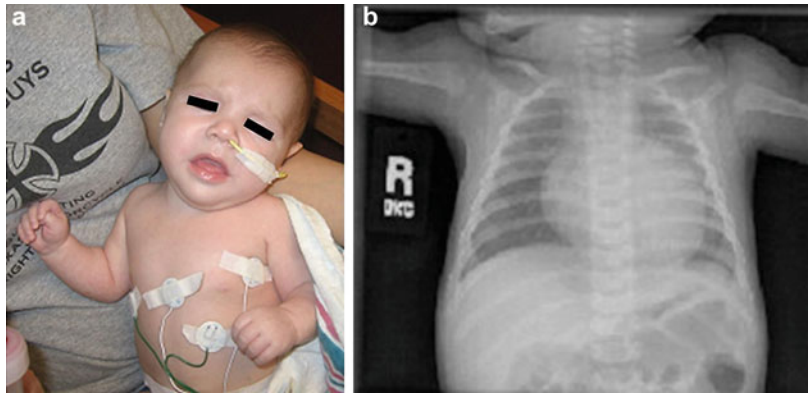

Fig. 3 (**a**, **b**) A 23-month-old boy (**a**) was seen because of respiratory distress and heart failure. A chest X-ray (**b**) showed a large globular-shaped heart. An echocardiogram showed a hypertrophic cardiomyopathy. He was noted to be hypotonic and had an enlarged liver. Muscle biopsy showed excessive glycogen storage with glycogen content 5.6 % (control: 0.94 ± 0.55 % wet weight). Muscle α-glucosidase was deficient (0.01; control: 0.42 ± 0.2 micromol/min/g of tissue). Muscle neutral α-glucosidase was 0.05 (control: 0.12 ± 0.6 micromol/min/g of tissue). Blood acid α-glucosidase was 1.3 (control: 10.0–49.0 pmol/punch/h). Blood neutral α-glucosidase was 52.3 (control: 23.8–132.6 pmol/punch/h). Urine Hex4 was 34.1 (control for <6 month: <19 nmol/mol creatinine). Mutation analysis revealed c.1846 G > A (exon 13) and c.2608 C > A (exon 18). The c.2608CA mutation is a nonsense mutation that results in a premature termination codon, a reported disease causing mutation. The c.1846 G > A mutation has not been previously reported as a mutation causing Pompe disease or a known polymorphism but has been seen once in the Duke University laboratory, in the homozygous state as the only mutation in a patient with Pompe disease. This patient received one dose of enzyme replacement therapy and tolerated his first dose of Myozyme well

Goldenhar Syndrome

Contents

In 1952, Goldenhar (1952) described a pair of monozygotic twins discordant for hemifacial microsomia, mandibular hypoplasia, auricular malformations, and epibulbar dermoids. Gorlin et al. (1963) later in 1963 coined the term "oculoauriculovertebral dysplasia" to describe patients with mandibular hypoplasia, microtia, epibulbar dermoids, and vertebral anomalies. The presence of vertebral anomalies and epibulbar dermoids delineates the so-called Goldenhar syndrome. Oculoauriculovertebral spectrum (OAVS) is a relatively common disorder affecting approximately 1 in 5,600 live births.

Synonyms and Related Disorders

Hemifacial microsomia; Oculoauriculovertebral dysplasia/spectrum

Genetics/Basic Defects

1. The term, "oculoauriculovertebral dysplasia spectrum," suggested to represent an etiologically diverse spectrum of congenital anomalies
    1. Oculoauriculovertebral dysplasia
    2. Facioauriculovertebral syndrome (Goldenhar-Gorlin syndrome)
    3. Hemifacial microsomia (second most common facial anomaly, second only to cleft lip and palate) (Sze et al. 2002)
    4. Hemifacial microtia
    5. Otomandibular dysostosis
    6. Original Goldenhar syndrome
    7. Goldenhar-Gorlin syndrome
    8. Anomalies of the first and second branchial arches (Converse et al. 1973)
2. Congenital anomalies
    1. Usually unilateral
    2. Primarily right sided
    3. More common in monozygous twins usually with one affected (Boles et al. 1987)
3. Causes: unknown but likely heterogeneous (Setzer et al. 1981; Burck 1983; Cohen et al. 1989; Kelberman et al. 2001)
    1. Usually sporadic occurrence
    2. Maternal teratogenic exposures
        1. Retinoic acid
        2. Thalidomide
        3. Primidone (Gastavson and Chen 1985)
        4. Cocaine (Lessick et al. 1991)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Maternal diabetes (Ewart-Toland et al. 2000)
4. Discordant occurrence in monozygotic twins: arising from a disturbance of blastogenesis leading to malformations
5. Autosomal dominant inheritance (Guizar-Vazquez et al. 1978; Zankl and Zang 1979; Godel et al. 1982; Regenbogen et al. 1982; Sanchez-Corona et al. 1982; Taysi et al. 1983; Robinow et al. 1986; Oliveira et al. 1989; Orstavik et al. 1990; Stoll et al. 1998; Gupta and Patton 1995; Tasse et al. 2007; Vendramini-Pittoli and Kokitsu-Nakata 2009)
    1. A report of a family with clinical diagnosis of OAVS, autosomal dominant inheritance pattern, and detection of a 14q23.1 duplication of 1.34 Mb in size which segregates with the phenotype (Ballesta-Martínez et al. 2013)
    2. This region contains *OTX2*, which is involved in the development of the forebrain, eyes, and ears, and appears to be a good candidate gene for OAVS
    3. *OTX2* duplication: implicated in hemifacial microsomia (Zielinski et al. 2014)
6. Autosomal recessive inheritance (Ellwood et al. 1968; Konigsmark et al. 1972; Schmid et al. 1985; Strisciuglio et al. 1986)
7. Associated chromosome abnormalities (Beleza-Meireles et al. 2014)
    1. Del(1)(p22.2–p31.1)
    2. Del(5p)
    3. Del(5q13.2)
    4. Del(5)(p15.33–pter)
    5. Monosomy 6q
    6. Trisomy 7
    7. Trisomy 7, mosaic
    8. Dup(7q)
    9. Dup(8q)
    10. Inv(9)(p11;q13)
    11. T(9;18)(p23;q12.2)
    12. Trisomy 9 (mosaic) (De Ravel et al. 2001)
    13. Dup(10)(p14–p15)
    14. Del(12p13.33)
    15. Dup(14q23.1)
    16. Del(14)(q31.1q31.3)
    17. Inv(14)(p11.2;q22.3)
    18. Del(15q24.1)
    19. Del(18q)
    20. Der(18)
    21. Trisomy 18
    22. R(21)
    23. Del(22q11.2)
    24. Del(22)(q13.31)
    25. Del(22qter)
    26. Dup(22)(q11.1–q11.21)
    27. Dup(22)(q11.2q13.1) (Hathout et al. 1998)
    28. Trisomy 22 (mosaic) (De Ravel et al. 2001)
    29. Partial 22 trisomy of the 22q11 region
    30. 47,XXY
    31. 49,XXXXY
8. aCGH copy number variation (CNV) loci reported in patients with OAVS (Beleza-Meireles et al. 2014)
    1. CNVs on 22q11.21 (Beleza-Meireles et al. 2015)
    2. Del(1)(p22.2–p31.1)
    3. Del(2p11.2)
    4. Del(2q11)
    5. Dup(4)(q35.113q13.1)
    6. Del(5)(pter → p15.33)
    7. Dup(8q11.23)
    8. Dup(9q34.11)
    9. Dup(11q21)
    10. Del(12p13.33)
    11. Del(12)(pter → p13.33)
    12. Dup(14q23.1)
    13. Dup(14)(q22.3–q23.3)
    14. Del(14)(q31.1–q31.3)
    15. Del(14q32.2)
    16. Del(15)(q24.1q24.2)
    17. Del(15q24)
    18. Dup(18)(p11.23–p11.31)
    19. Dup(20p12.2)
    20. Del(22)(q11.21–q11.22)
    21. Del(22q11.2)
    22. Dup(22)(q11.1–q11.21)
    23. Dup(22)(q11.1q11.21), Del(22)(q11.21q11.22)
    24. Dup(Yp–q11.221), Del(Y)(q11.222–q12)

25. Amplification Xp22.33
26. Trisomy X

4. Pathogenesis: unknown but likely heterogeneous
   1. Interference with vascular supply and focal hemorrhage in the developing first and second branchial arch region
   2. Impaired interaction of cranial neural crest cells with branchial arch mesenchyme
   3. A disorder of blastogenesis
5. Hypothesis: candidate genes for OAVS, particularly in familial cases (Forest-Potts and Sadler 1997)
   1. Homeobox genes, especially of the MSX class
      1. *Msx* critical for the differentiation of first branchial arch ectoderm-mesenchyme leading to various craniofacial structures
      2. Strongly expressed in cephalic neural crest cells prior to migration of the cells that contribute extensively to craniofacial development
   2. Encompasses previous partial pathogenetic explanations for OAVS, including neurocristopathy and developmental field defects, and represents a unifying concept regarding the wide spectrum of involvement in OAVS
   3. Mutations that result in partial loss of function of these genes could explain incomplete penetrance and clinical variability occurring in individuals with different genetic backgrounds.

Clinical Features

1. Broad phenotypic spectrum (Rollnick and Kaye 1983)
2. Major clinical features (Alfi et al. 2014)
   1. Ocular manifestations (Baum and Feingold 1973; Mansour et al. 1985)
      1. Epibulbar dermoids or lipodermoid (Goldenhar syndrome)
      2. Unilateral microphthalmia
      3. Upper eyelid coloboma
      4. Strabismus
      5. Diminished visual acuity
      6. Tilted optic disk
      7. Optic nerve hypoplasia (Margolis et al. 1984)
      8. Tortuous retinal vessels
      9. Macular hypoplasia and heterotropia
      10. Microphthalmia
      11. Anophthalmia
   2. Ear anomalies (Phelps et al. 1983; Rollnick et al. 1987)
      1. Microtia or absent external ear (Bennum et al. 1985)
      2. Preauricular tags and/or pits
      3. Middle ear anomaly
      4. Inner ear defects
      5. Variable deafness (Scholtz et al. 2001)
   3. Nasal features
      1. Prominent nasal dorsum
      2. Choanal atresia or stenosis
   4. Oral features
      1. Macrostomia: clefting of the oral commissure
      2. Cleft palate ± lip
      3. Malocclusion: cross bite, open bite, asymmetry, occlusal plane with ipsilateral shortening
   5. Vertebral defects
      1. Hemivertebrae
      2. Hypoplasia of vertebrae, usually cervical (Gosain et al. 1994; Healey et al. 2002)
      3. Abnormal ribs
   6. Hemifacial microsomia (Thomas 1980)
      1. Unilateral microtia
      2. Ipsilateral hypoplasia of malar, maxillary, and mandibular region, especially temporomandibular joint
      3. Ipsilateral macrostomia
      4. Ipsilateral hypoplasia of the facial musculature
      5. A wide variety of facial nerve presentations ranging from mild weakness of a single branch of the facial nerve to full paralysis of all facial nerve branches (Cline et al. 2014)
3. Other associated features
   1. Craniofacial features
      1. Cranial nerve (VII) palsy
      2. Orbital hypoplasia
      3. Malfunction of soft palate

4. Decreased parotid secretion
5. Anomalies in function or structure of the tongue
6. Low scalp hairline
7. Branchial cleft remnants in anterior-lateral neck
8. Mandibular hypoplasia (Rollnick et al. 1987)
9. Muscular hypoplasia of muscles of mastication
10. Absent, hypoplastic, or deformed temporomandibular joint

2. CNS anomalies (Wilson 1983; Schrander-Stumpel et al. 1992)
   1. Hydrocephaly (Kumar et al. 2000)
   2. Microcephaly
   3. Plagiocephaly
   4. Frontal/occipital encephalocele
   5. Cranial bifidum
   6. Lipoma
   7. Dermoid cyst
   8. Arnold-Chiari malformation
   9. Lissencephaly
   10. Holoprosencephaly/arhinencephaly
   11. Arachnoid cyst
3. Congenital heart diseases (5–58% depending on ascertainment of cases) (Friedman and Caracal 1974; Pierpont et al. 1982; Morrison et al. 1992; Kumar et al. 1993; Nakajima et al. 1998)
   1. Tetralogy of Fallot (with or without right aortic arch) and VSD (account for over half of the cases with congenital heart diseases)
   2. Pulmonary stenosis
   3. Patent ductus arteriosus
   4. Coarctation of aorta
   5. Total atrioventricular canal defect
   6. ASD
   7. Transposition of great vessel
   8. Rare isolation of the left innominate artery infradiaphragmatic total anomalous pulmonary venous connection
   9. Wolf-Parkinson-White syndrome
4. Respiratory tract anomalies (McCarthy et al. 2001)
   1. Tracheolaryngeal anomaly (Andrews and Shott 1992; Sutphen et al. 1995)
   2. Incomplete lobulation of the lung
   3. Pulmonary hypoplasia to aplasia
   4. Sequestration
   5. Focal tracheomalacia due to extrinsic vascular compression
   6. Obstructive sleep apnea
5. Gastrointestinal anomalies (Mandelberg et al. 1985)
   1. Esophageal atresia
   2. Tracheoesophageal fistula
   3. Diaphragmatic hernia
   4. Imperforate anus
6. Renal anomalies
   1. Renal agenesis
   2. Hydronephrosis
   3. Ectopic kidney
   4. Double ureter
   5. Hydroureter
7. Prenatal growth deficiency
8. Normal intelligence in most cases

4. Differential diagnosis (Beleza-Meireles et al. 2014)
   1. VATER (VACTERL) association (please see chapter "▶ VATER (VACTERL) Association")
   2. Nager syndrome (please see chapter "▶ Nager Acrofacial Dysostosis")
   3. Treacher Collins syndrome (please see chapter "▶ Treacher-Collins Syndrome")
   4. Townes–Brocks syndrome
      1. Imperforate anus
      2. Dysplastic ears (overfolded superior helices and preauricular tags) frequently associated with sensorineural and/or conductive hearing impairment
      3. Thumb malformations: triphalangeal thumbs, duplication of the thumb, preaxial polydactyly or hypoplasia of the thumbs
      4. Renal impairment with or without structural abnormalities
   5. CHARGE syndrome (please see chapter "▶ CHARGE Syndrome")
   6. Branchio-oto-renal spectrum disorders (branchio-oto-renal and branchio-otic syndromes)
      1. Malformations of the outer, middle, and inner ear

2. Conductive, sensorineural, or mixed hearing impairment
3. Branchial fistulae and cysts
4. Renal malformations ranging from mild renal hypoplasia to bilateral renal agenesis
5. Branchio-otic syndrome has the same features as branchio-oto-renal syndrome but without renal involvement.

7. Mandibulofacial dysostosis, Guion-Almeida type
   1. Oto-facial abnormalities (acrofacial dysostosis)
   2. Esophageal atresia
   3. Thumb anomalies
   4. Intellectual disability
   5. Zygomatic anomalies
   6. Microcephaly

Diagnostic Investigations

1. Radiography (Rees et al. 1972)
   1. Platybasia/occipitalization of atlas
   2. Hypoplasia of the mandibular-maxillary bones
   3. Fused vertebrae, especially cervical
   4. Segmentation anomaly of the vertebra
   5. Hemivertebrae
   6. Klippel-Feil anomaly
   7. Rib anomalies
   8. Aplasia of radius/thumb
   9. Spina bifida
2. Neuroradiological study (Marano et al. 2015): show striking common involvement of cranial nerves among patients with oculo-auriculo-vertebral spectrum, especially among those presenting with the more severe phenotype (Goldenhar syndrome)
   1. MR imaging: abnormal cranial nerves ranging from hypoplasia/aplasia to protean morphologic abnormalities
   2. CT imaging: isolated hypoplasia of the foramen ovale and/or of the inferior alveolar nerve bone canal, consistent with trigeminal branch hypo-/aplasia, thus disclosing also a possible distal cranial nerve involvement
3. Echocardiography: variable and nonspecific findings because cardiovascular abnormalities are complex in most cases
4. Array comparative genomic hybridization (aCGH) screening of OAVS patients (Beleza-Meireles et al. 2015)
   1. Copy number variations (CNVs) on 22q11.21: identified dosage anomalies in 12 out of 22 OAVS patients tested (54.5%)
   2. 22q11 locus may harbor genes that are important in aspects of the regulation of craniofacial symmetry and 1st and 2nd branchial arch development
5. Genome-wide exome or whole genome sequencing approach: may identify other genetic loci involved in OAVS (Beleza-Meireles et al. 2015)

Genetic Counseling

1. Recurrence risk: depending on the etiology and the mode of inheritance
   1. Patient's sib
      1. Isolated: empiric recurrence risk of 2%
      2. Autosomal dominant inheritance: recurrence risk not increased unless a parent is affected, in which case the recurrence risk is 50%
      3. Autosomal recessive inheritance: 25% of siblings affected, 50% of siblings carriers, and 25% of siblings normal
   2. Patient's offspring
      1. Isolated: unknown
      2. Autosomal dominant inheritance: 50%
      3. Autosomal recessive inheritance: recurrence risk not increased unless the spouse is also a carrier, in which case the recurrence risk is 50%
2. Prenatal diagnosis by ultrasonography (Tamas et al. 1986; Benacerraf and Frigoletto 1988; De Catte et al. 1996)
   1. Hemifacial microsomia
   2. Microphthalmia or anophthalmia
   3. Facial clefting as part of the oculo-auriculo-vertebral spectrum (Witters et al. 2001)

4. Cleft lip/palate
5. Unilateral facial cleft with macrostomia
6. Unilateral ear hypoplasia
7. Unilateral preauricular tag
8. Hemiatrophy of the nose
9. Hyposegmentation of the unilateral lung
10. Single umbilical artery
11. Imperforate anus
12. Polyhydramnios

3. Management
    1. Surgical removal of epibulbar dermoids, if needed.
    2. Manage associated conductive hearing loss.
    3. Airway management (Stehling 1978).
    4. Cleft lip/palate repair.
    5. Combined surgical-orthodontic approach for dental occlusion.
    6. Traditional osteotomies, followed by acute orthopedic movement and osseous fixation for adult patients with maxillomandibular hypoplasia, facial asymmetry, congenital micrognathia, and hemifacial microsomia.
    7. Alternative procedure: distraction osteogenesis.
    8. Assess cervical spine for instability before undergoing any general surgery. C1–C2 fusion or occipitocervical fusion may be needed (Kaymak et al. 2002)
    9. Multistage and multidisciplinary approach (many surgeries including ophthalmic, plastic, and maxillofacial) leading to a good, satisfactory aesthetic and functional outcome (Bogusiak et al. 2014). Good orthodontic preparation of the patient largely contributed to the final therapeutic success.
    10. Anesthesia (Madan et al. 1990): anticipate airway obstruction and difficulty in tracheal incubation, resulting from a combination of micrognathia, unilateral mandibular hypoplasia, and vertebral anomalies including vertebral fusion and odontoid elongation.

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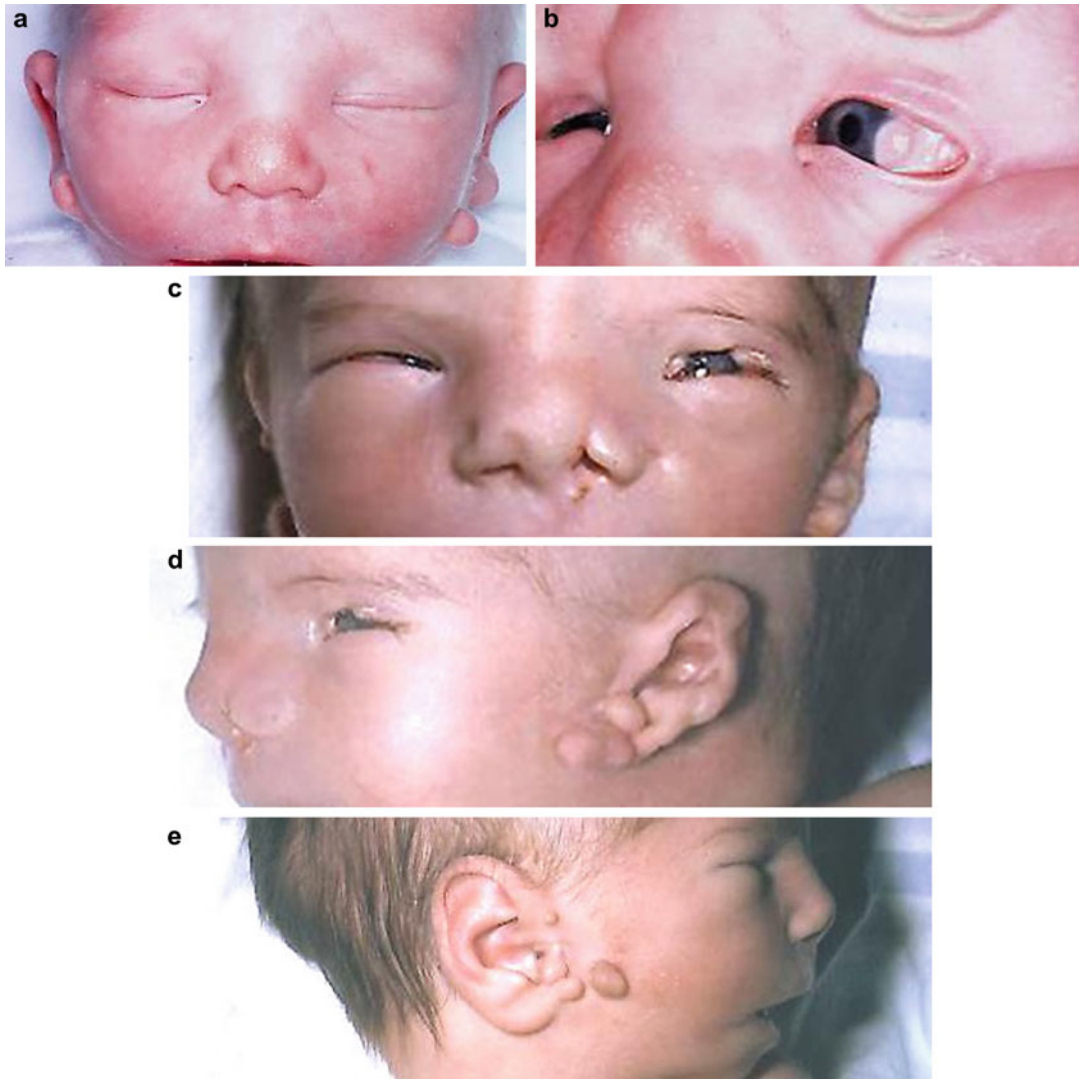

Fig. 1 (**a**–**e**) Two infants (**a**, **b**; **c**–**e**) with Goldenhar syndrome showing hemifacial microsomia, epibulbar dermoids, upper eyelid coloboma, clefting nose, macrostomia, and unilateral microtia with preauricular tag

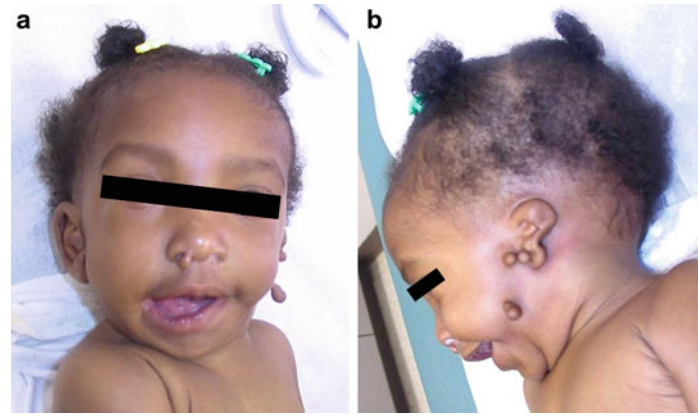

Fig. 2 (**a**, **b**) An 8-month-old child with hemifacial microsomia showing facial asymmetry, unilateral microtia, and preauricular tags

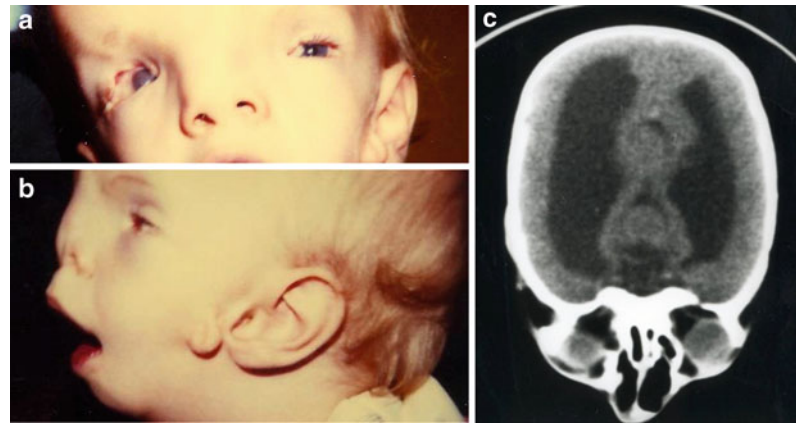

Fig. 3 (**a**–**c**) An infant (**a**, **b**) with primidone embryopathy presenting as Goldenhar syndrome showing hemifacial microsomia, facial palsy, upper eyelid coloboma, epibulbar dermoid, and hydrocephaly by MRI (**c**)

Gorlin Syndrome

Contents

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, was first reported by Jarisch and White in 1894 who described a patient with multiple basal cell carcinomas, scoliosis, and learning disability. Howell and Caro in 1959 were the first to associate the basal cell nevus with other multiple cutaneous cancers and associated developmental anomalies. The spectrum of disease associated with this syndrome, comprising the principal triad of multiple basal cell nevi, jaw keratocysts, and skeletal anomalies, was described in detail by Gorlin and Goltz in 1960. A spectrum of other neurological, ophthalmic, endocrine, and genital manifestations are now known to be variably associated with this triad (Manfredi et al. 2004). The prevalence is estimated to be 1 in 60,000 persons (Cohen 1999).

Synonyms and Related Disorders

Basal cell nevus syndrome; Fifth phacomatosis; Gorlin-Goltz syndrome; Multiple basal cell nevi; Nevoid basal cell carcinoma syndrome; Odontogenic keratocysts and skeletal anomalies

Genetics/Basic Defects

1. An autosomal dominant disorder with complete penetrance and variable expressivity (Bare et al. 1992; Bonifas et al. 1994; Gorlin 2004).
2. The gene responsible has been localized to chromosome 9q22.1-q31 (Farndon et al. 1992; Compton et al. 1994).
3. Causes:
    1. Between 50% and 85% of patients with Gorlin syndrome harbor germ-line mutations in the only susceptibility gene identified to date, *PTCH1*, a key component in the sonic hedgehog (*SHH*) signaling pathway (Bale and Yu 2001; de Melo Pino et al. 2015):
        1. Caused by mutations in the human homologue of the Drosophila patched gene, *PTCH* (Hahn et al. 1996; Johnson et al. 1996).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. *PTCH*: a tumor suppressor gene, encoding a transmembrane glycoprotein that acts as an antagonist in the hedgehog signaling pathway (Bak et al. 2003; Ragge et al. 2005).
3. *PTCH* inhibits signaling by the membrane protein Smoothened (Smo), and this inhibition is relieved by binding sonic hedgehog (*SHH*) to *PTCH*.
4. A gain of function mutation in Smoothened: demonstrated in type 1 mosaic form of basal cell nevus syndrome (Khamaysi et al. 2016).

2. A microdeletion at 9q22.3 involving a deletion of *PTCH* gene in a few cases (Shimkets et al. 1996; Sasaki et al. 2000; Olivieri et al. 2003; Midro et al. 2004; Boonen et al. 2005; Chen et al. 2006; Yamamoto et al. 2009).
3. Human patched 2 (*PTCH2*): a putative tumor suppressor gene in basal cell carcinoma and medulloblastoma on chromosome 1p32 (Smyth et al. 1999).
4. SUFU, another component in this pathway, is known to be involved in susceptibility to medulloblastoma but has never been reported in Gorlin syndrome patients to date. A *SUFU* germ-line splicing mutation (c.1022þ1G>A) has been identified for the first time in a family that was *PTCH1*-negative and who had signs and symptoms of Gorlin syndrome, including medulloblastoma (Pastorino et al. 2009).
5. Most germ-line mutations in the nevoid basal cell carcinoma syndrome lead to a premature termination of the PATCHED protein, and no genotype-phenotype correlations are evident (Wicking et al. 1997).
6. Type I mosaicism: some reported cases of segmentally arranged lesions of Gorlin syndrome can be taken as examples of type 1 mosaicism (Shelley et al. 1969; Camisa et al. 1985).
7. Type 2 mosaicism: the presence of a germline mutation in exon 18 of *PTCH1* inherited from her father, and a second *PTCH1* mutation involving exon 3 that was found in the affected skin but not in her contralateral, clinically normal skin or in her blood, thus providing evidence of the concept of superimposed mosaicism (Torrelo et al. 2013).

4. Odontogenic keratocysts (Agaram et al. 2004).
   1. A distinctive odontogenic cyst with a potential for aggressive behavior, local recurrence, and an association with nevoid basal cell carcinoma syndrome.
   2. A significant number of odontogenic keratocysts show clonal loss of heterozygosity of common tumor suppressor genes.
   3. The presence of clonal deletion mutations of genomic DNA in these cysts supports the hypothesis that they are neoplastic rather than developmental in origin.

Clinical Features

1. Clinical features (Bitar et al. 2002; Ahn et al. 2004; Gorlin 2004; Lo Muzio 2008):
   1. An increasing number of basal cell nevi:
      1. Mostly appearing from the age of puberty onward
      2. Having tendency to develop into basal cell carcinomas of the skin
      3. Most commonly in sun-exposed areas
   2. Dermal pits of the palms and soles:
      1. Particularly useful in diagnosis
      2. Pits more pronounced when the hands and feet are soaked in warm water for up to 10 min, appearing as white "punched-out" or pink "pinpricked" lesions
   3. Keratocysts of the jaws
   4. Skeletal anomalies:
      1. Spine and rib anomalies:
         1. Bifid ribs
         2. Thoracic and cervical vertebral anomalies (Ratcliffe et al. 1995)
         3. Scoliosis
         4. Spina bifida
         5. Osteoporosis
         6. Short fourth metacarpals
      2. Abnormal craniofacial configurations:
         1. Macrocephaly

2. Frontal, parietal, and temporal bossing
3. Hypertelorism
4. Broad nasal bridge
5. Maxillary retrognathia
6. Mandibular prognathism
7. Increased gonion angle
8. Increased facial height

5. Intracranial calcifications (Dahl et al. 1976; Donatsky et al. 1976; Kimonis et al. 1997; Evans et al. 1993):
   1. Falx cerebri
   2. Falx cerebelli
   3. Petroclinoid ligament
   4. Dura
   5. Pia
   6. Choroid plexus
6. Other features (Shanley et al. 1994):
   1. Sensitive to ultraviolet and ionizing radiation
   2. Occasional abnormalities (Evans et al. 1993; Kimonis et al. 1997):
      1. Dental agenesis
      2. Cleft palate and lip
      3. Mental deficiency
      4. Agenesis of corpus callosum
      5. Vermian dysgenesis
      6. Anosmia
      7. Hydrocephalus
      8. Cataract
      9. Coloboma of iris
      10. Retinal atrophy
      11. Glaucoma
      12. Strabismus
      13. Mandibular coronoid process hyperplasia
      14. Arachnodactyly
      15. Polydactyly
      16. Renal anomalies
      17. Other neoplasms such as medulloblastoma, meningioma, fibroma, lipomata, melanoma, neurofibromata of skin, cardiac fibromas, eyelid carcinomas, breast cancer, lung cancer, lymphoid leukemia, non-Hodgkin's lymphoma, ovarian dermoid, lymphomesenteric cysts, and hepatic mesenchymal tumors

2. Diagnostic criteria for nevoid basal cell carcinoma syndrome (Evans et al. 1993; Kimonis et al. 1997, 2004; Veenstra-Knol et al. 2005; Evans and Farndon 2010; Bree et al. 2011; Bresler et al. 2016). A diagnosis can be made when two major or one major and two minor criteria are fulfilled:
   1. Major criteria:
      1. Multiple (>2) basal cell carcinomas (BCC) or one BCC under the age of 20 years or >10 basal cell nevi
      2. Any odontogenic keratocyst histologically or observed on orthopantogram as an area of translucency or polyostotic bone cyst
      3. Palmar or plantar pits (three or more)
      4. Ectopic calcification: lamellar (sheet like) falx calcification or evidence of early calcification in an individual younger than 20 years
      5. Medulloblastoma, typically desmoplastic
      6. First-degree relatives with NBCCS
   2. Minor criteria:
      1. Congenital skeletal anomaly: bifid, fused, splayed, or missing ribs or bifid, wedged, or fused vertebra
      2. Occipital-frontal circumference >97 percentile (macrocephaly), with frontal bossing
      3. Macrocephaly
      4. Cardiac or ovarian fibromas
      5. Childhood medulloblastoma (primitive neuroectodermal tumor)
      6. Lymphomesenteric or pleural cysts
      7. Congenital malformation: cleft lip and/or palate, polydactyly, eye anomaly (hypertelorism, strabismus, cataract, glaucoma, coloboma, microphthalmia)

Diagnostic Investigations

1. Family history:
   1. Brain tumors (Evans et al. 1991a)
   2. Female organ tumors
2. Medical and dental history:
   1. Removal of jaw cysts
   2. Abscesses
   3. Skin lesions

3. Physical examination:
    1. Mandibular and maxillary swelling
    2. Head circumference
    3. Head shape
    4. Skin basal cell nevi
    5. Pits on the palms and soles
4. Radiographic studies (Bitar et al. 2002):
    1. Skull radiography for detection of calcified cerebral falx
    2. Jaw radiography for detection of maxillary and mandibular cystic lesions
    3. Chest radiography for rib and vertebral anomalies
5. Dermoscopy (Moreira et al. 2015):
    1. Palmar pitting: flesh-colored, irregular-shaped and slightly depressed lesions, some with red globules
    2. Early detection of basal cell carcinomas: arborizing vessels, ulceration, blue-gray globules, and spoke-wheel areas
6. CT scan: multiple bilateral unilocular cysts in the mandible and maxilla, along with calcification of anterior part of the falx cerebri (Hajalioghli et al. 2015)
7. MRI of the brain to detect meningiomas or medulloblastomas at an early age.
8. Ovarian ultrasonography for detection of ovarian cysts or fibromas.
9. MRI: calcified bilateral adnexal lesions with low signal intensity on T2-weighted MR sequences (Singh et al. 2014).
10. Echocardiograms to evaluate cardiac fibromas.
11. Cytogenetic analysis to detect rare interstitial 9q deletion associated with clinical features of NBCCS and additional features such as severe developmental delay or short stature (Chen et al. 2006).
12. Molecular genetic testing (Evans and Farndon 2010):
    1. Sequence analysis of exons 2–23 with intron-exon junctions and one of the splice forms of exon 1 to detect *PTCH1* gene mutation (Marsh et al. 2005; Klein et al. 2005)
    2. Deletion testing to detect exonic and whole *PTCH1* gene deletions
13. The high detection rate of *PTCH1* mutations in NBCCS patients enables molecular diagnostics to become a valuable tool for establishing an early diagnosis, especially in the case of atypical phenotype and for yet unaffected family members (Škodrić-Trifunović et al. 2015). Moreover, family members of the patients with the Gorlin syndrome should be examined to decrease the risk for developing skin tumors, like basal cell carcinoma, which could be prevented by decreased sun exposure and avoidance of x-ray imaging.

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib:
        1. An affected parent: a 50% risk
        2. Unaffected parents: a low risk
    2. Patient's offspring: a 50% risk
2. Prenatal diagnosis:
    1. Ultrasonography:
        1. Hydrocephalus
        2. Macrocephaly
        3. Cleft lip and palate
        4. Intracardiac tumor
        5. Fetal hydrops
        6. Fetal chylothorax
    2. Molecular genetic testing available, provided the disease-causing allele of an affected family member has been identified, by analyzing DNA extracted from fetal cells obtained by (Lo Muzio 2008):
        1. CVS
        2. Amniocentesis
3. Management (Van der Geer et al. 2009; Bresler et al. 2016):
    1. Frequent dermatologic surveillance: necessary
    2. Surgical excision of keratocysts identified early in life
    3. Basal cell carcinomas:
        1. Complete eradication of aggressive BCCs, surgical excision supplemented by cryotherapy, laser treatment for early lesion, and photodynamic therapy (Itkin and Gilchrest 2004; Oseroff et al. 2005).
        2. Preserve normal tissue to prevent disfigurement.

3. Tropical 5% imiquimod (Kagy and Amonette 2000; Marks et al. 2001; Stockfleth et al. 2002).
4. Cyclopamine: specifically inhibits smoothened activity and appears to be a promising agent in the treatment of medulloblastomas, BCCs, and breast and prostate cancer (Debeer and Devriendt 2005).
5. Radiotherapy: contraindicated.

4. Surgical excision of ovarian fibromas

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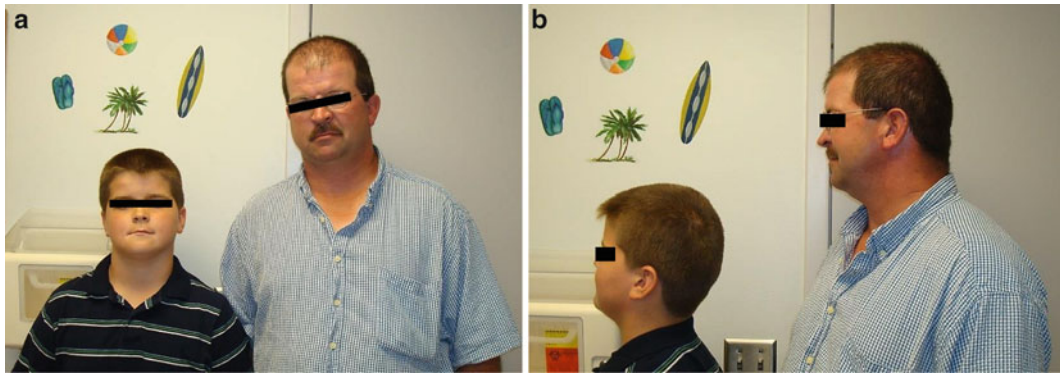

Fig. 1 (**a**, **b**) An 11-year-old boy and his father both have Gorlin syndrome. The boy had multiple odontogenic cysts removed from his jaw. Craniofacial CT scan showed extensive dural and choroid plexus calcifications and abnormal enlargement of subarachnoid space in the left frontal and anterior temporal regions. He was noted to have macrocephaly, forehead bossing, and plantar pits. His father had his multiple odontogenic cysts removed at 16 years of age. In addition, he has several soft subcutaneous tissue masses in his fingers and his right foot. The patient is heterozygous for a duplication of a single "A" nucleotide in exon 2 of the *PTCH* gene. The normal sequence with the base that is duplicated in braces is "TTGTT(A)CATTCA." This mutation is denoted c.278dupA at the cDNA level or p Tyr93Stop (Y93X). The c.278DupA mutation results in the replacement of a tyrosine codon with a Stop codon at position 93

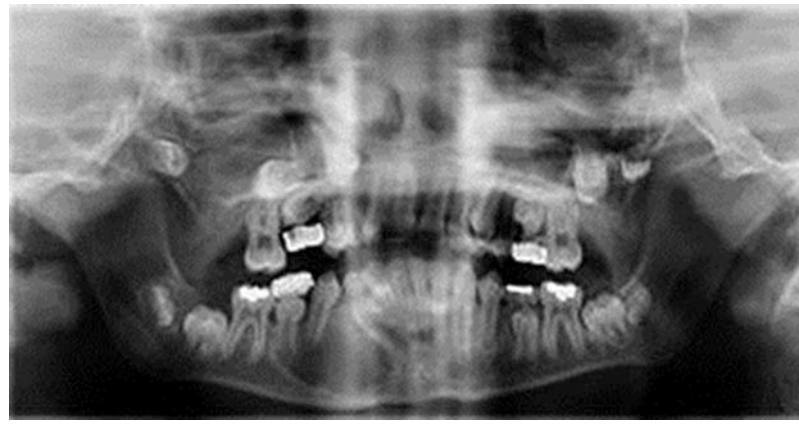

Fig. 2 Panoramic radiograph of jaw shows multiple odontogenic cysts

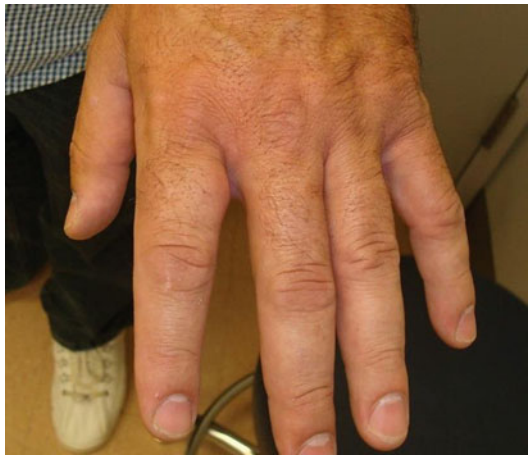

Fig. 3 A small subcutaneous nodule seen in the index fingers of the father

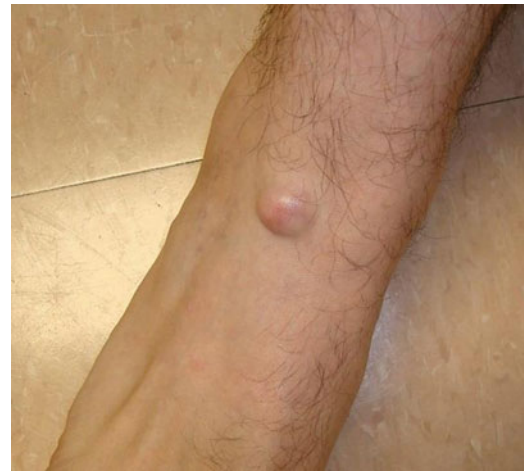

Fig. 4 A small subcutaneous nodule seen in the dorsal aspect of the foot of the father

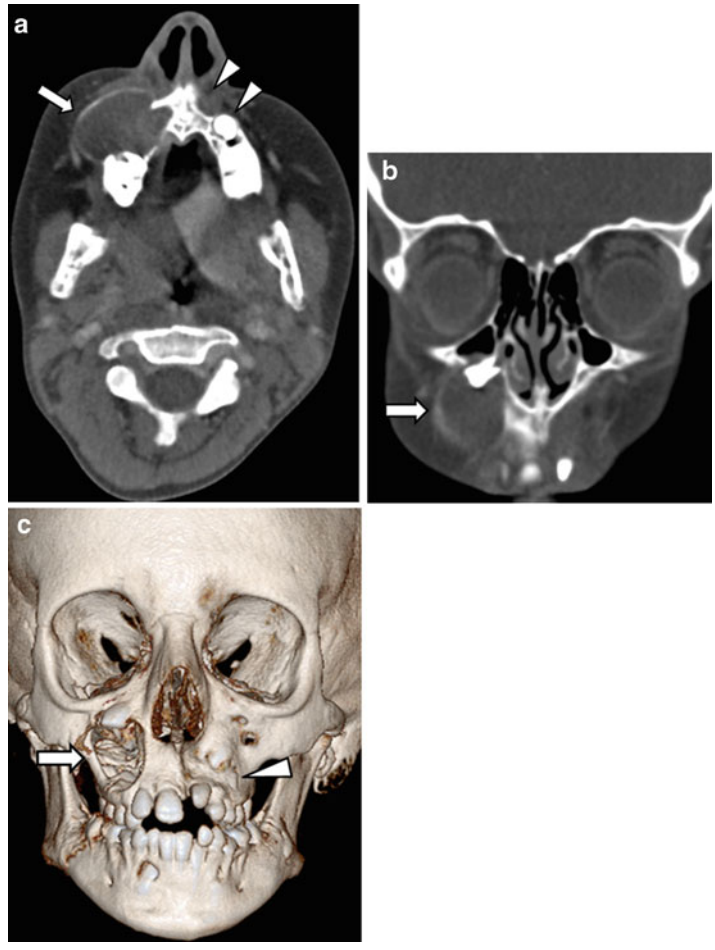

Fig. 5 (**a–c**) An 8-year-old female with a history of macrocephaly, developmental delay, pyloric stenosis, and multiple odontogenic keratocysts. A *PTCH1* p.Leu106Arg mutation confirmed the diagnosis of Gorlin syndrome. The mother was affected with Gorlin syndrome and had a history of skin cancer removal. CT images (**a–c**) demonstrate an expansile 3.5 cm fluid attenuating lesion in the right maxilla (*arrows*) causing destruction of the inferior wall of the maxillary sinus with extension into the right maxillary sinus. Three-dimensional reconstruction CT image shows a displaced tooth within the right maxillary sinus about the superior aspect of this lesion (**c**). The findings are compatible with an odontogenic keratocyst. Deformed left anterior maxilla (*arrow heads*) is seen secondary to postoperative changes for an odontogenic keratocyst removal 2 years previously (Courtesy of Dr. Grace Guo)

Greig Cephalopolysyndactyly Syndrome

Contents

Greig cephalopolysyndactyly (GCPS) syndrome is named after David Middleton Greig for his 1926 description of a patient with unusual head shape, hypertelorism, and limb anomalies. It is a rare, pleiotropic, multiple congenital anomaly syndrome characterized by the primary clinical triad of polysyndactyly, macrocephaly, and hypertelorism.

Synonyms and Related Disorders

Cephalopolysyndactyly; *GLI3* mutation; Pallister-Hall syndrome; Polysyndactyly with peculiar skull shape

Genetics/Basic Defects

1. Inheritance: autosomal dominant with high penetrance in majority of cases (Patel et al. 2014).
2. Caused by mutations in the transcription factor *GLI3* on chromosome 7p13 resulting in functional haploinsufficiency of *GLI3* (Pettigrew et al. 1991; Hurst et al. 2011). The mutations include the following:
    1. Point mutations (Wild et al. 1997; Kalff-Suske et al. 1999)
    2. Translocation mutations
    3. Deletion mutations
    4. Intragenic mutations
    5. Truncation mutations (frameshift and nonsense mutations) (Patel et al. 2014)
    6. Insertion mutations
3. Allelic to the Pallister-Hall syndrome (PHS) (Démurger et al. 2015) and one form of the acrocallosal syndrome:
    1. Severe GCPS phenotype is likely caused by deletion of contiguous genes and substantially overlaps with the mild end of the acrocallosal syndrome (an autosomal recessive disorder characterized by pre- or postaxial polydactyly, syndactyly, agenesis corpus callosum, ocular hypertelorism, macrocephaly, moderate to severe mental retardation, intracerebral cysts, seizures, and umbilical and inguinal hernias).
    2. *GLI3* mutations can also cause PHS, postaxial polydactyly type A, and other *GLI3* morphopathies. GCPS and PHS are likely allelic with distinct modes of pathogenesis.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Phenotypes caused by mutations in GLI3 are diverse, discrete, variable, and pleiotropic. The mutations in GLI3 that cause PHS and GCPS correlate with the phenotypes on two levels:
   1. Many types of inactivating mutations cause GCPS.
   2. Whereas PHS is caused almost exclusively by truncation mutations in the middle third of the gene.
5. Mutations in genes other than *GLI*: possible in some patients with a GCPS phenotype.
6. Update of human polydactyly entities by phenotype and mutated gene (Biesecker 2011):
   1. Phenotypes with overlapping manifestations, genetic heterogeneity, and distinct phenotypes generated from mutations in single genes.
   2. Among 310 clinical entities, 80 are associated with mutations in 99 genes.

Clinical Features

1. Variable clinical manifestations (Duncan et al. 1979; Kroisel et al. 2001; Debeer et al. 2003; Balk and Biesecker 2008; Curran and Cronin 2015; Démurger et al. 2015)
2. The primary clinical triad:
   1. Macrocephaly
   2. Hypertelorism
   3. Polysyndactyly
3. Developmental history:
   1. Feeding problems/failure to thrive
   2. Developmental delay, seizures, and psychomotor retardation: more likely in a child with rare CNS malformations or uncommon hydrocephalus and more common in individuals with large (>300 kb) deletions that encompass *GLI3*
4. Craniofacial features – highly variable:
   1. Significant hypertelorism (increased interpupillary distance) with or without telecanthus (increased inner canthal distance) in some patients
   2. Macrocephaly, not typically associated with CNS anomalies, such as hydrocephalus and seizures
5. Digital anomalies (Curran and Cronin 2015):
   1. Polydactyly:
      1. Classically described as preaxial.
      2. May occur in any limb.
      3. Postaxial may be more common than preaxial.
      4. Most common finding: postaxial polydactyly of the hands and preaxial polydactyly of the feet.
      5. Broad thumbs and broad great hallux
      6. Severity varies widely among individuals and among limbs in the same individual. This can vary from an apparently normal extremity, through subtle broadening of the thumb or hallux, tiny postaxial nubbins, to partially bifid digits, hypoplastic supernumerary digits, fully formed supernumerary digits, and higher order polydactyly.
   2. Cutaneous syndactyly – highly variable:
      1. Absent in many patients.
      2. Mild partial cutaneous syndactyly of a few digits in some patients.
      3. The spectrum continues through to complete cutaneous syndactyly of all digits, not unlike that seen in patients with Apert syndrome.
6. Less common anomalies:
   1. Craniosynostosis: metopic and sagittal synostosis (Hurst et al. 2011)
   2. Mental retardation: not common
   3. Agenesis of the corpus callosum
   4. Ventricular dilatation
   5. Umbilical and diaphragmatic hernias
   6. Risk of cognitive impairment appears to be associated with the GCPS-contiguous gene syndrome
7. Diagnostic criteria (Johnston et al. 2005):
   1. Presumptive diagnosis: a proband with:
      1. Preaxial polydactyly
      2. Syndactyly of toes 1–3 or fingers 3–4
      3. Ocular hypertelorism
      4. Macrocephaly
   2. Firm diagnosis:
      1. The presence of an affected first-degree relative whom the diagnosis has been independently established

2. A proband who has features of GCPS and a mutation in *GLI3*
3. Cautions in applying above diagnostic criteria:
   1. Clinical criteria: useful but not sufficiently specific to warrant a "firm" diagnosis on clinical grounds alone.
   2. A small but significant fraction of individuals with features of GCPS do not have mutations in *GLI3*.
   3. Features of GCPS are seen in many other syndromes.
8. Diagnostic criteria (combined clinical-molecular definition for the syndrome) (Biesecker 2008):
   1. A presumptive diagnosis with the classic triad:
      1. Preaxial polydactyly with cutaneous syndactyly of at least one limb
      2. Hypertelorism
      3. Macrocephaly
   2. Definitive diagnosis:
      1. A phenotype consistent with GCPS but which may not manifest all three attributes listed above
      2. The presence of a *GLI3* mutation
9. Additional definitive diagnostic criteria: persons with a GCPS-consistent phenotype who are related to a definitively diagnosed family member in a pattern consistent with autosomal dominant inheritance
10. Prognosis:
    1. A mild form: excellent general health and normal longevity reported in several large families
    2. Slight increase in the incidence of developmental delay or cognitive impairment
    3. Worse prognosis in patients with large deletions that include *GLI3*
11. Differential diagnosis (Biesecker 2006):
    1. Preaxial polydactyly type IV/postaxial polydactyly type A/B (Radhakrishna et al. 1999)
    2. GCPS-contiguous gene syndrome (Johnston et al. 2003)
    3. Acrocallosal syndrome (ACLS):
       1. Inherited in an autosomal recessive manner.
       2. Preaxial polydactyly type IV (Baraitser et al. 1983) or postaxial polydactyly.
       3. Syndactyly.
       4. Agenesis of the corpus callosum (rare in GCPS).
       5. Ocular hypertelorism.
       6. Macrocephaly.
       7. Moderate to severe mental retardation.
       8. Intracerebral cysts.
       9. Seizures.
       10. Umbilical and inguinal hernias.
       11. The milder end of the ACLS phenotype can overlap with the severe end of the GCPS phenotype caused by interstitial deletions of 7p13 that delete *GLI3* and additional neighboring genes.
       12. Frequency of consanguinity, sibling recurrences with unaffected parents, and preliminary mapping data suggest that ACLS can be a disorder distinct from severe GCPS.
    4. Gorlin syndrome (please see chapter "▶ Gorlin Syndrome")
    5. Carpenter syndrome (please see chapter "▶ Carpenter Syndrome")
    6. Teebi syndrome
    7. Pallister-Hall syndrome

Diagnostic Investigations

1. Radiographic studies of digital anomalies (Debeer et al. 2003)
2. CNS imaging studies:
   1. For individuals showing signs of increased intracranial pressure, developmental delay, loss of milestones, or seizures
   2. To evaluate hydrocephalus or other CNS abnormalities
3. Chromosome analysis (Williams et al. 1997): performed either as a first test or in all patients who have GCPS but no mutation was found by sequencing:
   1. Detection of visible pure chromosomal deletions involving 7p13 or a deletion combined with a translocation

2. Detection of familial translocation: a risk for offspring with unbalanced translocations in addition to their risk of having a child with GCPS

4. Molecular genetic testing:
   1. Indications:
      1. Confirmatory diagnostic testing
      2. Prenatal diagnosis
   2. FISH analysis: Using hybridization of the labeled BAC clone to metaphase spreads detects deletions in the estimated 5–10% of individuals with large deletions.
   3. Comparative genomic hybridization (CGH):
      1. An array of *GLI3* is available on a limited clinical basis.
      2. CGH array would be expected to detect a deletion that encompasses more than one target on the array (Johnston et al. 2007).
   4. Other methodologies:
      1. Loss-of-heterozygosity (LOH) analysis to detect large deletions
      2. Sequencing of the *GLI3* coding exons or scanning with denaturing high-performance liquid chromatography (DHPLC), single-strand conformation polymorphism (SSCP), or other conformation detection methods: an appropriate first screen for patients with typical GCPS
      3. Quantitative PCR

Genetic Counseling

1. Recurrence risk (Biesecker 2014)
   1. Patient's sib:
      1. De novo cases: recurrence risk low.
      2. Fifty percent of siblings are affected if one of the parents is affected.
      3. No instances of germline mosaicism reported, but it remains a possibility.
      4. Proband with an unbalanced structural chromosome constitution:
         1. Neither parents with a structural chromosome rearrangement: risk to sibs negligible.
         2. A parent with a balanced structural chromosome rearrangement: risk to sibs increases and depends upon the specific chromosome rearrangement.
   2. Patient's offspring:
      1. Fifty percent risk of inheriting the mutation and having an affected offspring: since intrafamilial variability is generally low, affected offspring are expected to have clinical findings similar to those of the parent.
      2. Offspring of an individual with a balanced or unbalanced chromosomal rearrangement: at risk of having a similar or related rearrangement.
2. Prenatal diagnosis (Biesecker 2014; Raposo et al. 2015)
   1. Ultrasound studies in pregnancies at 50% risk may detect the following findings:
      1. Polydactyly
      2. Syndactyly
      3. Broad halluces on both feet
      4. CNS malformations such as hydrocephalus
   2. Chromosome analysis of fetal cells in at-risk families with a parent having a cytogenetically visible 7p13 deletion or a balanced chromosomal rearrangement.
   3. Molecular genetic testing for GLI3 gene: antenatal molecular diagnosis is technically straightforward to perform.
   4. Preimplantation genetic diagnosis (PGD): may be available for families in which the disease-causing mutation or chromosome abnormality has been identified in an affected family.
3. Management:
   1. Symptomatic treatment with plastic or orthopedic surgery indicated for significant limb malformations
   2. Surgical repair:
      1. Preaxial polydactyly of the thumbs: a higher priority for surgical correction than postaxial polydactyly of the hand or polydactyly of the foot because of the importance of the thumbs for prehensile grasp

2. Severe syndactyly of the fingers
3. Surgical correction of the feet for orthopedic complications, cosmetic benefits, and easier fitting of shoes

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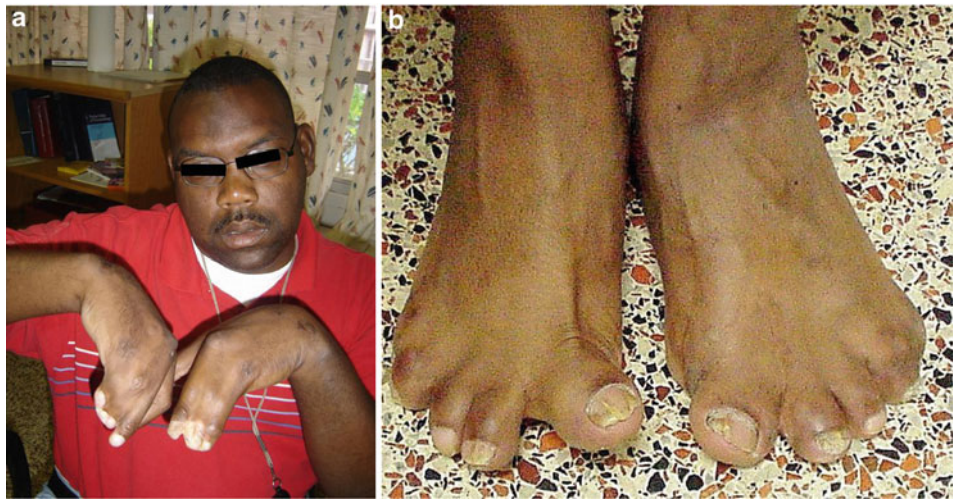

Fig. 1 (**a**, **b**) A 34-year-old patient (**a**) with typical facial features characterized by macrocephaly and hypertelorism. He also has mental retardation and seizure disorder. The hands show postaxial polydactyly and complete cutaneous syndactyly of digits 2–5 with fusion of nails. The feet (**b**) show a partially duplicated hallux with cutaneous syndactyly of several digits

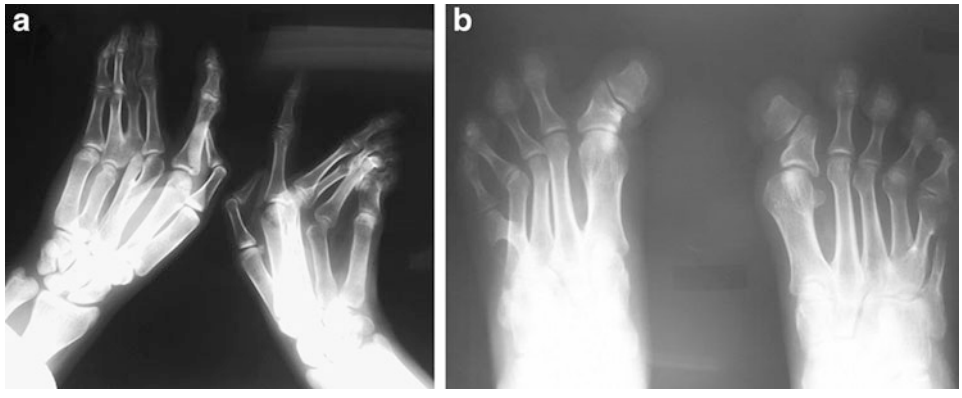

Fig. 2 (**a**, **b**) Radiographs of the same patient. The hands (**a**) show six phalanges with partial fusion of the third and fourth metacarpals and partial fusion of the fourth and fifth proximal phalanges. The feet (**b**) shows a partially duplicated hallux

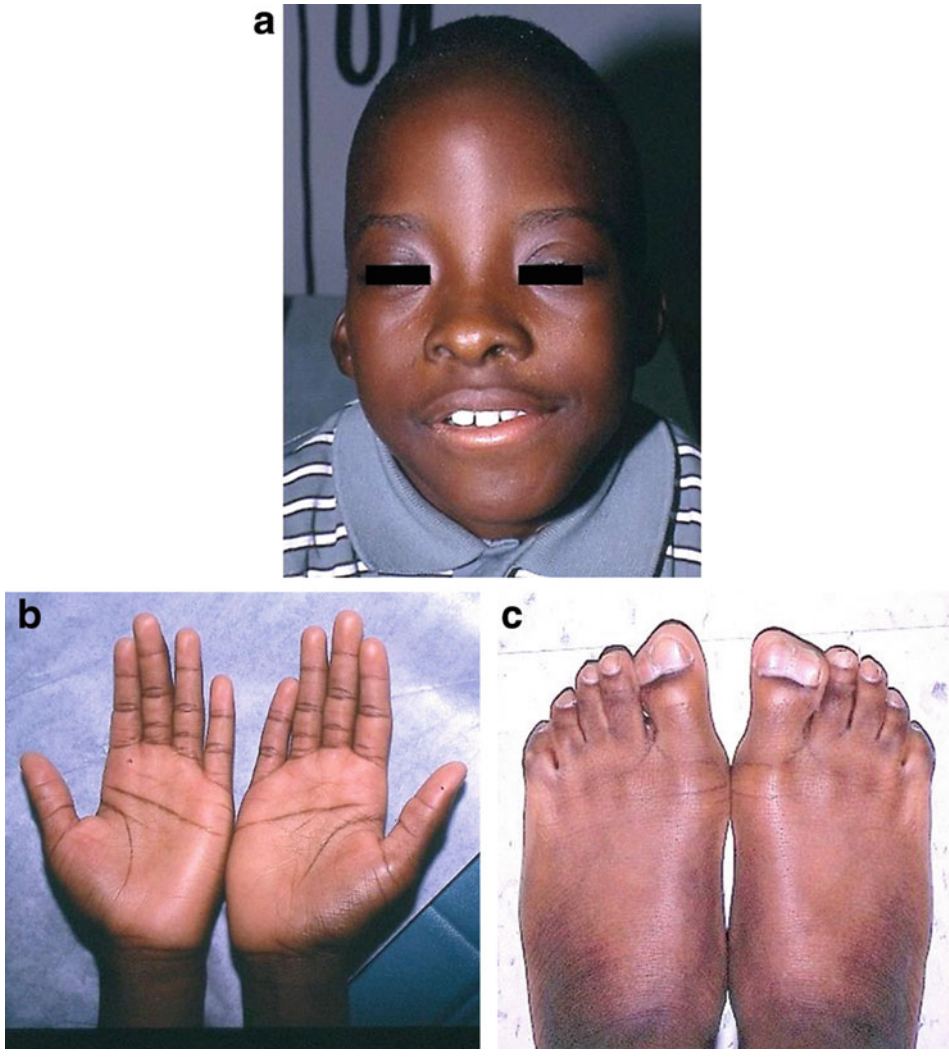

Fig. 3 (**a**–**c**) Another patient (**a**) with macrocephaly, ocular hypertelorism, transverse palmar creases (**b**), and a partially duplicated great hallux (**c**)

Hallermann-Streiff Syndrome

Contents

Hallermann-Streiff syndrome was independently described by Hallermann in 1948 and Streiff in 1950. The syndrome is characterized by proportionate short stature and craniofacial dysostoses consisting of skeletal, ophthalmologic, and cutaneous defects.

Synonyms and Related Disorders

Francois dyscephalic syndrome (François 1982)

Genetics/Basic Defects

1. Sporadic in virtually all cases
2. Inheritance pattern unknown

Clinical Features

1. Characteristic craniofacial features
    1. Dyscephaly (malformation of the cranium and bones of the face) (89–90%)
        1. Calvarium
            1. Brachycephaly
            2. Thin calvarium
            3. Delayed closure of fontanelles
            4. Wide cranial sutures
        2. Cranial base
            1. Platybasia
            2. Depressed sella
            3. Elevated anterior cranial fossa
        3. Parrot-like face
            1. A beaked nose
            2. Hypoplastic mandible
    2. Hypotrichosis (80–82%)
        1. Alopecia
            1. Characteristic sutural alopecia (hair loss following the lines of the cranial sutures)
            2. Frontal alopecia
            3. Alopecia at the scalp margins
        2. Hypotrichosis involving the eyebrows and eyelashes
        3. Brittle and sparse scalp hair
    3. Cutaneous atrophy (68–70%)
        1. Face (nose)
        2. Scalp
        3. Cutaneous atrophy with telangiectasia (François and Victoria-Troncoso 1981; Singh et al. 2013)
    4. Ocular abnormalities (Cohen 1991; David et al. 1999)
        1. Congenital cataracts (81–90%)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Microphthalmos (78–83%)
3. Nystagmus
4. Strabismus
5. Glaucoma (Aracena and Sangueza 1977)
6. Blue sclera
7. Fundal anomalies
8. Conjunctival defects
9. Corneal abnormalities
10. Down-slanting palpebral fissures
11. Intraocular hypertension
12. Lower lid coloboma
13. Iris atrophy
14. Persistent pupillary membrane
15. Enophthalmos
16. Bilateral retinal detachments (Haque et al. 2009)
17. Epicanthal folds

5. Mouth (Hutchinson 1971; Ohishi et al. 1986)
   1. Microstomia
   2. Narrow/high-arched palate
   3. Dental/alveolar abnormalities (80–85%) (Slootweg and Huber 1984)
      1. Natal teeth
      2. Partial anodontia/hypoplasia
      3. Persistent deciduous teeth
      4. Irregular implantation of the teeth
      5. Anterior open bite
   4. Generalized odontodysplasia (Damasceno et al. 2014)

2. Musculoskeletal abnormalities
   1. Proportionate short stature (45–69%)
   2. Syndactyly
   3. Lordosis
   4. Scoliosis
   5. Spina bifida
   6. Winged scapulae
   7. Hyperextensible joints including temporomandibular joints
   8. Hip dislocation
   9. Periodic osteoporosis
3. Other abnormalities
   1. Mild to severe mental retardation (15%)
   2. Calcified falx cerebri
   3. Neurologic abnormalities
      1. Neurofibromatosis
      2. Epilepsy
   4. Genital anomalies (10–12%)
      1. Hypogenitalism
      2. Cryptorchidism
      3. Hypospadias
      4. Subseptate uterus
      5. Clitoral hypertrophy
   5. Cardiac defects (2–9%) (Dinwiddie et al. 1978)
      1. Pulmonic stenosis
      2. Atrial septal defect
      3. Ventricular septal defect
      4. Patent ductus arteriosus
      5. Tetralogy of Fallot
   6. Endocrinological abnormalities
      1. Immune deficiency
      2. Hypoparathyroidism
      3. Hypothyroidism
      4. Hypopituitarism
   7. Ear anomalies (9%)
   8. Hematopoietic abnormalities (7%)
   9. Pulmonary anomalies (3%)
      1. Obstructive sleep apnea
      2. Tracheomalacia (Salbert et al. 1991)
      3. Recurrent pulmonary infections
      4. Cor pulmonale
   10. Gastrointestinal abnormalities (3%)
   11. Muscular hypotrophy (3%)
   12. Hepatic anomalies (2%)
   13. Renal anomalies (1–2%): bilateral duplication of renal collecting system
4. Prognosis (Steele and Bass 1970)
   1. Some patients succumb in infancy to respiratory infections and pulmonary insufficiency, possibly related to airway obstruction and abnormal compliance.
   2. Majority of patients with a normal life span.
5. Diagnostic criteria
   1. Major features
      1. Dyscephaly with beak nose and mandibular hypoplasia
      2. Dental abnormalities
      3. Proportional short stature
      4. Hypotrichosis
      5. Cutaneous atrophy
      6. Microphthalmia
      7. Congenital cataracts
   2. Minor features
      1. Narrow/high-arched palate

2. Ocular features
    1. Blue sclera
    2. Antimongoloid palpebral fissures
    3. Synechiae irides
    4. Choroid atrophy
3. Hypoplastic genitalia
4. Musculoskeletal features
    1. Elevated scapulae
    2. Scoliosis
    3. Lordosis
    4. Hyperextensible joints
5. Mental retardation

Diagnostic Investigations

1. Radiography (Christian et al. 1991; Cohen 1991)
    1. Skull
        1. A large, poorly ossified skull
        2. Delayed closure of fontanelles with persistent wide sutures
        3. The presence of Wormian bones
        4. Brachycephaly
        5. Platybasia
        6. Depressed sella turcica
        7. Frontal or parietal bossing
        8. Small orbits
        9. Disproportion between the large cranial vault and the small facial skeleton
        10. Midfacial hypoplasia
            1. Hypoplastic mandibular ramus
            2. Possible absent condyles
            3. Anteriorly displaced temporomandibular joint
            4. Hypoplastic malar bones
        11. A birdlike nose
        12. Micrognathia
        13. Dental anomalies
            1. The presence of natal teeth
            2. Retained decidual teeth
            3. Partial anodontia
            4. Supernumerary and hypoplastic teeth
            5. Anterior open-bite malocclusion
        14. Odontodysplasia
            1. All teeth showing wide pulp chambers and roots with thin dentinal walls and open apices, resembling ghost teeth and indicating a diagnosis of odontodysplasia (Damasceno et al. 2014)
            2. Developmental malformations in the hard structures of the deciduous and permanent teeth (especially in dentin), causing a "ghost teeth" appearance (Gungor et al. 2015)
    2. Long bones
        1. Thin/gracile
        2. Retarded bone age
    3. Other skeletal anomalies
        1. Scaphocephaly
        2. Cervical vertebral anomalies
        3. Mild platyspondyly
        4. Scoliosis
        5. Lordosis
        6. Elevated scapulae
        7. Hip dislocation
        8. Spina bifida
        9. Syndactyly
2. Overnight polysomnography to confirm obstructive sleep apnea
3. Endocrine evaluation for hypothyroidism, hypoparathyroidism, or hypopituitarism
4. Chromosome study: no diagnostic cytogenetic characteristics

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased
    2. Patient's offspring: not increased
2. Prenatal diagnosis: not been reported
3. Management
    1. Surgery
        1. Repair of cardiovascular defect
        2. Ophthalmological procedure (cataract removal)
        3. Rhinoplasty
        4. Facial augmentation
        5. Dental surgery (Patterson et al. 1982)
            1. General restorative dentistry
            2. Orthodontic palatal expansion
            3. Realignment of the dental arches

6. Mandibular advancement
7. Nasal lipofilling to treat the atrophy of the nasal skin (Bénateau et al. 2015)

2. General anesthesia and airway management (Sataloff and Roberts 1984; Malde et al. 1994)
   1. Difficult laryngoscopy and endotracheal intubation secondary to micrognathia, microstomia, and serious upper airway compromise
   2. Brittle and easily broken natal teeth during laryngoscopy
   3. Orotracheal intubation precluded by the anterior placement or absence of the temporomandibular joints
   4. Difficult nasotracheal intubation secondary to hypoplastic nose and deviated nasal septum
   5. Consider preoperative tracheotomy or prepare for emergency tracheotomy
3. Long-term nasal continuous positive airway pressure therapy for obstructive sleep apnea (Ryan et al. 1990)
4. Management for endocrine problem if present

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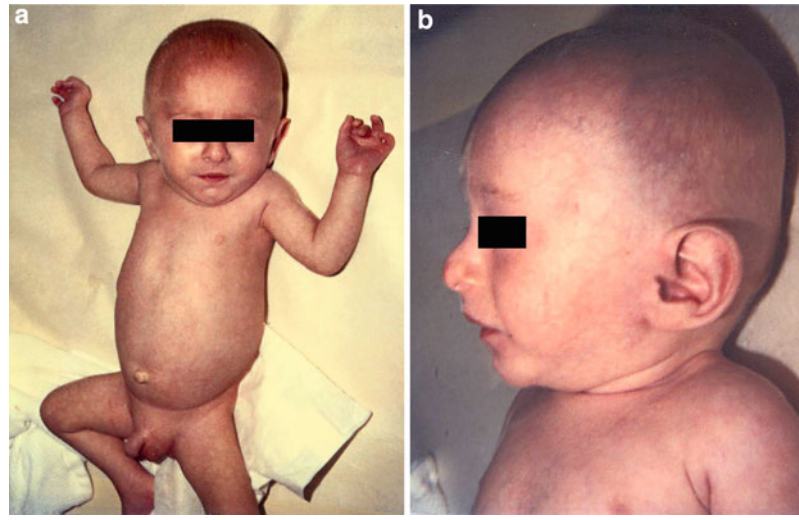

Fig. 1 (**a**, **b**) An infant with Hallermann-Streiff syndrome showing brachycephaly, frontal and parietal bossing, microphthalmia, thin, pointed nose, mandibular hypoplasia, and hypotrichosis

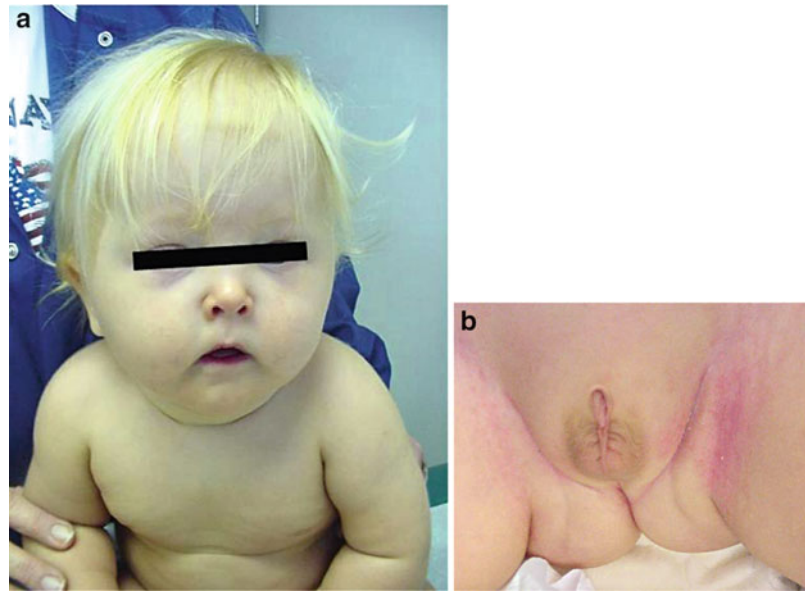

Fig. 2 (**a**, **b**) A male infant with Hallermann-Streiff syndrome showing frontal bossing, microphthalmia, thin nose, mandibular hypoplasia, hypotrichosis involving eyelashes and eyebrows (**a**), and genital hypoplasia (**b**)

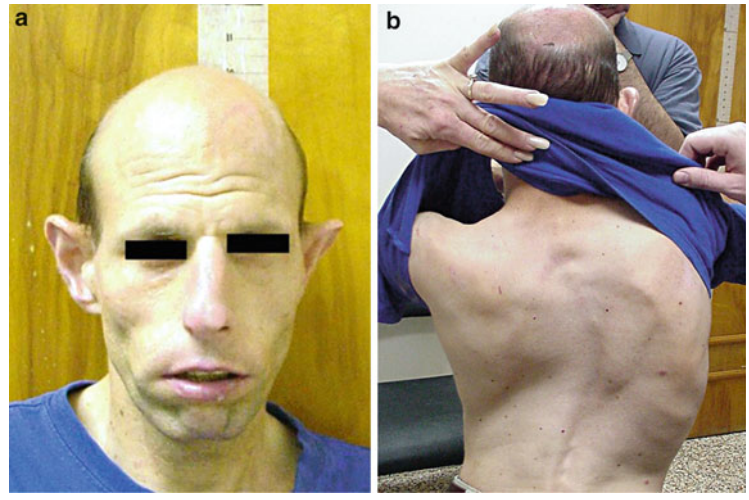

Fig. 3 (**a**, **b**) An adult with Hallermann-Streiff syndrome with mental retardation, short stature, alopecia, scanty eyelashes, a beaked nose (**a**), and scoliosis (**b**)

Harlequin Ichthyosis

Contents

Harlequin ichthyosis is a rare severe scaling disorder and the most devastating congenital ichthyosis, which manifests in utero and is often fatal early in life.

Synonyms and Related Disorders

Autosomal recessive congenital ichthyosis; Collodion baby; Congenital ichthyosis erythroderma; Congenital ichthyosis of harlequin type; Harlequin fetus; Lamellar ichthyosis

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. *ABCA12* gene
    1. Located on chromosome 2q34
    2. Consists of 53 exons and codes a 2595–amino acid protein member of the adenosine triphosphate (ATP)-binding cassette transporter family (Lefévre et al. 2003; Akiyama et al. 2005; Kelsell et al. 2005)
3. Caused by loss-of-function mutations in *ABCA12* (Akiyama and Shimizu 2008; Akiyama 2010)
    1. Truncation mutations: most mutations
        1. Nonsense mutations
        2. Frameshift mutations (deletion/insertion mutations)
        3. Splice site mutations
    2. Missense mutations
    3. Exon deletion
    4. Single amino acid deletions
4. Novel homozygous mutation p.R287X resulted from complete paternal isodisomy (Castiglia et al. 2009)
    1. Nonmosaic chromosome 2 trisomy from chorionic villus karyotyping while postnatal peripheral blood karyotype was normal female.
    2. These findings indicate that trisomic rescue is one step of the mutational cascade leading to reduction to homozygosity for the *ABCA12* mutation in the embryo.
5. Pathomechanisms of ichthyosis involving *ABCA12* mutations (Akiyama 2006, 2010): several morphological abnormalities including abnormal lamellar granules in the keratinocyte granular layer and a lack of extracellular lipid lamellae within the stratum corneum observed in harlequin ichthyosis (Akiyama et al. 2005)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Lack of *ABCA12* function subsequently leads to disruption of lamellar granule lipid transport in the upper keratinizing epidermal cells resulting in malformation of the intercellular lipid layers of the stratum corneum.
2. Cultured epidermal keratinocytes from a harlequin ichthyosis patient carrying *ABCA12* mutations demonstrated defective glucosylceramide transport, and this phenotype was recoverable by in vitro *ABCA12* corrective gene transfer.
3. To date, intracytoplasmic glucosylceramide transport has been studied using cultured keratinocytes from a total of three patients harboring *ABCA12* mutations (Akiyama et al. 2005, 2006, 2007).
    1. One patient was a homozygote for a splice site mutation c.3295-2A > G.
    2. Another patient was a compound heterozygote for p.Ser387Asn and p.Thr1387del.
    3. Only one heterozygous mutation p.Ile1494Thr was identified in the other patient.
    4. Cultured keratinocytes from all the three patients showed apparently disturbed glucosylceramide transport, although this assay is not quantitative.
6. More than 93% of patients with harlequin ichthyosis have been reported to have mutations in the *ABCA12* gene (Richard and Bale 2014; Rajpopat et al. 2011).
7. At least 60% of lamellar ichthyosis and congenital ichthyosis erythroderma cases originate from mutations in the *TGM1*, *NIPAL4,* and *ALOX12B* genes (Oji et al. 2010). TGM1 mutations cause > 50% of autosomal recessive congenital ichthyosis cases in the USA (Farasat et al. 2009). The *TGM1* gene encodes the transglutaminase (TGase)-1 protein, a critical enzyme implicated in cornified cell envelope synthesis (Nemes et al. 1999; Eckert et al. 2005). More than 135 *TGM1* etiological sequence variants have been reported to date, most of which consist of missense and nonsense mutations (Farasat et al. 2009; Herman et al. 2009; Oji et al. 2010).
8. Report of a male with harlequin ichthyosis with a de novo deletion of the long arm of chromosome 18 [46,XY,del(18)(q21.3)] suggesting the possible gene localization within the deleted region (Stewart et al. 2001).

Clinical Features

1. Major clinical features
    1. Large, thick, and yellowish armor-like plaques (plate-like scales) with reddish, moist, oozing fissures and cracks, covering the whole body
    2. Severe ectropion (complete eversion of the nonkeratinizing mucosa of the eyelids with occlusion of the eyes)
    3. Eclabium (eversion of the nonkeratinizing mucosa of the lips)
    4. "Frog-like" grotesque appearance of the face
    5. Crumpled and flattened ears
    6. Flattened nasal tip with anteversion of the nares (nasal hypoplasia)
    7. Permanently opened mouth unable to suck properly
    8. Swollen extremities secondary to tight sausage-like encasement by the thickened stratum corneum
    9. Semiflexed rigid extremities (allowing little limb movement) with hypoplastic fingers
2. Minor clinical features
    1. Absent eyebrows and eyelashes
    2. Absent scalp hair
3. Associate anomalies
    1. Renal tubular defects
    2. Altered thymic structures
    3. Pulmonary hypoplasia
4. Natural history
    1. Restricted fetal movement caused by dense masses of hyperkeratotic scale
    2. Prematurity in most cases
    3. Perinatal death (usually in the first few weeks) secondary to
        1. Respiratory compromise due to mechanical limitation of rib cage excursion
        2. Sepsis
        3. Hypothermia

4. Dehydration
5. Malnutrition
6. Severe anemia
7. Renal failure

4. The phenotype at birth is a collodion baby, where the neonate is covered with a taut, shiny, membrane-like skin or a severe phenotype called harlequin ichthyosis subsequently evolve into phenotypes of varying severity, like lamellar ichthyosis and congenital ichthyosiform erythroderma (Richard and Bale 2014; Oji et al. 2010)
5. Rare survivals
   1. Variable neurological impairment
   2. Short stature
   3. Failure to thrive
   4. At risk for severe keratitis due to ectropion of all eyelids

5. Genotype-phenotype correlations (Richard and Bale 2014; Rajpopat et al. 2011; Aggarwal et al. 2015)
   1. Severe *ABCA12* mutations leading to complete destruction of function or loss of production of *ABCA12* protein cause harlequin ichthyosis phenotype.
   2. Milder mutations lead to lamellar ichthyosis phenotype.

Diagnostic Investigations

1. Light microscopy findings.
   1. Extraordinary compact orthohyperkeratosis (thickened orthokeratotic stratum corneum)
   2. Keratin plugs in hair follicles and sweat ducts
   3. Absent lamellar bodies and abundant vesicles in both the stratum granulosum and stratum corneum
   4. Abnormal lipid droplets and vacuoles in the cytoplasm of keratinized cells in the thick stratum corneum
2. Ultrastructural findings (Akiyama et al. 1998).
   1. Abnormal lipid droplets and vacuoles in the cytoplasm of keratinized cells in the thick stratum corneum
   2. Absent normal lamellar granules in the cytoplasm of granular layer keratinocytes
   3. Lack of lamellar structure in the extracellular space between the first cornified cell and the granular cell
3. Biochemical analysis of skin samples: a defect of conversion from profilaggrin to filaggrin.
4. Family history for evidence of consanguinity.
5. Sequence analysis *ABCA12*, *TGM1*, *ALOX12B*, *ALOXE3*, *NIPAL4*, *CYP4F22*, and *PNPLA1* genes and sequence analysis of *NIPN* and *CERS3* genes can help patients and their families to understand their disease (Richard and Bale 2014; Ortega-Recalde et al. 2015).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: patient not surviving to reproductive age
2. Prenatal diagnosis possible in families at risk
   1. Ultrasonography (2D, 3D, and 4D) at 18–24 weeks (Bongain et al. 2002; Kudla and Timmerman 2010).
      1. Minimal fetal movement with stiff limbs in a semiflexed position
      2. Swollen limbs with hypoplastic fingers and toes and short phalanges
      3. Shriveled hands that do not open
      4. Characteristic facial features
         1. Flat face profile
         2. Open eyes
         3. Ectropion
         4. Cataracts
         5. Flat nose
         6. Thick lips
         7. Eclabium
         8. Absence of typical ear morphology (hypoplasia of the ears)
         9. Large open mouth
         10. Micrognathia
         11. Partitioned cystic formations in front of the eyes
      5. Short neck
      6. Thick skin
      7. Choroid plexus cysts

8. Short umbilical cord
9. Hyperechogenic amniotic fluid
10. Absence of associated visceral anomalies

2. Amniocentesis (Akiyama 1998; Akiyama et al. 1999): demonstration of clumping of keratinocyte cells in the amniotic fluid containing lipid droplets and amorphous electron-dense material.
3. Electron microscopy of the fetal skin biopsy specimen from fetoscopy at 20–22 weeks.
   1. Abnormal vacuoles in keratinized cells
   2. Abnormal lamellar granules in the hair canal
4. Molecular genetic testing: After identification of ABCA12 as the causative gene for harlequin ichthyosis, it is feasible to perform DNA-based prenatal diagnosis for harlequin ichthyosis by chorionic villus or amniotic fluid sampling (Akiyama et al. 2007; Yanagi et al. 2008) or preimplantation genetic diagnosis (Bale and Richard 2009). Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

3. Management (Prasad et al. 1994)
   1. Temperature control.
   2. Electrolyte and fluid balance.
   3. Adequate caloric intake.
   4. Prevention of infection with antibiotics.
   5. Topical steroids to reduce secondary inflammation.
   6. Tretinoin creams or ointments or oral retinoid treatment to reduce the amount of scale (Singh et al. 2001). Early use of systemic retinoids promotes accelerated shedding of the hyperkeratotic plates, whereas continued use reduces scale and improves ectropion and eclabium (Harvey et al. 2010).
   7. Pain management with anti-inflammatory drugs and morphine sulfate if necessary.
   8. Ocular management.
      1. Intensive topical eye ointment
      2. Treat keratitis promptly
      3. Surgical management of the ectropion by skin release surgery with autologous skin grafting in patients with severe exposure keratitis or cosmetically unacceptable ectropion
   9. Careful handling to avoid hard friction and physical contract for prevention of blistering.
   10. Most neonates don't survive. With aggressive neonatal care, survival and evolutions into a milder ichthyosis have been reported (Rajpopat et al. 2011).

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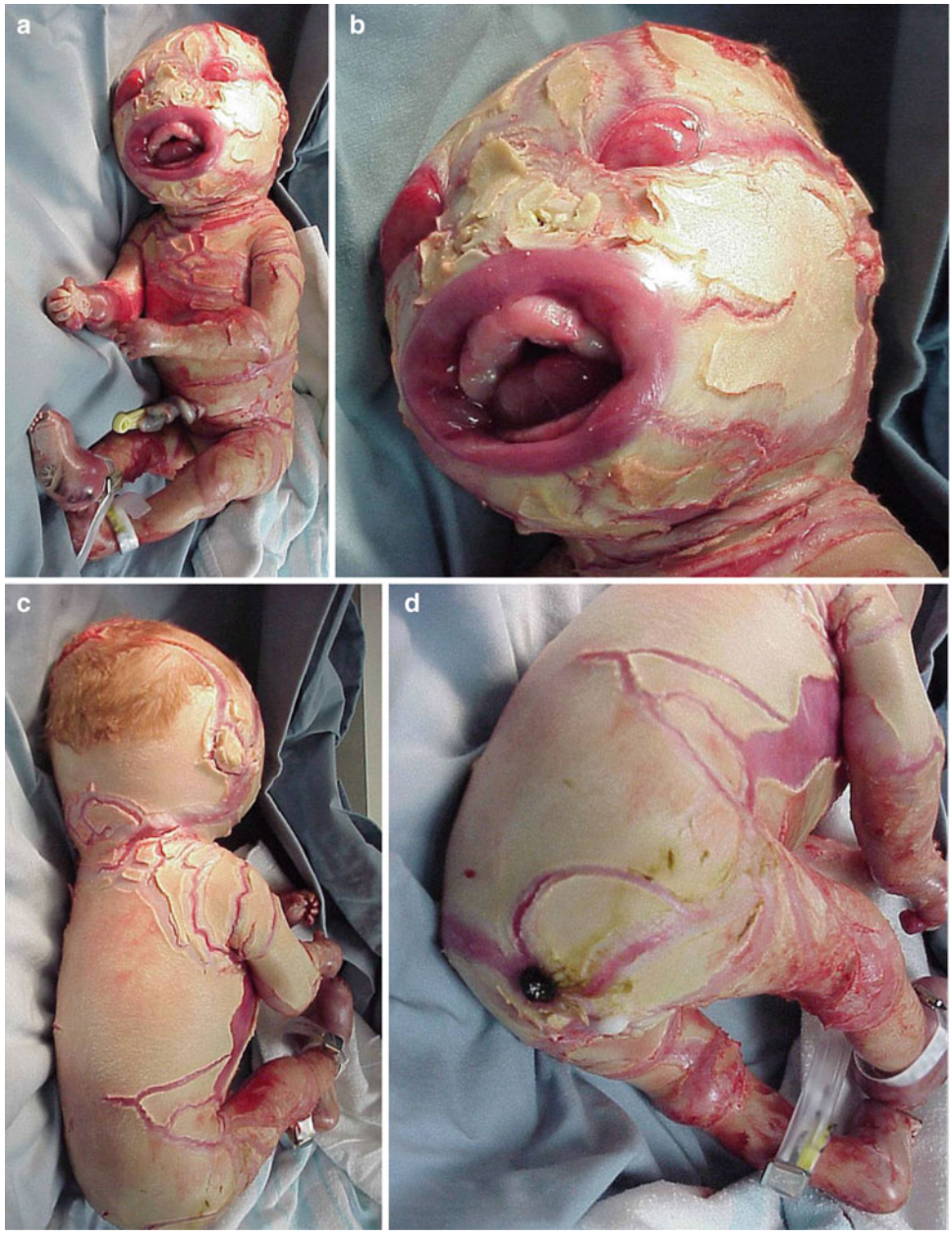

Fig. 1 (**a**–**d**) A newborn with harlequin ichthyosis, covered with yellowish plaques (severe hyperkeratosis) with moist fissures and cracks and grotesque appearance of face with ectropion, eclabium, a flat nose, crumpled/flat ears, and swollen/semiflexed rigid limbs

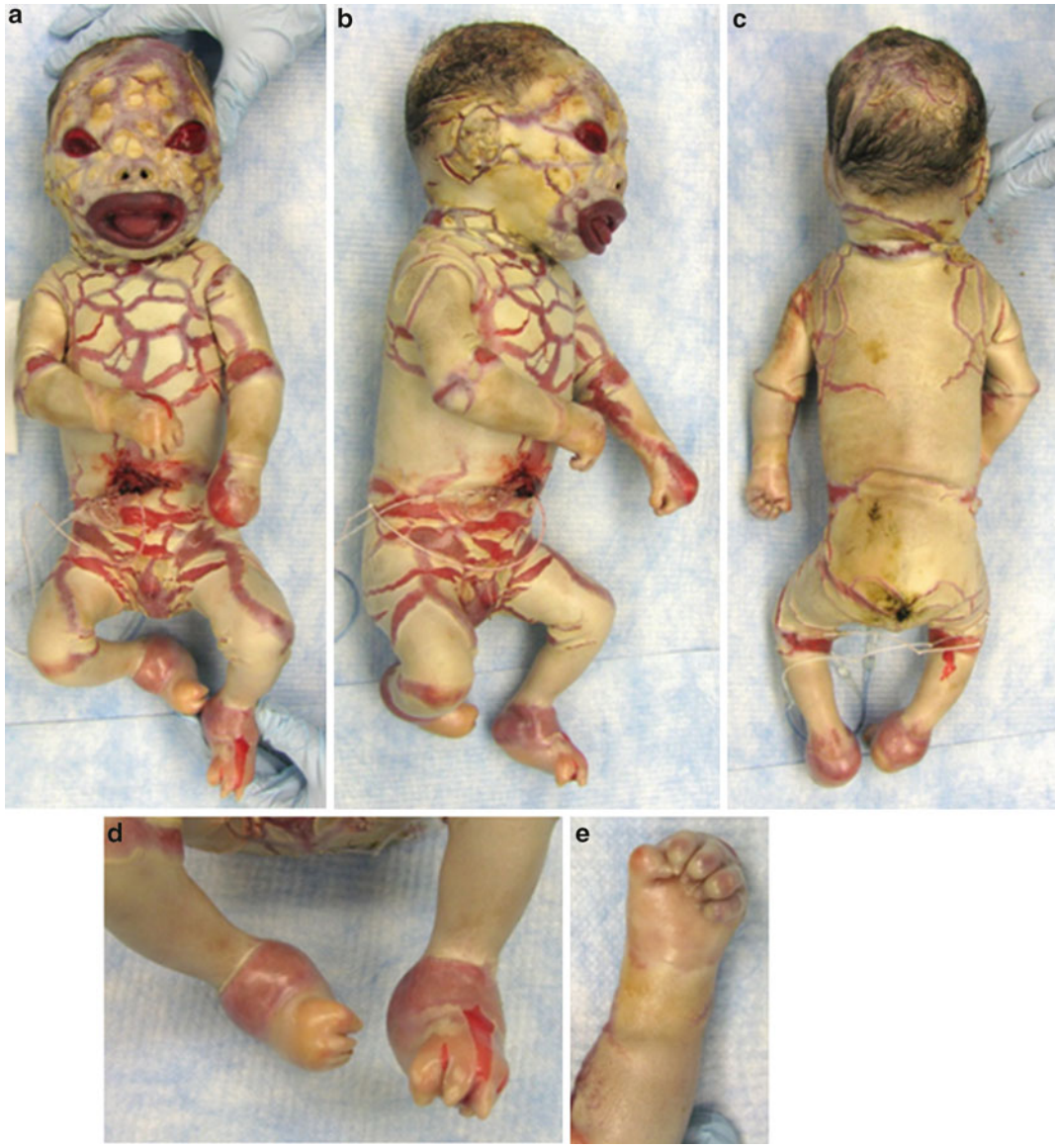

Fig. 2 (**a**–**e**) The baby was born to a 19-year-old primigravida mother of Yemeni origin via normal spontaneous vaginal delivery. The APGARs were 7 and 9 at 1 and 5 min respectively. The weight was 2,065 g, crown-heel length 47.4 cm, and crown to rump 32.5 cm. The newborn showed severe ectropion, flattened nose, eclabium of lips, "fish mouth" deformity, crumped and flattened ears, alopecia with absent eyebrows and eyelashes, and ambiguous genitalia with non-notable penis or scrotum (**a**, **b**). Skin (**a**–**c**) showed diffuse hyperkeratotic plates with deep erythematous creases. Erythema was noted diffusely on parts of the skin, especially in cracked regions. The upper and lower extremities had flexion contractures. The hands and feet were clubbed and swollen with flexion contractures of the fingers with hypoplastic fingers and nails (**d**, **e**). An apparently homozygous K1086X nonsense mutation was identified in the *ABCA12* gene in the skin punch specimen. An A > T nucleotide substitution in exon 23 results in the replacement of a Lysine codon with a stop codon (AAA) at amino acid position 1086. This mutation is denoted c.3256 A > T at the cDNA level or p.Lys1086Stop (K1086X) at the protein level. The K1086X nonsense mutation in the *ABCA12* gene is predicted to cause loss of normal protein function whether through protein truncation or nonsense-mediated mRNA delay. Although this mutation has not been reported previously, its presence is consistent with the diagnosis of Harlequin ichthyosis in this individual. Target carrier testing of both parents has not been carried out (Courtesy of Dr. Shabnum Chaudhery)

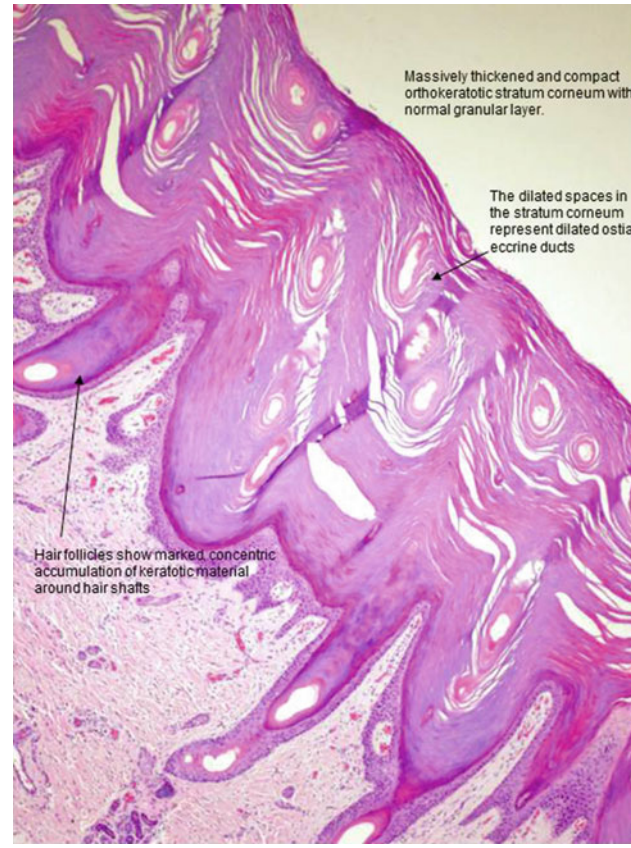

Fig. 3 Microscopic examination of the skin punch specimen showed massive hyperkeratosis with normal to decreased granular cell layer and papillomatosis of the epithelium. The dilated spaces in the stratum corneum represent dilated ostial or eccrine ducts (A12-250) The figure shows massively thickened and compact orthokeratotic stratum corneum with normal granular layer. The dilated spaces in the stratum corneum represnt dilated ostia of eccrine ducts (*short arrow*). Hair follicles show marked concentric accumulation of keratotic material around hair shafts (*long arrow*) (Courtesy of Dr. Shabnum Chaudhery)

Hemangiomas of Infancy

Contents

Hemangiomas of infancy (infantile hemangiomas) are the most common benign pediatric tumors, characterized by an initial phase of rapid proliferation followed by slow involution and often leading to complete regression (Bruckner and Frieden 2003). The incidence of infantile hemangiomas in Caucasian infants is 3–10% (Margileth and Museles 1965). Multiple lesions are found in 15–30% of patients with infantile hemangiomas (Kilcline and Frieden 2008). Most infantile hemangiomas are sporadic, although families with multiple affected individuals have been reported (Blei et al. 1998; Walter et al. 1999).

In addition to common infantile hemangiomas, there are other rare vascular tumors that present fully grown at birth and behave quite differently, as designated by the acronyms: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH) (Mulliken and Enjolras 2004). Some hemangiomas may be life or function threatening or have associated structural congenital anomalies.

Synonyms and Related Disorders

Diffuse neonatal hemangiomatosis; Infantile hemangiomas; Multifocal infantile hemangiomas; Noninvoluting congenital hemangiomas (NICH); PHACE syndrome; Rapidly involuting congenital hemangiomas (RICH); Vascular malformations

Genetics/Basic Defects

1. Infantile hemangiomas (Kwon et al. 2013)
    1. Current theories on the origin of hemangiomas (Bauland et al. 2006)
        1. Nonendothelial cells in hemangioma formation
        2. Angioblast theory
        3. Manifestation of a developmental field defect
        4. Placental origin
        5. Derangement of angiogenesis
        6. Mutation in cytokine regulatory pathway
    2. The origin of infantile hemangiomas: likely heterogeneous and multifactorial (Grimmer et al. 2011)
    3. In one study, 12% of 1,058 children with infantile hemangiomas were reported to have a first-degree relative with hemangiomas (Haggstrom et al. 2007).
    4. Somatic mutation(s) in a single, endothelial cell progenitor with ensuing clonal

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expansion causes hemangioma of infancy (Boye et al. 2001; Walter et al. 2002).
5. An autosomal dominant inheritance has been described (Blei et al. 1998).
6. A follow-up family linkage study demonstrated linkage to chromosome 5q31-33 (Walter et al. 1999).
7. Infantile hemangiomas: the only lesions positive for a marker called GLUT1, independent of the stage (North et al. 2000; Mulliken and Enjolras 2004)
8. Subsequent sequencing of candidate genes in the region (Walter et al. 2002)
    1. Somatic mutations in genes encoding vascular endothelial growth factor receptors, VEGFR-2 (FLK/KDR) and VEGFR-3 (FLT4), in DNA isolated from two infantile hemangioma tissue specimens (Walter et al. 2002).
    2. Further evidence in support of a genetic component is provided by missense mutations found in genes encoding VEGFR-2 and the integrin-like receptor, tumor endothelial marker 8 (TEM8) (ANTXR1) (Jinnin et al. 2008).

2. Congenital vascular tumors (RICH and NICH): Different mutations possibly account for the behavioral divergence, either rapid involution or noninvolution, and the absence of immunoreactivity in the congenital vascular tumors (Mulliken and Enjolras 2004).
3. Vascular malformations (Vikkula et al. 2001)
    1. Localized errors of angiogenic development
    2. Most cases are cutaneous (also called vascular "birthmarks").
    3. Usually obvious in the newborn, grow commensurately with the child, and gradually expand in adulthood (Mulliken and Glowacki 1982)
    4. Can occur in visceral organs, such as the respiratory and gastrointestinal tract, but are more common in the brain (Mulliken and Young 1988)
    5. Composed of tortuous vascular channels of varying sizes and shapes, lined by a continuous endothelium, and surrounded by abnormal complement of mural cells
    6. Can be life threatening due to obstruction, bleeding, or congestive heart failure
    7. Most anomalies occur sporadically.
    8. There are families exhibiting autosomal dominant inheritance.
    9. Genetic studies of such families have resulted in the identification of mutated genes, directly giving proof of their important role in the regulation of angiogenesis: a mutation in the gene encoding the endothelial-specific receptor tyrosine kinase TIE2, the angiopoietin receptor (Vikkula et al. 1996).

Clinical Features

1. Natural history of growth and regression of infantile hemangioma (Bruckner and Frieden 2003; Restrepo et al. 2011; Kwon et al. 2013) (Figs. 1 and 2)
    1. Nascent phase
        1. A premonitory mark evident at birth or during the first few weeks of life in approximately 50% of neonates (Finn et al. 1983; Mulliken et al. 2000)
        2. The nascent lesions may appear as a telangiectatic macule surrounded by a pale halo, a pale macule, an erythematous macule, or less commonly as a bruise or scratch (Hidano and Nakajima 1972).
    2. Proliferating phase
        1. Most hemangiomas begin growth phase in the first few weeks of life.
        2. Occasionally deeper hemangiomas are not noticed until a few months of age.
        3. Rapid growth usually most pronounced during the first 3–6 months of life and reaching maximum size by 9–12 months of age
    3. Involuting phase
        1. Time of onset unpredictable
        2. Some begin at a few months.
        3. Most by 12–18 months
    4. Involuted phase
        1. Completed involution occurs at an estimated rate of 10% per year (Bowers et al. 1960).

2. Approximately 50% of patients followed up had "no trace" of hemangiomas on its resolution (Lister 1938).
3. Cutaneous changes
    1. Mild residual changes: telangiectasia, atrophic wrinkling, or yellowish discoloration
    2. Redundant skin with underlying fibrofatty residua or scarring if ulceration occurred
    3. Alopecia

2. Three clinical morphologies (Drolet et al. 1999; Chiller et al. 2002; Haggstrom et al. 2007)
    1. Superficial hemangiomas: present with a bright red color and are located at the superficial dermis
    2. Deep hemangiomas: involve the deep dermis and subcutis and appear as blue or skin-colored nodules
    3. Mixed hemangiomas: have components of both superficial and deep infantile hemangiomas
3. Another subclassification of infantile hemangiomas (Chiller et al. 2002; Haggstrom et al. 2006)
    1. Localized/focal hemangioma: discrete and oval/round, red, and raised
    2. Segmental hemangioma:
        1. Extend across a large anatomic region and have a geographic shape and typically at high risk for complications
        2. Larger, plaquelike, and geographical in a segmental distribution
    3. Indeterminate hemangioma: mixed features of both focal and segmental hemangiomas
4. Sites of involvement of infantile hemangiomas
    1. A large series (Finn et al. 1983)
        1. Head and neck (60%)
        2. Trunk (25%)
        3. Extremities (15%)
    2. Facial hemangiomas of infancy (Waner et al. 2003)
        1. Nonrandomly distributed
        2. Majority: Focal tumorlike lesions tend to occur near lines of embryonic fusion.
        3. Less commonly: involve a region of skin corresponding to a derivation from the embryologic mesenchymal prominences and tend to be more plaquelike in character
    3. So-called segmental hemangiomas of infancy: more likely to be associated with complications, structural anomalies, or extracutaneous hemangiomas of infancy (Chiller et al. 2002)
5. Location and morphology of infantile hemangiomas and associated risks (Bruckner and Frieden 2003)
    1. Large segmental facial: PHACE syndrome (*P*osterior fossa malformations, *H*emangioma, *A*rterial anomalies, *C*oarctation of the aorta and cardiac defects, *E*ye abnormalities, and occasionally sternal defects) (Frieden et al. 1996)
    2. Nasal tip, ear, large facial (especially with prominent dermal component): permanent scarring and disfigurement
    3. Periorbital and retrobulbar: ocular axis occlusion, astigmatism, amblyopia, and tear duct occlusion
    4. Segmental "beard area" and central neck: airway hemangioma
    5. Perioral, lips: ulceration, disfigurement
    6. Lumbosacral spine: tethered spinal cord and genitourinary anomalies
    7. Perineal, axilla, neck, and perioral: ulceration
    8. Multiple hemangiomas: visceral involvement (especially liver, gastrointestinal tract) with high risk of congestive heart failure
6. Complications (Chamlin et al. 2007; Kwon et al. 2013)
    1. Ulcerations: most common
        1. Pain
        2. Irritability
        3. Difficulty in feeding and sleeping
        4. Infection
        5. Bleeding: most often mild or moderate (most ulcerations are superficial), only rarely requiring transfusion
        6. Disfigurement
        7. Permanent scaring
        8. A subset of hemangiomas at greatest risk
            1. Proliferative phase
            2. Mixed (superficial deep) subtype, with segmental pattern, occurring in

certain anatomic sites, namely, the lower lip, neck, and anogenital region
3. Localized lesions, which are far more common, also develop ulceration.

2. Periorbital infantile hemangiomas: at risk for visual compromise (Ceisler et al. 2004)
1. Astigmatism due to pressure from the infantile hemangioma on the cornea
2. Amblyopia
3. Exophthalmos or displacement of the globe
4. Other possible complications include strabismus, exposure keratopathy, and optic neuropathy.

3. Airway infantile hemangiomas
1. Location: beard distribution, central neck
2. Difficulty breathing with cough, stridor, hoarse cry, and/or cyanosis
3. Subsequent respiratory failure

4. Visceral infantile hemangiomas
1. Occur most often in the gastrointestinal tract, liver, pancreas, spleen, and CNS
2. Commonly asymptomatic
3. Complications depending on the particular site of involvement
1. Gastrointestinal bleeding
2. High-output cardiac failure due to a large liver
3. Obstructive jaundice
4. CNS injuries
4. Presence of multifocal cutaneous hemangiomas: a strong predictor for visceral involvement although visceral infantile hemangioma can occur in the absence of cutaneous infantile hemangiomas

5. Associated anomalies and syndromes
1. PHACE syndrome
1. Diagnosis: based on a defined set of major and minor criteria (Metry et al. 2009a, b)
2. Pathogenesis: likely due to a disruption in early embryonic development
3. Typically present with large, segmental, facial hemangiomas
4. Cerebrovascular abnormalities common: increased risk of stroke (Siegel et al. 2012)
5. Developmental delay due to structural brain anomalies
2. Lumbosacral infantile hemangiomas: at risk of underlying developmental anomalies, such as anorectal and urinary tract defects

7. GLUT1 positive (independent of stage), also positive for Lewis Y antigen and Fc gamma receptor II

8. Congenital hemangiomas (Nasseri et al. 2014)
1. Rare lesions
2. Arise and proliferate in utero (Bronshtein et al. 1992; Marler et al. 2002)
3. Sometimes diagnosed prenatally
4. Fully developed at birth
5. GLUT1 negative
6. Denotes a vascular tumor that had grown to its maximum size at birth and does not exhibit accelerated postnatal growth (Boon et al. 1996)
7. Two major subtypes
1. Involuting congenital hemangioma (RICH): involutes completely within the first 6–14 months of life (Boon et al. 1996)
2. Noninvoluting congenital hemangioma (NICH): grows proportionally with the child and does not regress (Enjolras et al. 2001)
8. Congenital vascular tumor (NICH or RICH) can coexist with infantile hemangioma.
9. RICH may transform into NICH (Mulliken and Enjolras 2004).

9. Diffuse neonatal hemangiomatosis
1. Characterized by multiple cutaneous and visceral hemangiomas
2. Associated with a 60–90% mortality rate in the first few months of life, usually as a result of high output cardiac failure caused by arteriovenous shunting (Haik et al. 1983; Golitz et al. 1986; Stratte et al. 1996; Dotan and Lorber 2013)
3. Familial cases have been described (Ronan and Solomon 1984), including a case of diffuse neonatal hemangiomatosis with eyelid, conjunctiva, and iris hemangiomas (Chang et al. 1998).

10. Classification by the International Society for the Study of Vascular anomalies (Mulliken and Glowacki 1982) classifying vascular anomalies according to natural history and endothelial cell features
    1. Vascular (or vasoproliferative) neoplasms
        1. Infantile hemangiomas
        2. Congenital hemangiomas
            1. Rapidly involuting congenital hemangioma (RICH)
            2. Noninvoluting congenital hemangioma (NICH)
        3. Kaposiform hemangioendothelioma and tufted angiomas (with or without Kasabach-Merritt syndrome)
        4. Spindle cell hemangioendothelioma
        5. Epithelioid hemangioendotheliomas
        6. Other rare hemangioendotheliomas (composite, retiform, and others)
        7. Angiosarcoma
        8. Dermatologic acquired vascular tumors (i.e., pyogenic granuloma)
    2. Vascular malformations
        1. Slow-flow vascular malformations
            1. Capillary malformation
            2. Venous malformation
            3. Lymphatic malformation
        2. Fast-flow vascular malformations
            1. Arterial malformation
            2. Arteriovenous malformation
            3. Arteriovenous fistula
        3. Combined vascular malformations (various combinations of the above)
11. Differential diagnosis of multifocal vascular tumors, vascular malformations, and arteriovenous malformations (Elsayes et al. 2007; Glick et al. 2012)
    1. Infantile hemangioma: most common vascular tumor of infancy
    2. Multifocal lymphangioendotheliomatosis with thrombocytopenia
    3. Pyogenic granuloma
    4. Tufted angioma
    5. Kaposiform hemangioendothelioma
    6. Glomuvenous malformation
    7. Blue rubber bleb nevus syndrome
    1. A rare disorder characterized by multiple distinctive cutaneous and gastrointestinal venous malformations
    2. The name of syndrome: derived from the bluish color of the associated cutaneous lesions and their rubbery consistency at palpation (Bean 1958)
    3. Usually sporadic and generally presents at birth or in early childhood (Kassarjian et al. 2003)
    4. Cutaneous lesions may number from a few to more than 1,000.
    5. Preferentially involve the trunk and upper extremities
    6. Painful lesions
    7. Size: range from a few millimeters to several centimeters in diameter
    8. May be associated with vascular malformations of the gastrointestinal tract (Crosher et al. 1988; Gallo and McClave 1992)
        1. Manifestations: hematemesis, melena, or hematochezia
        2. Risk of life-threatening gastrointestinal hemorrhage
        3. Consumptive coagulopathy and iron deficiency anemia secondary to occult bleeding episodes
    9. May be associated with development of certain tumors, including medulloblastoma, chronic lymphocytic leukemia, renal cell carcinoma, and squamous cell carcinoma (Kassarjian et al. 2003)
8. Proteus syndrome: associated soft tissue abnormalities include vascular malformations, lipomas and fatty hypertrophy, regional fatty atrophy, hyperpigmentation, and nevi (Elsayes et al. 2007).
9. "► Klippel-Trenaunay Syndrome" (please see the chapter) and Parkes Weber syndrome
    1. The port-wine stain (a cutaneous capillary vascular malformation): present in 98% of patients and is the most common manifestation (Jacob et al. 1998)

2. Typically does not markedly progress or regress with time (unlike a hemangiomas)
3. May involve gastrointestinal tract in about 20% of patients (Baskerville et al. 1985; Schmitt et al. 1986; Wilson et al. 2001)
4. Cavernous hemangiomas can occur within abdominal solid organs and the mediastinum and retroperitoneum (Kuo et al. 2003).
5. Complication most often related to the vascular system
    1. Stasis dermatitis
    2. Thrombophlebitis
    3. Cellulitis
    4. Deep venous thrombosis
    5. Pulmonary embolism
    6. Coagulopathy
    7. Congestive heart failure (in patients with associated arteriovenous malformations)

10. "► Kasabach–Merritt Syndrome" (please see the chapter)
    1. Can result in severe disturbances of blood coagulation, such as disseminated intravascular coagulation
    2. In diffuse neonatal hemangiomatosis
        1. Widespread hemangiomas of the skin and viscera
        2. Can be complicated by Kasabach-Merritt syndrome, congestive heart failure, and gastrointestinal bleeding
    3. Other vascular lesions
        1. Angiosarcoma
        2. Arteriovenous malformations

Diagnostic Investigations

1. Histopathologic diagnosis (Kwon et al. 2013; Lowe et al. 2012)
    1. Currently gold standard
    2. Features vary depending on the stage of the life of infantile hemangiomas.
        1. Early stage: presence of rapidly proliferating, plump, endothelial-like cells and pericytes
        2. Later stage during the proliferating phase: fibrous septae containing large vessels separate lobules of plump endothelial-like cells and the presence of mitotic figures, apoptotic bodies, and mast cells within the infantile hemangiomas.
        3. Final involutional phase: presence of flattening of the endothelial-like cells, reduction in mitotic figures, decrease in vessels, and appearance of fibrofatty tissue
2. Immunohistochemical diagnosis (North et al. 2000)
    1. Positive staining of endothelial cells in infantile hemangioma tumor specimens with GLUT1, present at all stages: can differentiate infantile hemangiomas from other vascular tumors and malformations
    2. The immunodiagnostic marker (GLUT1): useful in differentiating infantile hemangiomas from other vascular anomalies such as congenital hemangiomas, which are present at birth and will not stain with GLUT1
3. Vasoproliferative neoplasms (infantile hemangioma) (Burrows et al. 1998)
    1. Grayscale ultrasound
        1. Well defined
        2. Solid
        3. Homogenous
        4. Variable echogenicity
    2. Doppler ultrasound
        1. Hypervascular
        2. Arterial and venous waveforms
        3. High vessel density (>5 vessels/cm^2)
        4. High Doppler shift (>2 kHz)
    3. MRI (Fig. 3)
        1. Iso-to-intermediate signal on T1 weighted
        2. Bright signal on T2 weighted
        3. High-intensity flow enhancement on gradient echo
        4. Internal flow voids
        5. Vigorous enhancement after contrast administration

4. Slow-flow vascular malformations (Burrows et al. 1998)
    1. Venous
        1. Grayscale ultrasound: solid echogenic mass with phleboliths, often multispacial and compressible
        2. Dropper ultrasound: monophasia (venous) or no flow pattern
        3. MRI: T1-weighted heterogeneous intermediate signal, no flow voids, T2 fast spin-echo fat-saturated or short T1 inversion recovery high-signal intensity, T1-weighted SE postgadolinium: enhancement
    2. Lymphatic
        1. Grayscale ultrasound: variable multicystic, multispacial masses, with or without fluid and/or debris levels
        2. Dropper ultrasound: multispacial, macrocystic mass with no flow except in septa
        3. MRI: T1-weighted low-intermediate signal intensity; T2-weight high-signal intensity; T1-weighted postgadolinium: no enhancement, except within septa
    3. Venolymphatic: combined venous and lymphatic components above
5. Fast-flow vascular malformations (arteriovenous malformations and fistulas) (Burrows et al. 1998)
    1. Grayscale ultrasound: cluster of vessels with no intervening well-defined mass
    2. Dropper ultrasound: arterial and venous signals from vessels in the lesions with arterialization of venous structures
    3. MRI: T1-weighted and T2-weight sequences show serpiginous signal voids without a focal mass

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: a twofold increased risk according to multifactorial inheritance (Grimmer et al. 2011)
    2. Patient's offspring:
        1. Isolated: unknown but can be a twofold increase
        2. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis and management
    1. Ultrasonography: Vascular anomalies (congenital hemangiomas) are diagnosed prenatally with increasing frequency (Marler et al. 2002).
        1. Overall diagnostic accuracy of 59%
        2. Capillary-lymphatic-venous malformation correctly diagnosed most often (67%), followed by lymphatic malformation (62 and hemangioma (59%)
        3. Most diagnoses : made during the mid- to late second trimester and third trimester
        4. Can be detected as early as the end of the first trimester (Boon et al. 1996; Berenguer et al. 2003)
    2. MRI: further define the characteristics of the lesion and monitor growth (Ozcan 2010)
    3. Maternal steroids: administered for a fetus with an intrahepatic hemangioma and deteriorating cardiac function, with subsequent stabilization and successful delivery of a healthy neonate (Sheu et al. 1994; Morris et al. 1999)
    4. Maternal interferon (Chuileannain et al. 1999)
    5. Cesarean section to prevent trauma associated with passage through the birth canal and massive hemorrhage (Nolan et al. 2012)
3. Management (Donnelly et al. 2000; Bruckner and Frieden 2003; Kwon et al. 2013)
    1. Major goals of management (Frieden et al. 1997)
        1. Preventing or reversing life- or function-threatening complications
        2. Preventing permanent disfigurement
        3. Minimizing psychosocial stress for the patient and family
        4. Avoiding aggressive and potentially scarring procedures

5. Preventing or adequately treating ulceration to minimize scarring, infection, and pain
2. Management of ulceration
   1. Local wound care
      1. Compresses
      2. Tropical antibiotics
      3. Occlusive dressings
      4. Systemic antibiotics in infected ulcerated hemangiomas
   2. Vascular-specific pulsed dye laser
   3. Pain management
3. Active nonintervention: a valuable approach for children with small, innocuous hemangiomas
4. Propranolol (a nonselective beta blocker)
   1. Induces apoptosis of endothelial cells in the capillaries
   2. Lowers intravascular pressure of the lesions
   3. Blocks vascular growth factors, mainly vascular endothelial growth factor and basic fibroblast growth factor
   4. Topical therapy with 1% propranolol ointment: safe and effective method of treating superficial infantile hemangiomas (Xu et al. 2012)
   5. Used for shrinking severe hemangiomas of infancy with excellent results (Léauté-Labrèze et al. 2008)
5. Systemic corticosteroids:
   1. Used as mainline therapy for hemangiomas since the 1960s (Zarem and Edgerton 1967; Fost and Esterly 1968)
   2. Used particularly for large and/or aggressive hemangiomas that are causing or threatening to cause functional impairment or severe disfigurement
6. Intralesional and topical corticosteroids:
   1. To avoid side effects associated with systemic corticosteroids
   2. Primarily in treating periorbital hemangiomas (Kushner 1979)
7. Interferon-α
   1. Reserve for infants with life-threatening or severely function-threatening hemangiomas who have failed to respond to steroid therapy
   2. Severely limited its use in infantile hemangiomas due to its neurotoxicity
8. Other systemic agents
   1. Vincristine: effective in treating vascular tumors associated with Kasabach-Merritt phenomenon (Haisley-Royster et al. 2002) and large, endangering hemangiomas (Boehm and Kobrinsky 1993; Moore et al. 2001)
   2. Cyclophosphamide (Vlahovic et al. 2009)
9. Pulse dye laser treatment: remains controversial for the treatment of proliferating infantile hemangioma as adverse outcomes including ulceration and scarring have been described (Witman et al. 2006), although successfully used for vascular birthmarks, namely, capillary malformations or "port-wine stains" for years
10. Embolization
11. Surgical excision (Holland and Drolet 2010)
    1. An option for function- or life-threatening hemangiomas when medical therapy fails or is not tolerated
    2. For removal of residual fibrofatty tissue or correction of scarring after involution
    3. May be pursued at an earlier age if it is clear that the child will ultimately need a procedure for the residual effects
12. Other treatments
    1. Intermittent pneumatic and continuous compression: used to treat lesions on the extremities and symptomatic hemangiomas (Stringel 1987; Kaplan and Paller 1995)
    2. A contact probe cooled by liquid nitrogen to treat isolated, raised lesions
    3. Radiation therapy as a last resort for infants with life- or function-threatening hemangiomas that have not responded to other therapeutic modalities (Ogino et al. 2001)

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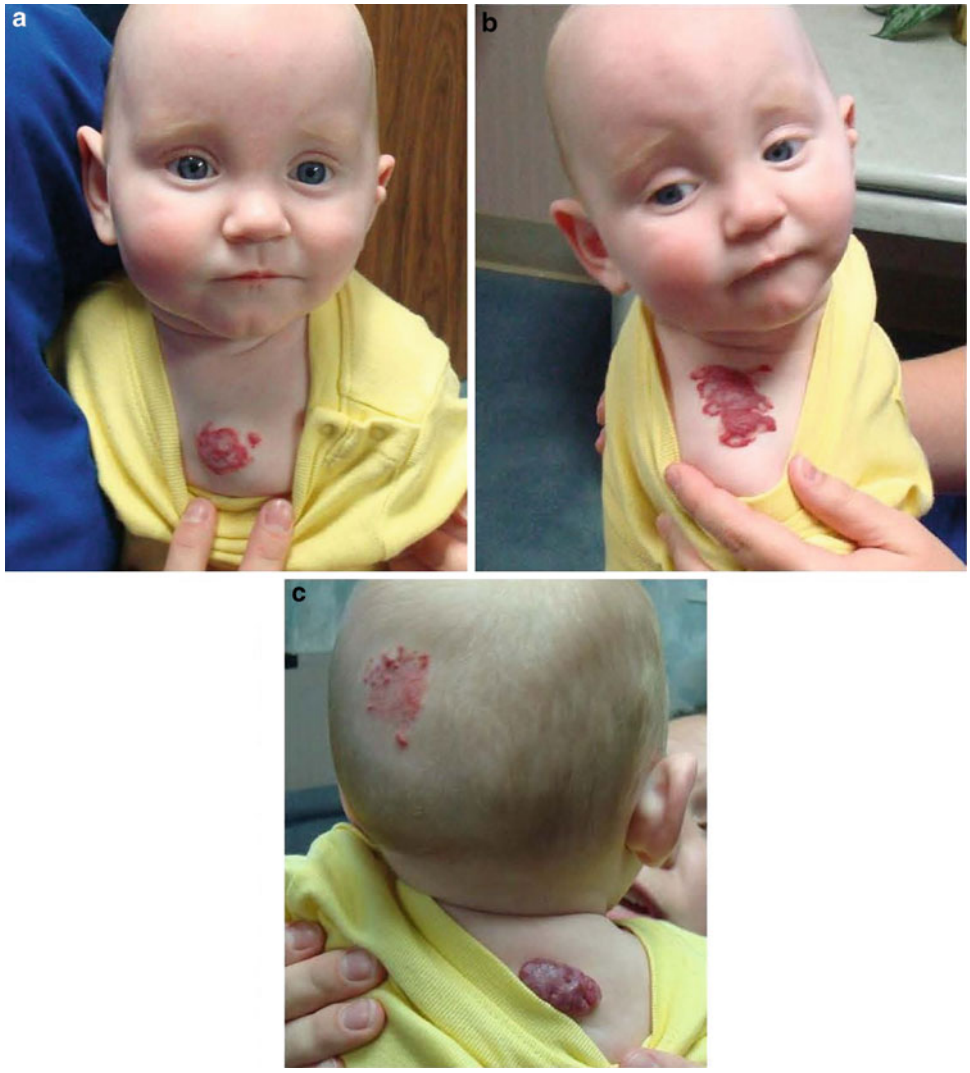

Fig. 1 (**a**, **b**, **c**) This infant was noted to have hemangiomas, a preauricular skin tag on his left ear, and a limbal dermoid on the left lower conjunctiva. There were multiple hemangiomas, located on the back of the head, chest, right shoulder, and the right side of his back. Chromosomes were normal 46,XY

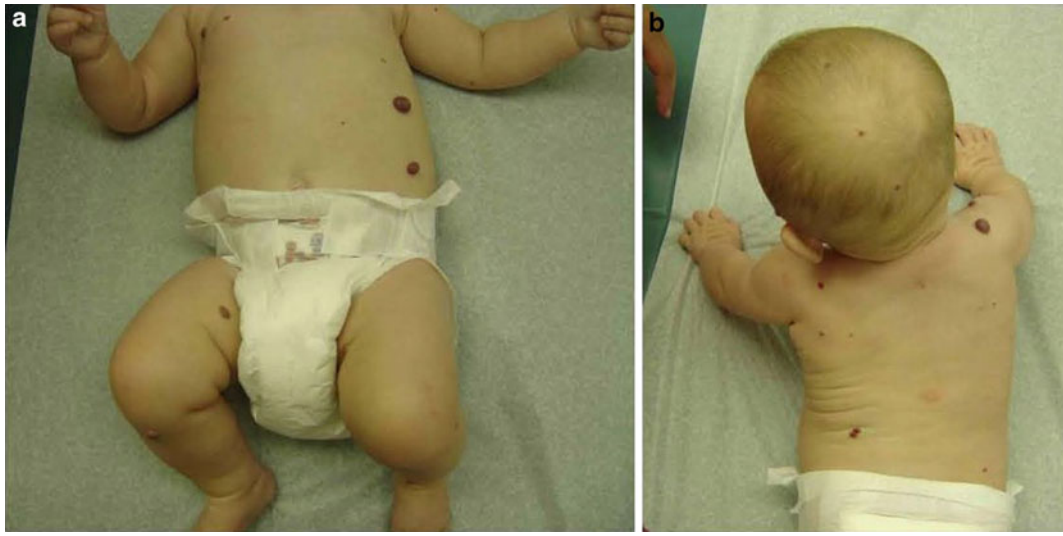

Fig. 2 (**a**, **b**) This 9-month-old female infant was evaluated for multiple raised strawberry-like hemangiomas throughout the body, especially several large ones (>1–1.5 cm) at the shoulders, abdomen, and the chest

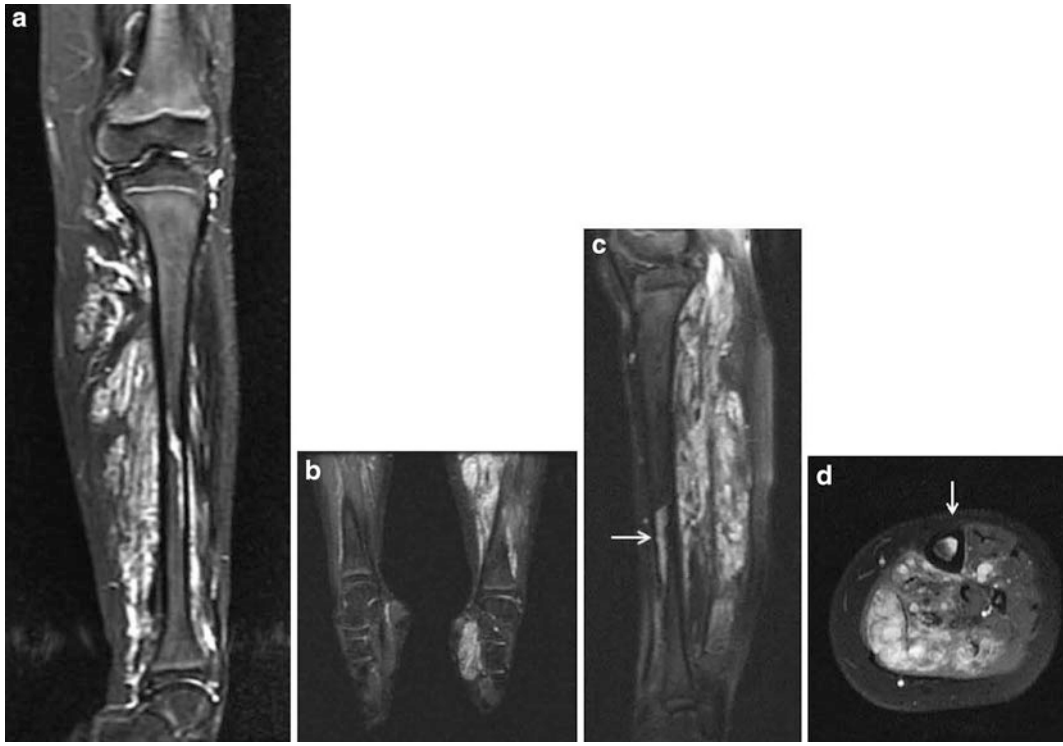

Fig. 3 (**a**–**d**) This 6-year-old female was seen for her enlarged left calf associated with limp and occasional pain. These symptoms seemed to be gradually worsening over the year. She had a hemangioma excised from the left foot at 18 months of age. Family history showed presence of some type of vascular malformation in many female relatives. On examination, there was soft tissue fullness and mild ecchymotic discoloration on the left side of the mons pubis, consistent with a hemangioma. The girth of the left calf was wider than the girth of the right. She had minimal tenderness to palpation of the left calf, but no tenderness to palpation over the left thigh or right calf. MRI showed a large, predominantly intramuscular infiltrating, enhanced hemangioma in the left lower extremity extending from the upper thigh to the foot (**a**, **b**). Infiltrative lesion was also seen in the left pelvis (not shown). There was an intraosseous extension in the mid- to lower tibial shaft (*arrows*) (**c**, **d**) (Courtesy of Dr. Grace Guo)

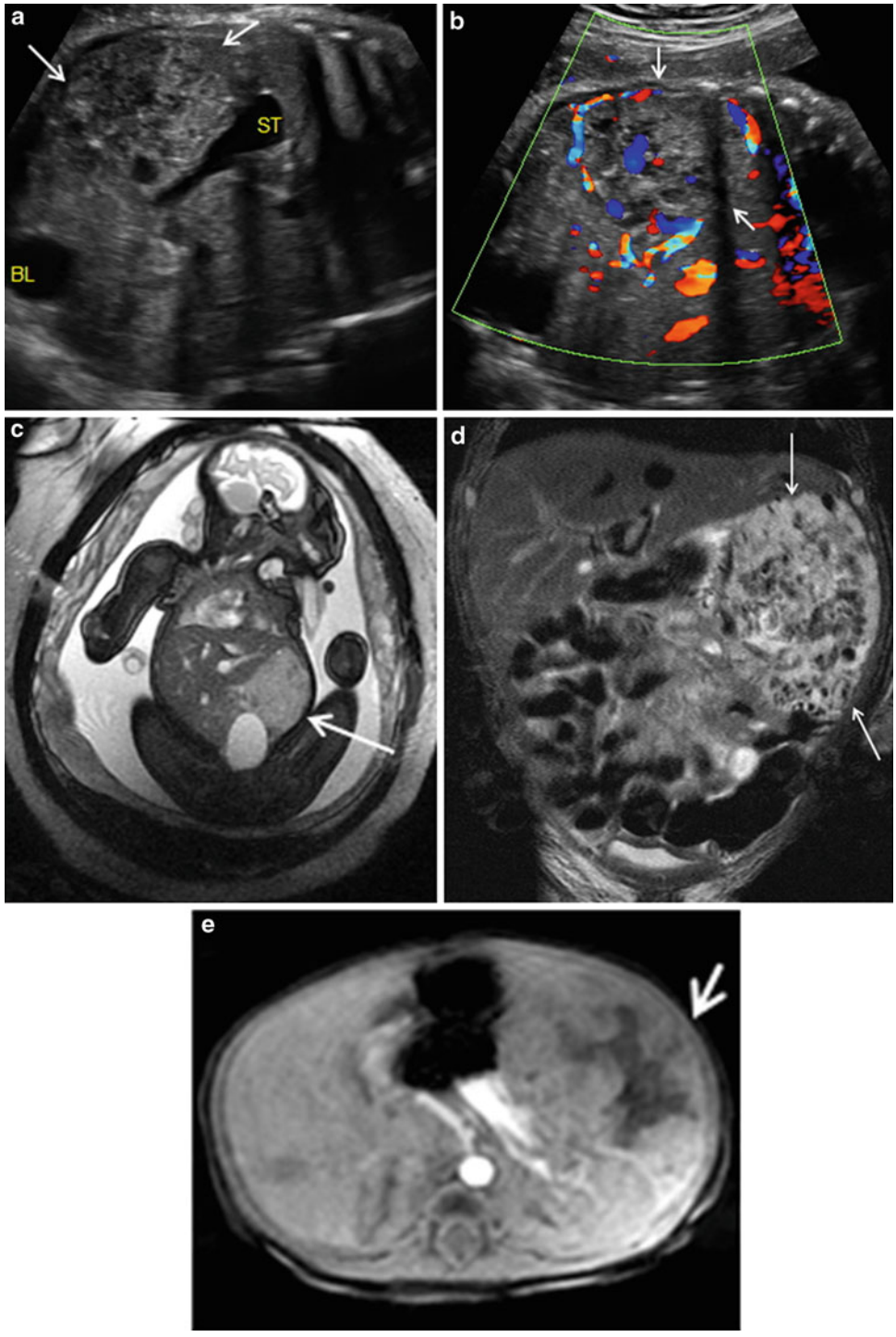

Fig. 4 (**a**–**e**) A 2-day-old female was seen with a history of prenatal diagnosis of intraabdominal mass. At 34 weeks' gestational age, fetal US showed a large, well-defined mass in the left upper abdomen with mixed echogenicity (*arrows*) (**a**) and prominent vascularity (*arrow*) (**b**). Fetal MRI showed a mass located just inferior and lateral aspect of the left lobe of the liver (*arrow*) (**c**). Postnatal MRI showed the mass with predominantly T2 hyperintense and multiple vascular flow voids (*arrows*) (**d**). There was minimal enhancement on initial postcontrast imaging and

Fig. 4 (continued) nodular peripheral enhancement seen on 5-min delayed postcontrast imaging (*arrow*) (**e**). The lesion was most consistent with a giant pedunculated congenital hepatic hemangioma. After birth, the patient has high output cardiac failure secondary to mitral valve regurgitation and shunting with large hemangioma. At 3 months of age, surgical excision of the left liver mass was performed. Pathologic examination confirmed the diagnosis of congenital hepatic hemangioma (GLUT1 negative) with central infarction and calcification (Courtesy of Dr. Grace Guo)

Hemophilia A

Contents

Hemophilia A is a congenital X chromosome-linked coagulation disorder characterized by deficiency in factor VIII clotting activity that results in prolonged oozing after injuries, tooth extractions, or surgery and delayed or recurrent bleeding prior to complete wound healing. It affects approximately 1 in 5,000 to 1 in 10,000 male births.

Synonyms and Related Disorders

Classic hemophilia; Factor VIII deficiency; Hemophilia B; von Willebrand disease

Genetics/Basic Defects

1. Inheritance (Hedner et al. 2000)
    1. An X-linked recessive disorder
    2. New mutations in approximately one third of patients
    3. Hemophilia A in females
        1. Rarely reported
        2. Possible explanation
            1. Extreme skewing of X chromosome inactivation resulting in unusually low factor VIII levels in female hemophilia A carriers
            2. Rare individuals carrying a hemophilia A mutation associated with an X chromosome-autosome translocation or other cytogenetic abnormality, which may result in exclusive inactivation of the normal X chromosome
            3. Rare individuals carrying a hemophilia A mutation in the rearranged X chromosome
2. Molecular genetics (Hedner et al. 2000)
    1. Caused by absent or decreased factor VIII (FVIII) procoagulant function, resulting from mutations in FVIII (*F8*) gene, mapped on chromosome Xq28.
    2. A unique rearrangement within the FVIII gene (intron 22 gene inversion), recently identified as a common, recurrent mechanism for hemophilia A.
        1. Accounting for approximately 45% of all severe hemophilia A patients.
        2. The mutation almost always arises during a male meiosis.
        3. The mother of an apparently new mutation patient with an identified gene inversion can generally be assumed to be a carrier, with the recombination event

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often identified in the maternal grandfather's allele.
3. The remaining 55% of severe hemophilia patients are shown to have a more conventional molecular defect in the FVIII gene.
    1. Approximately 50% of patients with specific point mutations in exons or at splice junctions within the FVIII gene
    2. Approximately 5% of patients with deletions which remove varying-sized segments of the FVIII gene
    3. Rare small insertions and deletions
4. Nearly all patients with mild or moderately severe hemophilia A have some residual level of FVIII activity, shown to have a point mutation within the FVIII coding sequence, resulting in a single amino acid substitution.
5. Clinical severity of the hemophilia A phenotype correlates very closely with the amount of residual factor VIII activity.

Clinical Features

1. Clinical features suspecting a coagulation disorder (Hedner et al. 2000)
    1. Hemophilic arthropathy (Wyseure et al. 2016)
        1. Arthropathy is a form of joint disease that develops secondary to joint bleeding.
        2. Presents with synovial hypertrophy, cartilage, and bony destruction.
        3. The arthropathy can develop despite clotting factor replacement.
        4. Especially disabling in the aging population.
    2. Deep muscle hematomas
    3. Intracranial bleeding in the absence of major trauma
    4. Cephalohematoma or intracranial bleeding at birth
    5. Prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision
    6. Prolonged bleeding or renewed bleeding following surgery or trauma
    7. Unexplained gastrointestinal bleeding or hematuria
    8. Menorrhagia, especially at menarche
    9. Prolonged nosebleeds, especially recurrent and bilateral
    10. Excessive bruising, especially with firm, subcutaneous hematomas
2. Severe hemophilia A (43% of hemophiliacs)
    1. Spontaneous bleeding
        1. Joints: the most frequent symptom
        2. Other sites
            1. Kidneys
            2. Gastrointestinal tract
            3. Brain
    2. Without treatment
        1. Bleeding from minor mouth injuries and large "goose eggs" from minor head bumps during the toddler period
        2. Rare intracranial bleeding resulting from head injuries
        3. Almost always with subcutaneous hematomas
        4. Frequency of bleeding
            1. Relating to the FVIII clotting activity
            2. Varying from two to five spontaneous bleeding episodes each month
            3. Bleeding episodes more frequent in childhood and adolescence than in adulthood
    3. Age of diagnosis
        1. Usually diagnosed during the first year of life
        2. Relating to the FVIII clotting activity
3. Moderately severe hemophilia A (26% of hemophiliacs)
    1. Seldom with spontaneous bleeding
    2. Without treatment
        1. Prolonged or delayed oozing after relatively minor trauma
        2. Frequency of bleeding
            1. Varying from once a month to once a year
            2. Bleeding episodes more frequent in childhood and adolescence than in adulthood

3. Usually diagnosed before the age of 5–6 years
4. Mild hemophilia A (31% of hemophiliacs)
   1. Absent spontaneous bleeding
   2. Without treatment
      1. Occurrence of abnormal bleeding with surgery, tooth extraction, and major injuries
      2. Frequency of bleeding
         1. Varying from once a year to once every 10 years
         2. Bleeding episodes more frequent in childhood and adolescence than in adulthood
   3. Often not diagnosed until later in life
5. Carrier females (Graham et al. 1986)
   1. Risk of bleeding in approximately 10% of carrier females
   2. Mild symptoms
6. Complications of untreated bleeding
   1. Intracranial hemorrhage: the leading cause of death
   2. Chronic joint disease: the major cause of disability
7. Life expectancy: 60–70 years
8. Differential diagnosis (Brower and Thompson 2008; Konkle et al. 2014)
   1. Inherited bleeding disorders associated with a low factor VIII clotting activity
      1. Type 1 vWD (mild von Willebrand disease)
         1. An autosomal dominant disorder
         2. Predominant feature: mucous membrane bleeding
         3. Quantitative deficiency of von Willebrand factor (low vWF antigen, factor VIII clotting activity, and ristocetin cofactor activity) in 80% of patients
      2. Type 2 vWD
         1. Quantitative deficiency of vWF with a decrease of the high-molecular-weight multimers
         2. Low normal to mildly decreased vWF antigen and factor VIII clotting activity
         3. Low functional vWF level in a ristocetin cofactor assay
      3. Type 2 N (Normandy) vWD
         1. An uncommon variant due to several missense mutations in the amino terminus of the vWF protein, resulting in defective binding of factor VIII to vWF
         2. Low factor VIII clotting activity usually showing autosomal recessive inheritance
         3. Indistinguishable clinically from mild hemophilia A, which can be differentiated with molecular genetic testing of the FVIII gene, molecular genetic testing of the vWF gene, or measuring binding of factor VIII to vWF using ELISA or column chromatography
      4. Type 3 vWD (severe von Willebrand disease)
         1. An autosomal recessive disorder
         2. Frequent episodes of mucous membrane bleeding and joint and muscle bleeding similar to hemophilia A
         3. $<1\%$ vWF level
         4. Two to eight FVIII clotting activity
      5. Mild combined factor V and factor VIII deficiencies
         1. A rare autosomal recessive disorder
         2. Deficiency of a chaperone protein (ERGIC-53)
   2. Acquired hemophilia A (Collins et al. 2010)
      1. A bleeding disorder caused by an autoantibody to factor VIII.
      2. Estimated incidence: 1.5/million/year.
      3. Predominantly affects older patients.
      4. Acute onset of severe and life-threatening bleeding or widespread subcutaneous bleeds.
      5. Bleeding sites atypical of congenital hemophilia.
      6. Presence of underlying diseases and conditions.
      7. No personal or family history of bleeding.
      8. High mortality with both early and late deaths: estimated at between 9% and 22%.

9. Prolonged aPTT (activated partial thromboplastin time) with a normal prothrombin time (PT).
10. Mixing test: failure of normal plasma to correct the aPTT by more than 50% is usually taken as evidence that an inhibitor is present (Kasper 1991).

3. Other bleeding disorders with normal factor VIII clotting activity
    1. Hemophilia B
        1. An X-linked recessive disorder caused by mutations in the factor IX (FIX) gene
        2. Clinically indistinguishable from hemophilia A
        3. Diagnosis based on factor IX clotting activity of <40%
    2. Factor XI deficiency
        1. An autosomal recessive disorder
        2. Homozygotes with factor XI coagulant activity of <1–15%
        3. Heterozygotes with factor XI coagulant activity of 25–75%
    3. Factor XII, prekallikrein, or high-molecular-weight kininogen deficiencies
        1. Do not cause clinical bleeding
        2. A prolonged activated partial thromboplastin time (aPTT)
    4. Prothrombin (factor II) or factor V, X, or VII deficiencies
        1. Autosomal recessive disorders
        2. Clinical features: easy bruising and hematoma formation, epistaxis, menorrhagia, and bleeding after trauma and surgery
        3. Diagnosis established by specific coagulation factor assays
    5. Fibrinogen disorders
        1. Congenital afibrinogenemia: an autosomal recessive disorder characterized by prolonged bleeding from minor cuts due to the lack of fibrinogen to support platelet aggregation
        2. Hypofibrinogenemia: inherited either in an autosomal dominant or recessive fashion with mild to moderate bleeding symptoms or may be asymptomatic
        3. Dysfibrinogenemia: an autosomal dominant disorder with symptoms similar to hypofibrinogenemia
    6. Factor XIII deficiency
        1. An autosomal recessive disorder
        2. Occurrence of umbilical stump bleeding in >80% of cases
        3. Intracranial bleeding occurring spontaneously or following minor trauma in 30% of cases
        4. Subcutaneous hematomas
        5. Muscle hematomas
        6. Defective wound healing
        7. Recurrent spontaneous abortion
        8. Rare joint bleeding
    7. Platelet function disorders
        1. General features: bleeding problems similar to thrombocytopenia (skin and mucous membrane bleeding, recurring epistaxis, gastrointestinal bleeding, menorrhagia, excessive bleeding during or immediately after trauma and surgery)
        2. Bernard-Soulier syndrome: an autosomal recessive disorder involving the vWF receptor and platelet GPIb characterized by thrombocytopenia and large platelets
        3. Glanzmann thrombasthenia: an autosomal recessive disorder involving the GPIIb-IIIa receptor necessary for platelet aggregation

Diagnostic Investigations

1. Coagulation screening test
    1. Prolonged partial thromboplastin time (PTT) in severe and moderately severe hemophilia A
    2. PTT often normal in mild hemophilia A
2. Coagulation factor assay for factor VIII clotting activity
    1. Normal range: 50–150%
    2. Low to low normal: above 35%
        1. Usually do not have bleeding.

2. Bleeding can occur in association with mild von Willebrand disease.
3. Factor VIII clotting activity unreliable in the detection of carriers
4. Diagnosis of hemophilia A established in patients with low FVIII clotting activity (<35%) in the presence of a normal von Willebrand factor (vWF) level
    1. Activity <1%: severe hemophilia A
    2. Activity 1–5%: moderately severe hemophilia A
    3. Activity 5–35%: mild hemophilia A

3. Hemophilia imaging (Maclachlan et al. 2009)
    1. Hemophilia arthropathies: radiography, ultrasound, MRI (Cross et al. 2013)
    2. Intramuscular hemorrhage: MRI
    3. Soft tissue hemorrhage (pseudotumors): CT/MRI
    4. Intracranial hemorrhage: CT/MRI
    5. Complications secondary to administration of blood products (liver cirrhosis, liver failure, hepatocellular carcinoma): CT/MRI
4. Molecular genetic diagnosis (Brower and Thompson 2008)
    1. Severely affected and isolated hemophiliac: in ~90% of those patients, the pathogenic gene defect could be identified (Becker et al. 1996).
    2. Targeted mutation analysis
        1. An *F8* intron 22-A gene inversion: accounts for nearly half of families with severe hemophilia A (Kaufman et al. 2006)
        2. An F8 intron 1 gene inversion: accounts for 2–3% of severe hemophilia A (Bagnall et al. 2002)
    3. Mutation scanning or sequence
        1. Seventy-five to ninety-eight percent mutation detection rate in individuals with hemophilia A who do not have one of the two common inversions
        2. Gross gene alterations (including large deletions or insertions, frame shift and splice junction changes, and nonsense and missense mutations) of F8: account for approximately 50% of mutations detected in severe hemophilia A (Kemball-Cook et al. 1998; El-Maarri et al. 2005; Kaufman et al. 2006)
        3. Missense mutations within the exons coding for the three A domains or the two C domains: account for most of the mutations detected in mild to moderately severe hemophilia A (Kemball-Cook et al. 1998; Kaufman et al. 2006)
    4. Deletion analysis
        1. Available clinically to detect exonic, multiexonic, or larger deletions in affected males
        2. Also available for direct diagnosis in potential carrier females
    5. Indirect genetic linkage analysis (Ljung and Tedgård 2003)
        1. Using linked polymorphic markers (restriction fragment length polymorphisms, RFLP) to trace the inheritance of the hemophilia gene within a pedigree if mutation is not found
        2. Limitation of linkage analysis
            1. Uninformative patterns of polymorphic markers
            2. Ethnic variation
            3. Linkage disequilibrium
            4. Need for participation of family members
            5. Not useful in sporadic families which constitute more than half of the hemophilia families

Genetic Counseling

1. Recurrence risk
    1. Obligatory carrier (Ljung and Tedgård 2003).
        1. A woman whose father has hemophilia
        2. A woman who has given birth to two boys with hemophilia, excluding identical twins
        3. A woman who has given birth to one son with hemophilia and a daughter who has a son with hemophilia

2. Establish the genetic probability for carriership for women in a pedigree who are not genetic obligatory carriers based on:
    1. Pedigree data
    2. Clotting factor (FVIII:C) analysis
3. Patient's sib (sib of a male proband): risk to the sibs depending on the carrier status of the mother.
    1. Mother is a carrier: a 50% risk of having a male sib with hemophilia A and a 50% risk of having a carrier female sib
    2. Possibility of maternal germline mosaicism: a low recurrence risk of having a male sib with hemophilia A if the mother has a normal factor VIII clotting activity and no evidence of her carrying her son's FVIII disease-causing mutation in her leukocytes, unless she has germline mosaicism
4. Patient's offspring.
    1. No sons will inherit the mutant allele and therefore will not be affected with hemophilia A.
    2. All daughters will be carriers for hemophilia A.
5. Somatic mosaicisms were detected in 18.8% of the de novo mutations in the patients' mothers, indicating that this phenomenon should be considered in genetic counseling (Becker et al. 1996).
6. Risk assessment in genetic counseling should include consideration of the possibility of somatic mosaicism in families with apparently de novo mutations, especially families with the subtype of point mutations (Leuer et al. 2001).

2. Prenatal diagnosis available to pregnancies of carrier women with hemophilia A (Konkle et al. 2014)
    1. Fetal karyotyping to determine male fetus (46,XY) (Graham 1977).
    2. DNA extracted from fetal cells by amniocentesis or CVS analyzed for:
        1. The known FVIII disease-causing mutation: A case of hemophilia A was prenatally suspected because PCR CVS revealed an inversion within intron 1 in part for hemophilia A (Jovandaric and Jesic 2015).
        2. The informative linked polymorphic markers (Chowdhury et al. 2003).
    3. Fetal blood sample obtained by percutaneous umbilical blood sampling (PUBS) for assay of factor VIII clotting activity if the disease-causing FVIII mutation is not known and if linkage testing is not informative.
    4. Preconception genetic counseling is required to inform patients of the available options and the complex and time-consuming nature of F8 testing (Kessler et al. 2014).
    5. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member.
3. Management (Aledort 1982; Mannucci 2003a, b)
    1. Prophylactic treatment using plasma-derived concentrate of coagulation factor in the past.
        1. Preventing majority of bleeding episodes
        2. Minimizing the impact of arthropathy
        3. Complications
            1. Concentrates manufactured from plasma, pooled from thousands of donors, and invariably contaminated with blood-borne viruses that caused posttransfusion hepatitis B and non-A, non-B (hepatitis C) in practically all treated hemophiliacs.
            2. Optimistic perception of hemophilia: benefits of concentrates seemed to outweigh hepatitis risks.
            3. Tragedy: 60–80% of persons with severe hemophilia became infected with the human immunodeficiency virus (HIV) with contaminated concentrates in the early 1980s.
    2. Infusion of plasma-derived or recombinant FVIII (Helixate, Kogenate, Recombinate, ReFacto) (Bhattacharyya et al. 2003; Vandendriessche et al. 2003).

1. Markedly improves both the life expectancy and the quality of life of patients suffering from hemophilia A
2. Still at risk for life-threatening bleeding episodes and chronic joint damage
3. Side effect of clotting factor substitution therapy: develop neutralizing antibodies against FVIII, rendering further substitution ineffective (10–40% of cases)

3. Promising new recombinant factor VIII products are in advanced stages of clinical trials, and studies are underway to address how to optimally use current resources to improve quality of life for individuals with severe hemophilia A (Powell 2009).
4. Factor VIII/factor IX prophylaxis for severe hemophilia (Carcao and Srivastava 2016).
    1. With the development of new bioengineered clotting factor concentrates (CFCs) with extended half-life (EHL), prophylaxis regimens are likely to change.
    2. EHL CFCs (particularly EHL factor IX) may make prophylaxis more convenient, may allow for more individualization of prophylaxis, may improve adherence to prophylaxis, may expand prophylaxis to patients with less severe forms of hemophilia, and may allow patients to achieve an early normal life.
5. Orthopedic management (Rodriguez-Merchan 2008).
    1. Hemarthrosis: arthrocentesis.
    2. Synovitis: synoviorthesis and synovectomy.
    3. Flexion contractures.
        1. Tendon-lengthening procedures
        2. Supracondylar osteotomy to correct a fixed-knee contracture
        3. Implantation of an external fixator
    4. Hemophilic arthropathy.
        1. Subchondral bone cysts: cheilectomy and curettage
        2. Alignment osteotomy
        3. Joint debridement
        4. Arthrodesis
        5. Joint prosthesis
        6. Total knee arthroplasty
        7. Total hip arthroplasty
    5. Intramuscular hematomas: usually reabsorb without complication when hematological treatment is adequate.
        1. Iliopsoas hematoma
        2. Compartment syndrome (fasciotomy)
        3. Pseudotumors
    6. Orthopedic surgery in patients with inhibitors: contemporary orthopedic and hematological advances such as recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsværd, Denmark) and activated prothrombin complex concentrates (aPCC; FEIBA, Baxter Corp, Deerfield, IL) enable major orthopedic operations to be performed on hemophilia patients with inhibitors, despite these patients having a higher risk of bleeding complications than patients with hemophilia who do not have inhibitors (Rodriguez-Merchan et al. 2007).
6. Obstetrical issues.
    1. Asymptomatic carrier
        1. Uncommon intracranial hemorrhage in affected male fetuses (1–2%)
        2. Cesarean section reserved for complicated deliveries
    2. Symptomatic carrier (baseline factor VIII clotting activity <35%)
        1. Somewhat protected by the natural rise of factor VIII clotting activity during pregnancy
        2. Delayed postpartum bleeding when factor VIII clotting activity returns to baseline within 48 h
7. Neonatal issues.
    1. Early determination of the genetic status of male infants at risk
        1. Assay factor VIII clotting activity from a cord blood sample obtained by venipuncture of the umbilical vein

2. Molecular genetic testing for the FVIII mutation identified in the family
2. Avoid circumcision and heel sticks in infants at risk with a family history of hemophilia A (Car and Tortella 2015), unless:
    1. Hemophilia A is excluded.
    2. Factor VIII concentrate is administered just prior and subsequent to the procedure to prevent delayed oozing and poor wound healing.
8. Analysis of patient's DNA.
    1. Permits identification of the gene lesions that cause hemophilia
    2. Allows the disease to be controlled through carrier detection and prenatal diagnosis
9. New extended half-life clotting factor products, newer agents being developed for patients with inhibitors, and new nonfactor replacement therapies for hemophilia (Car and Tortella 2015).
10. Future gene therapy (Vandendriessche et al. 2003).
    1. Providing a cure for the disease
    2. Providing constant, sustained FVIII synthesis in the patient
        1. Obviate the risk of spontaneous bleeding
        2. Obviate the need for repeated FVIII infusions
        3. Obviate the risk of viral infections associated with plasma-derived FVIII
    3. Requires the use of a gene delivery system that is efficient, safe, nonimmunogenic, and allows for long-term gene expression
    4. Must compare favorably with existing protein replacement therapies
    5. Initiation of several gene therapy phase I clinical trials in patients suffering from severe hemophilia A
        1. Fewer bleeding episodes reported in some patients
        2. Occasional detection of low levels of clotting factor activity
11. Gene therapy for hemophilia: past, present, and future (George and Fogarty 2016).
    1. Over the past several decades, great strides have been taken in the clinical development of gene therapy for hemophilia.
    2. The most advanced contemporary clinical trials, which use gene transfer and an AAV-8 vector platform, have demonstrated the ability to substantially correct the deficiency in coagulation factor activity in an enduring fashion in selected subjects.
    3. Provided that later stage trials are successful, the approach will represent a shift in the current treatment paradigm (i.e., periodic intravenous infusion to replace the missing coagulation factor) that has dominated the treatment landscape in developed countries for nearly 40 years.

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Fig. 1 A boy with hemophilia A who is asymptomatic with prophylactic infusions of recombinant FVIII

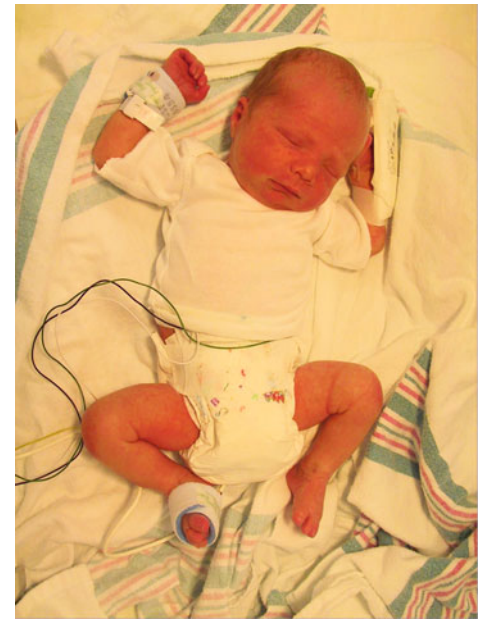

Fig. 2 An infant boy with hemophilia A who was found to have low factor VIII activity. The mother and maternal grandmother had histories of nosebleeds and prolonged bleeding after small cuts and bruise easily

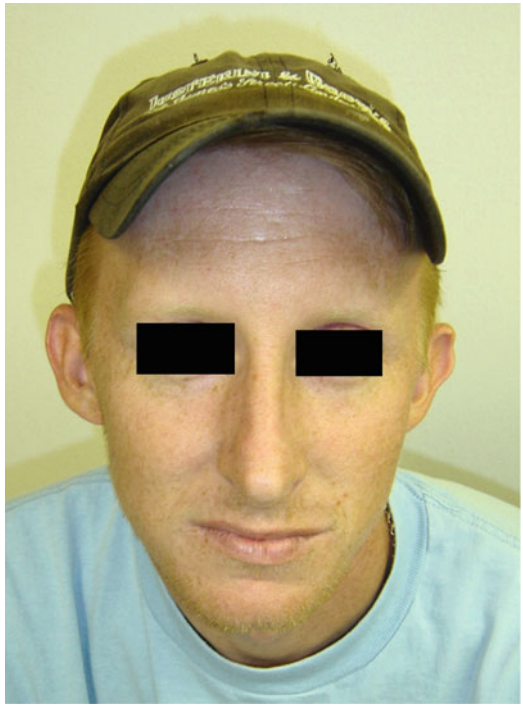

Fig. 3 A 30-year-old man with hemophilia B

Hereditary Hearing Loss

Contents

Hearing loss can be divided into conductive, sensorineural, mixed, and central types (Gifford et al. 2009). Conductive hearing loss (CHL) results from interference with the mechanical transmission of sound through the external and middle ear. Sensorineural hearing loss (SNHL) results from a failure to transduce vibrations to neural impulses effectively within the cochlea or transmit these impulses down the vestibulocochlear nerve. Mixed hearing loss involves a combination of CHL and SNHL, usually due to damage throughout the middle ear and the inner ear. Central hearing loss refers to defects in the brainstem or higher processing centers of the brain. Both CHL and SNHL may be caused by a wide variety of congenital/hereditary and acquired factors.

Understanding genetic basis of hearing loss is important because almost 50% of profound hearing loss (affecting almost 1 in 1,000 newborns) is caused by genetic factors and more than 120 independent genes have been identified (Bayazit and Yilmaz 2006).

Genetics/Basic Defects

1. Causes of conductive hearing loss (Bayazit and Yilmaz 2006; Gifford et al. 2009; Hilgert et al. 2009).
    1. Congenital
        1. Microtia/atresia
        2. Tympanic membrane abnormalities
        3. Ossicular malformations
    2. Acquired
        1. Infections
            1. Acute otitis media
            2. Otitis externa
            3. Ossicular erosion
        2. Otitis media with effusion
        3. Foreign body including cerumen
        4. Cholesteatoma
        5. Trauma
            1. Ossicular disruption
            2. Tympanic membrane perforation
2. Nonhereditary causes of sensorineural hearing loss (SNHL).
    1. In utero infections
        1. *Cytomegalovirus* (CMV): the most common environmental (nongenetic) cause of congenital hearing loss
        2. Measles
        3. Mumps
        4. Rubella
        5. Varicella
        6. Syphilis

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2. Anatomic abnormalities of the cochlea or temporal bone
3. Exposure to ototoxic drugs during pregnancy
    1. Alcohol
    2. Isotretinoin
    3. Cisplatinum
4. Hyperbilirubinemia
5. Infections
6. Trauma
    1. Physical
    2. Acoustic
7. Radiation therapy for head and neck tumors

3. Hereditary hearing loss: mutations and polymorphisms.
    1. Recessive gene mutations
        1. Homozygosity
            1. Same mutation is present in both alleles
            2. Having two identical alleles as a specific autosomal (or X chromosome in a female) gene locus
            3. Can cause hearing impairment
        2. Heterozygosity
            1. Having two different alleles as a specific autosomal (or X chromosome in a female) gene locus.
            2. "Compound heterozygote": both alleles have different disease-causing mutations and can cause hearing impairment.
            3. "Carrier": only one of the alleles has the disease-causing mutation and the other allele is normal and does not have hearing impairment.
    2. Dominant gene mutations
        1. Presence of a mutation in only one of the alleles: enough for the individual to have the disease
        2. Penetrance in the dominant gene
            1. Likelihood that a person carrying a particular mutant gene will have an altered phenotype.
            2. May differ in different individuals.
            3. Presence of a dominant mutation in the parents does not always mean that the siblings will always have hearing impairment.
        3. Expression of a disease-causing gene
            1. May cause differences in the phenotype.
            2. Expression may be one of the reasons why the same genotype or mutations are manifested by different phenotypes in genetic hearing loss.
    3. Genetic polymorphism
        1. Most polymorphisms have no detectable clinical effects.
        2. If one of the alleles is mutated and the other allele has a polymorphism, the individual will probably not have hearing impairment.
4. Genetic nonsyndromic hearing loss (NSHL) (Finsterer and Fellinger 2005): to date, there are 46 nonsyndromic deafness genes reported in the literature (Hilgert et al. 2009).
    1. Autosomal dominant NSHL.
        1. Constitutes 18% of NSHL
        2. Affects almost 50% of the siblings.
        3. Usually postlingual hearing loss except for DFNA3, DFNA6, DFNA8, DFNA12, DFNA13 (De Leenheer et al. 2001), DFNA19, and DFNA14
        4. *WFS1* gene mutations cause:
            1. Autosomal dominant low-frequency SNHL
            2. Wolfram syndrome (hearing loss, diabetes mellitus, diabetes insipidus, and optic atrophy)
        5. *KCNQ4* gene mutations.
            1. Frequent cause of autosomal dominant NSHL.
            2. Missense mutations cause hearing loss beginning at a young age and affecting all frequencies.
            3. Deletion mutations cause a milder phenotype with later onset and affecting only the high frequencies.
            4. W276S mutation in *KCNQ4*: may be a mutational "hot spot" (van Camp et al. 2002).
        6. *COCH* gene mutations.
            1. Frequent mutations: P51S in Belgium and the Netherlands
            2. Cause progressive hearing loss and vestibular impairment with late onset

7. *TECTA* gene mutations cause autosomal dominant mid-frequency HL and high-frequency HL.
8. *TBC1D24* mutation causes autosomal dominant nonsyndromic hearing loss (Azaiez et al. 2014).
9. Dominant mutations in *GJB2* cause:
    1. Autosomal dominant NSHL
    2. Syndromic hearing loss associated with diverse skin disorders (include diffused palmoplantar keratoderma-hyperkeratosis, Vohwinkel syndrome, and keratitis-ichthyosis-deafness [KID] syndrome) (Richard et al. 2002; de Zwart-Storm et al. 2008)

2. Autosomal recessive NSHL
    1. Constitutes 80% of all NSHL cases
    2. Usually prelingual and severe hearing loss except for DFNB8 in which hearing loss is postlingual and rapidly progressive
    3. Affects almost 25% of siblings
    4. DFNB1 (Kelsell et al. 1997; Denoyelle et al. 1999): caused by a mutation in the *GJB2* gene on chromosome 13q12-13 that codes for a gap junction protein called connexin 26
        1. *GJB2* mutations: the most frequent cause of autosomal recessive nonsyndromic hearing loss in most world populations, frequent in the Caucasian, Jewish, and Asian populations (Carrasquillo et al. 1997; Zelante et al. 1997; Kelley et al. 1998; Morell et al. 1998; Abe et al. 2000)
        2. 35delG mutation: most frequent in the majority of Caucasian populations and may account for up to 70% of all *GJB2* mutations (Estivill et al. 1998; Snoeckx et al. 2005)
    5. *SLC26A4* gene mutations
        1. The second most frequent cause of autosomal NSHL
        2. Associated phenotypic spectrum: ranges from Pendred syndrome at one extreme to isolated NSHL with enlarged vestibular aqueduct at the other (DFNB4 locus)
    6. *MYO15A* gene mutations
        1. Cause congenital severe-to-profound hearing loss at the DFNB3 locus.
        2. All 28 identified mutations have been found by linkage analysis in consanguineous families, most of which originate from Pakistan.
    7. *OTOF* gene mutations
        1. Cause prelingual, profound autosomal recessive NSHL
        2. Suggest as the major cause of auditory neuropathy
    8. *CDH23* gene mutations: cause both Usher syndrome type 1D and moderate-to-profound progressive autosomal recessive NSHL at the DFNB12 locus
    9. *TMC1* gene mutations
        1. One of the more frequent causes of autosomal recessive NSHL in consanguineous populations
        2. Characterized by prelingual severe-to-profound hearing loss
3. X-linked recessive NSHL
    1. Constitutes 1–3% of all NSHL cases
    2. Usually prelingual hearing loss except for DFN6
    3. Frequently affects boys
    4. DFN2 and DFN4: mostly cause severe prelingual sensorineural hearing loss
    5. *POU3F4* gene (at locus DFN3) mutations
        1. Cause X-linked mixed or purely sensorineural HL
        2. Deafness with fixation of the stapes (DFN3): the most frequent X-linked form of hearing impairment (De Kok et al. 1995)
        3. May be associated with Mondini dysplasia, cochlear hypoplasia, and/or stapes fixation
4. Mitochondrial hearing loss (Kokotas et al. 2007; Yelverton et al. 2013)
    1. Mutations in mitochondrial genes: the majority are the cause of a broad

spectrum of maternally inherited multisystem disorders.
2. At present, more than 50 mitochondrial mutations leading to syndromic or nonsyndromic deafness have been identified (Zheng et al. 2012).
3. Variants involving *MT-RNR1* and *MT-TS1*, encoding the 12S ribosomal RNA (rRNA) and transfer tRNASer$^{(UCN)}$ respectively, are the most common.

5. Genetic syndromic hearing loss.
   1. Usher syndrome
      1. The most common cause of autosomal recessive syndromic hearing loss (Smith et al. 1994)
      2. Affects almost 50% of the blind and deaf people in the USA
      3. Mutations
         1. USH1A-G
         2. USH2A-C
         3. USH3
   2. Pendred syndrome
      1. Almost 50% of families with *SLC26A4* (PDS) gene mutation on chromosome 7q21-q34
      2. The same mutation can also cause DFNB4 (Li et al. 1998)
   3. Jervell and Lange-Nielsen syndrome: mutations in the following potassium channel genes:
      1. JLNS1 locus in the *KVLQT1* gene located on chromosome 11p15.5
      2. JLNS2 locus in the *KCNE1* (*IsK*) gene located on chromosome 21q22.2
   4. Biotinidase deficiency: resulting from deficiency of an enzyme required for the normal recycling of the vitamin biotin
   5. Waardenburg syndrome (WS): has four subgroups (Van Camp and Smith 2010)
      1. Type I: *PAX3* on 2q35
      2. Type II: *MITF* on 3p14.1-p12.3; *SLUG* on 8q11
      3. Type III: *PAX3* on 2q35
      4. Type IV: *EDNRB* on 13q22; *EDN3* on 20q13.2-q13.3; *SOX10* on 22q13
   6. Branchio-oto-renal (BOR) syndrome
      1. *EYA1* gene mutation on chromosome 8q13.3 (in 50% of patients).
      2. Mutations on chromosome 1q31 may also cause this syndrome (Abdelhak et al. 1997).
   7. Stickler syndrome
      1. The STL1 locus in the *COL2A1* gene located on chromosome 12q13.11-q13.2 is responsible for type 1.
      2. The STL2 locus in the *COL11A1* gene located on chromosome 1p21 is responsible for type 2.
      3. The STL3 locus in the *COL11A2* gene located on chromosome 6p21.3 is responsible for type 3.
   8. Treacher Collins syndrome (TCOF): caused by *TCOF1* gene mutation on chromosome 5q32-q33.1
   9. Alport syndrome
      1. X-linked (85%): *COL4A5* gene (Xq22) mutation is responsible.
      2. *COL4A3* and *COL4A4* (on 2q36-q37) mutation: responsive for the autosomal recessive and autosomal dominant types.
         1. Autosomal recessive (15%)
         2. Autosomal dominant (rare)
   10. Norrie disease
      1. Caused by *Norrin* gene mutation on Xp11.3.
      2. *Norrin* gene is considered to control vascularization in the cochlea and retina.
6. Mitochondrial hearing loss.
   1. Constitutes <1% of all HHL cases.
   2. Only maternal DNA is transmitted to the child while paternal DNA is not.
   3. All children are at risk of having hearing impairment when the mitochondrion of the mother possesses a disease-causing mutation.
7. Heterogeneity of genetic hearing loss.
   1. Genetic hearing loss: a heterogeneous condition although it is mostly caused by a mutation in a single gene (Hardisty et al. 1999).

2. Syndromic, nonsyndromic, recessive, or dominant hearing loss may be caused by the same mutation in a single gene.
3. Recessive or dominant NSHL can be caused by connexin 26, connexin 31, and *MYO7A* mutations.
4. *COL11A2*, PDS, *MYO7A*, and connexin 26 mutations can cause syndromic or nonsyndromic hearing loss (De Leenheer et al. 2001; Tamagawa et al. 2002).

Clinical Features

1. Classification of hearing impairment (HI) (Ječmenica et al. 2015): for partition of the threshold of hearing for tone on important speech frequencies includes mild, moderate, moderately severe, severe, and profound HI.
    1. Mild, moderate, moderately severe, severe, and profound HI: for partition of the threshold of hearing for tone on important speech frequencies
    2. Conductive HI: the result of insufficient functioning of the conduction part, outer and middle ear
    3. Sensorineural hearing impairment (SNHI): the result of damaged membranous labyrinth, the organ of Corti, or some of the structures involved in the transmission of sound to the temporal cortex
    4. Mixed HI: involves dysfunction of both parts of the hearing organ, conductive and perceptive
    5. Transient or permanent HI (with regard to duration)
    6. Progressive or nonprogressive (in relation to behavior)
    7. Unilateral or bilateral (in relation to the side on which the lesion is present)
    8. Genetic (hereditary) and acquired (according to the origin)
    9. Prenatal, perinatal, congenital, and postnatal (depending on the time of onset)
    10. Prelingual and lingual (depending on the time of HI manifestation)
2. Usher syndrome (Bayazit and Yilmaz 2006)
    1. The most common cause of autosomal recessive syndromic hearing loss (Smith et al. 1994).
    2. Almost 50% of the blind and deaf people in the USA have this syndrome.
    3. Type 1
        1. Severe hearing loss and vestibular dysfunction
        2. Retinitis pigmentosa (a progressive degeneration of the retina leading to loss of night vision, restriction of the visual fields, and blindness) starting in childhood
    4. Type 2
        1. Mild to moderate hearing loss
        2. Normal vestibular function
        3. Retinitis pigmentosa occurring after childhood
    5. Type 3
        1. Progressive hearing loss and vestibular dysfunction
        2. Retinitis pigmentosa occurring any time in life
3. Pendred syndrome (Reardon et al. 1997)
    1. Severe congenital sensorineural hearing loss.
    2. Euthyroid goiter
        1. Due to a specific defect in the organification of iodine
        2. Can be demonstrated by the perchlorate test
    3. Labyrinthine bone abnormality like Mondini dysplasia seen in 86% of cases.
    4. Vestibular dysfunction can occur.
    5. Onset may be delayed and clinically unapparent.
    6. Rarely associated with hypothyroidism.
4. Jervell and Lange-Nielsen syndrome (Splawski et al. 1997)
    1. Congenital hearing loss
    2. Elongation of the QT interval on electrocochleography (QT $>$ 440 ms)
    3. Syncope and sudden death due to a cardiac problem

5. Biotinidase deficiency: clinical manifestations within the first few months of life if untreated
    1. Skin rashes.
    2. Seizures.
    3. Hair loss.
    4. Hypotonia.
    5. Vomiting.
    6. Acidosis.
    7. Seventy five percent of the affected infants develop hearing loss if untreated.
    8. Biotinidase deficiency is a completely preventable form of genetic deafness with supplementation of biotin.
6. Waardenburg syndrome
    1. Sensorineural hearing loss
        1. Accounts for 1–2% of individuals with profound hearing loss
        2. Can be bilateral or unilateral of varying severity
    2. Pigmentation abnormality in the skin and hair
    3. White forelock
    4. Dystrophia canthorum (lateral displacement of the inner canthi of the eyes)
    5. Pinched nose
    6. Heterochromia iridis (different iris colors)
    7. Gastrointestinal features
        1. Constipation
        2. Hirschsprung disease
    8. Neural tube and limb defects
7. Branchio-oto-renal (BOR) syndrome
    1. Conductive, sensorineural, or mixed hearing loss
        1. Some degree of hearing loss in almost 80% of gene carriers
        2. Can be delayed in onset
    2. Branchial cleft cyst
    3. Auricle or external auditory canal abnormality
    4. Preauricular pits
    5. Renal abnormalities
        1. Renal dysplasia
        2. Polycystic kidney
        3. Malformation of the calyces
    6. Inner ear abnormalities
        1. Mondini dysplasia
        2. Stapes fixation
8. Stickler syndrome
    1. Progressive sensorineural hearing loss
    2. Cleft palate
    3. Abnormal development of the epiphysis
    4. Vertebral abnormalities
    5. Osteoarthritis
9. Treacher Collins syndrome
    1. Hearing loss
        1. Conductive in 55% of cases
        2. Sensorineural hearing loss usually occurs at high frequencies
    2. Symmetric and hypoplastic zygoma
    3. Lower palpebral fissure
    4. Malformed and small ear
    5. Auditory pit
10. Alport syndrome
    1. Progressive bilateral hearing loss
        1. In almost 50% of cases
        2. Usually begins in the second decade
        3. Initially involves high-frequency hearing loss
    2. Renal disorder
        1. Glomerulonephritis
        2. Hematuria
        3. Renal failure
    3. Ocular abnormalities
        1. Cataract
        2. Spherophakia
        3. Retinal flecks
        4. Anterior lenticonus
11. Norrie disease
    1. Progressive sensorineural hearing loss
    2. Eye disorders
        1. Pseudotumor
        2. Retinal lesions
            1. Hyperplasia
            2. Hypoplasia
            3. Necrosis
        3. Cataract
    3. Mental retardation
12. Mitochondrial mutations causing syndromic hearing loss that may be associated with:
    1. Diabetes mellitus
    2. Neurologic disorder
    3. Progressive myoclonic epilepsy
    4. Ataxia
    5. External ophthalmoplegia

6. Retinopathy
7. Arrhythmia

13. Mitochondrial mutations causing nonsyndromic hearing loss that may be associated with:
    1. Palmoplantar keratoderma
    2. Neurologic disorder

Diagnostic Investigations

1. Obtain family history (ACMG Statement 2002; Smith et al. 2010; Gifford et al. 2009).
    1. Pedigree
        1. Consanguinity
        2. Paternity
        3. Hearing status of the parents and siblings
    2. Ethnicity and country of origin
    3. Inheritance pattern of hearing loss
        1. Autosomal dominant
        2. Autosomal recessive
        3. X-linked
        4. Mitochondrial
    4. Audiometric characteristics in any deaf and hearing-impaired family members
        1. Age of onset
        2. Progression
        3. Conductive hearing loss
        4. Nonsyndromic hearing loss
        5. Auditory neuropathy
    5. Evidence of vestibular dysfunction
    6. Syndromic versus nonsyndromic features
2. Evaluate and inquire the following conditions in the patient and/or relatives:
    1. Visual anomalies
        1. Heterochromia iridis
        2. Retinitis pigmentosa
        3. Myopia
        4. Retinal detachment
        5. Early cataracts
    2. Facial/cervical dysmorphology
        1. Synophrys
        2. Dystopia canthorum
        3. Preauricular pits
        4. Aural atresia
        5. Branchial cysts
        6. Cleft palate
        7. Dental anomalies
    3. Endocrine abnormalities
        1. Thyromegaly
        2. Diabetes
    4. Cardiac signs and symptoms
        1. Syncope
        2. Sudden death
        3. Arrhythmia
        4. Prolonged QT interval
        5. Fainting spells
        6. Congenital heart defect
    5. Renal abnormalities
        1. Hematuria
        2. Proteinuria
        3. Structural defects
    6. Integumentary changes
        1. Premature graying
        2. White forelock
        3. Abnormal pigmentation
        4. Dry skin/keratoderma
3. Obtain patient history with respect to specific risk factors.
    1. Intrauterine infections such as:
        1. Toxoplasmosis
        2. Rubella
        3. CMV
        4. Herpes simplex
    2. Meningitis
    3. Extracorporeal membrane oxygenation (ECMO)
    4. History of hypoxia
    5. Prenatal alcohol exposure
    6. Exposure to ototoxic drugs
4. Perform physical examination
    1. Otologic examination
    2. Airway examination
    3. Documentation of dysmorphisms
    4. Neurologic evaluation including assessment of vestibular function in older patients
5. Laboratory tests/imagings (Grundfast et al. 2000; Parving 2007; Martini et al. 2009)
    1. Viral antibodies
        1. Rubella
        2. CMV
        3. HIV
        4. Others
    2. Bacterial antibodies
        1. Syphilis

2. Toxoplasmosis
3. Others

3. Thyroid studies for suspected Pendred syndrome
    1. TSH (Thyroid stimulating hormone)
    2. T3
    3. T4
    4. Perchlorate test
4. Urine analysis
    1. A positive proteinuria or hematuria can reflect Alport syndrome
    2. Viral cultural isolation
    3. Measurement of electrolyte levels
5. Electrocardiogram for suspected Jervell and Lange-Nielsen syndrome
6. Ophthalmologic examination including electroretinography and slit lamp examination
7. Renal and cardiac ultrasonography
8. Radiographic testing
    1. Bilateral acoustic neuromas: frequently detected radiographically in NF2
    2. Temporal Bone CT scan
        1. Can help visualize cochlear abnormalities such as the Mondini deformity in Pendred (enlarged vestibular aqueduct) and Waardenburg syndrome
        2. Can detect internal auditory canal aberrations associated with X-linked mixed hearing loss with stapes gusher and might reveal cochlear dysplasia
    3. MR imaging
        1. With gadolinium enhancement: the study of choice in patients with a family history of NF2
        2. Used when the hearing loss is progressive but the CT scan is normal
9. Cytogenetic testing: FISH for velocardiofacial/DiGeorge syndrome
10. Array CGH
11. Mutation analysis
    1. Connexins
        1. *GBJ2*
        2. *GBJ6*
    2. Other relevant genes such as:
        1. *WFS1*
        2. *SLC26A4*
12. Effective use of next-generation sequencing technique to detect pathogenic mutations in affected individuals who were not candidates for classical genetic studies (Qing et al. 2014)
13. Next-generation sequencing: allows for development of comprehensive genetic panels, which test for up to 129 genes while improving the accuracy and efficiency of testing (Jasper et al. 2015)

6. Universal newborn hearing screening
    1. Evoked otoacoustic emission (OAE) testing: detects the evoked sound from the cochlea in response to clicks or tones
    2. Auditory brain stem response (ABR, also known as BAER or BSER)
        1. Measures the electroencephalographic waveform response from the vestibulocochlear nerve
        2. Has potential of detecting the following hearing losses:
            1. Hearing loss due to auditory neuropathy, a condition to which the newborn intensive care unit population is particularly prone
            2. Hearing loss resulting from middle and inner ear disorders
    3. Combination of OAE and ABR
7. Other hearing tests to diagnosis and characterization of hearing loss
    1. Tympanometry
        1. External ear canal of individuals (except newborn) is sealed with probe tip.
        2. Measure sound reflection by tympanic membrane while ear canal pressure is varied.
        3. An effective assessment of middle ear pressure and function.
    2. Audiometry
        1. Behavioral observation audiometry.
            1. Infant in a soundproof room is presented with warbled pure tones, speech, or white and narrowband noise through loudspeakers.
            2. Observe responses such as the auropalpebral reflex, startle responses, and head turning

2. Visual reinforcement audiometry: child is seated between two speakers and conditioned to look toward the active speaker.
3. Play audiometry.
    1. Tones of varying frequencies are delivered through headphones or a bone vibrator.
    2. Child is conditioned to perform play activities, such as dropping a block or placing a peg in a board.
4. Conventional audiometry.
    1. Tones of varying frequencies are delivered through headphones or a bone vibrator.
    2. Child is instructed to raise a hand or push a button when a tone is heard.
5. Pure tone audiometry (air and bone conduction): involves determination of the lowest intensity at which an individual "hears" a pure tone.
6. Air conduction audiometry.
    1. Presents sounds through earphones.
    2. Threshold depends on the condition of the external ear canal, middle ear, and inner ear.
7. Bone conduction audiometry.
    1. Presents sounds through a vibrator placed on the mastoid bone or forehead, thus bypassing the external and middle ears.
    2. Thresholds depend on the condition of the inner ear.
8. Conditioned play audiometry.
    1. Used to test children from age 2.5–5 years.
    2. A complete frequency-specific audiogram for each ear can be obtained from a cooperative child.
9. Audioprofile
    1. Recording of several audiograms on a single graph.
    2. These audiograms may be from one individual at different times, but more frequently they are from different members of the same family segregating deafness usually in an autosomal dominant fashion.
    3. By plotting numerous audiograms with age on the same graph, the age-related progression of hearing loss can be appreciated within these families.
    4. Often the composite picture is a characteristic of specific genetic causes of autosomal dominant nonsyndromic hearing loss.
    5. One of the most characteristic audioprofiles is associated with DFNA6/14/38 hearing loss caused by mutations in *WFS1*.
8. Degree and effects of hearing loss (Bachmann and Arvedson 1998; Gifford et al. 2009)
    1. Normal hearing (no hearing loss) (0–15 dB loss): can detect all aspects of speech
    2. Minimal hearing loss (16–25 dB loss)
        1. May miss up to 10% of speech
        2. May respond inappropriately
    3. Mild hearing loss (26–40 dB loss)
        1. May miss up to 50% of speech
        2. May be labeled as "behavior problem" and "poor listener"
    4. Moderate hearing loss (41–55 dB loss)
        1. May miss 50–100% of speech
        2. Speech quality likely to be poor
        3. Limited vocabulary
        4. Low self-esteem possible
    5. Moderate to severe hearing loss (56–70 dB loss)
        1. 100% of normal volume speech lost
        2. Delayed speech and poor intelligibility
        3. Social isolation likely
    6. Severe hearing loss (71–90 dB loss)
        1. Loud voices only heard within 12 in. of ear
        2. Delayed speech and language if loss is prelingual
        3. Declining speech abilities and atonal voice if loss is postlingual
    7. Profound hearing loss (>90 dB loss)
        1. Sound vibrations felt rather than heard
        2. Visual cues primary for communication
        3. Peer group of hearing-impaired children preferred
9. Triage/testing and triage paradigm (ACMG Statement 2002)

1. If a form of syndromic deafness is suspected: perform gene-specific mutation screening.
2. If nonsyndromic deafness is suspected and the patient is a simplex case:
    1. CMV testing should be performed.
        1. A negative test for CMV antibodies in early infancy may exclude CMV-related hearing loss.
        2. A positive result must be interpreted with caution.
    2. *GJB2* (connexin 26) mutation screening by sequence analysis.
        1. A negative test result does not exclude a genetic etiology.
        2. A positive test result may make it possible to avoid other expensive and potentially invasive tests.
3. If nonsyndromic deafness is suspected and the patient is a multiplex case with other hearing-impaired first-degree relatives: proceed directly to connexin 26 testing.
4. If nonsyndromic deafness is suspected and the pedigree suggests dominant inheritance: connexin-related deafness is not excluded and gene-specific mutation screening for other loci may be available.
5. If nonsyndromic deafness is suspected and the pedigree suggests mitochondrial DNA inheritance: testing for the A1555G mutation (associated with aminoglycoside-induced hearing loss) and the A7445G mutation, both of which are associated with some rare familial cases of hearing loss, may be appropriate after common *GJB2* mutations are excluded.
6. If nonsyndromic deafness is suspected and both parents are deaf:
    1. Connexin-related deafness will be strongly suspected (since mutations in *GJB2* are the most common cause of deafness in the United States and the vast majority of marriages between deaf individuals who produce deaf offspring are between individuals with *GJB2* mutations).
    2. Possible to ascribe a genetic etiology to the hearing loss in many persons after triage/testing:
        1. For example, a child may be diagnosed with *GJB2*-related deafness.
        2. If two clearly pathologic alleles are found, the cause of that child's deafness will be known with virtual certainty and can accurately predict the chance of recurrence in a subsequent child.
    3. Alternatively, mutation screening may be negative:
        1. A negative mutation screen must not be taken to mean that the deafness is not genetic: important to be conveyed to parents of deaf children who undergo genetic testing (Brunger et al. 2000).
        2. The probability that the deafness is genetic in patients with an unremarkable family history of deafness and a negative test result for connexin 26 will vary based on the number of hearing siblings. The proportional distribution of the different mutations in the connexin 26 locus also varies in different ethnic groups (Kenneson et al. 2002).

Genetic Counseling

1. Recurrence risk (Smith et al. 2010)
    1. Patient's sib
        1. Autosomal dominant hereditary hearing loss
            1. A 50% risk of inheriting the mutant allele if one of the proband's parents has a mutant allele.
            2. Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable.

2. Autosomal recessive hereditary hearing loss
    1. A 25% risk of being deaf.
    2. A 50% risk of having normal hearing and being a carrier.
    3. A 25% risk of having normal hearing and not being a carrier.
    4. Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable.
    5. For siblings with the identical *GJB2* genotype as the probands with severe-to-profound deafness: a 91% risk of having severe-to-profound deafness and a 9% risk of having mild-to-moderate deafness.
    6. For siblings with the identical *GJB2* genotype as the proband with mild-to-moderate deafness: a 66% risk of having mild-to-moderate deafness and a 34% risk of having severe-to-profound deafness.
3. X-linked hereditary hearing loss
    1. A carrier mother has a 50% risk of transmitting the deafness-causing mutation with each pregnancy: sons who inherit the mutation will be deaf; daughters who inherit the mutation are carriers and likely to have normal hearing.
    2. A non-carrier mother: the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.
    3. Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable.
4. Mitochondrial disorders with hearing loss as a possible feature
    1. The risk to the sibs depends on the genetic status of the mother: the mother of a proband usually has the mitochondrial mutation and may or may not have symptoms (note that the father is not at risk of having the disease-causing mtDNA mutation).
    2. If the mother has the mitochondrial mutation, all sibs are at risk of inheriting it.

2. Patient's offspring
    1. Autosomal dominant hereditary hearing loss.
        1. A 50% risk of transmitting the mutant allele to each child.
        2. In case of an apparent de novo mutation in the proband (neither parent of a proband with an autosomal dominant condition has the deafness-causing mutation or clinical evidence of the disorder), explore possible nonmedical explanations (alternate paternity or maternity such as with assisted reproduction or undisclosed adoption).
        3. Clinical severity and disease phenotype may differ between individuals with the same mutation, depending on the specific syndrome; thus, age of onset and/or disease progression may not be predictable.
    2. Autosomal recessive hereditary hearing loss: all of the offspring are obligate carriers.
    3. X-linked hereditary hearing loss: males with X-linked hereditary hearing loss will pass the deafness-causing mutation to all of their daughters and none of their sons.
    4. Mitochondrial disorders with hearing loss as a possible feature.
        1. All offspring of females with an mtDNA mutation are at risk of inheriting the mutation.
        2. Offspring of males with a mtDNA mutation are not at risk.

2. Prenatal diagnosis
    1. Prenatal diagnosis for some forms of hereditary hearing loss is technically possible by analysis of DNA extracted from fetal cells obtained by:

    1. Amniocentesis usually performed at approximately 15–18 weeks' gestation
    2. Chorionic villus sampling (CVS) at approximately 10–12 weeks' gestation
  2. The deafness-causing allele(s) of a deaf family member must be identified before prenatal testing can be performed.
  3. Preimplantation genetic diagnosis (PGD): may be available for families in which the deafness-causing mutation(s) have been identified.
3. Management
  1. Multidisciplinary team consisting of:
    1. An otolaryngologist
    2. An audiologist
    3. A clinical geneticist
    4. A pediatrician
    5. An educator of the deaf
    6. A neurologist
    7. A pediatric ophthalmologist
  2. Treatment
    1. Determine the appropriate habilitation option such as:
      1. Hearing aids
      2. Vibrotactile devices
    2. Cochlear implantation: considered in children over age 12 months with severe-to-profound hearing loss.
    3. Early auditory intervention through amplification, otologic surgery, or cochlear implantation is essential for optimal cognitive development in children with prelingual deafness.
  3. On the basis of genetic testing for the couple with hearing loss, human assisted reproductive technology is a viable option to avoid the birth of infant with hereditary deafness (Liu et al. 2015).

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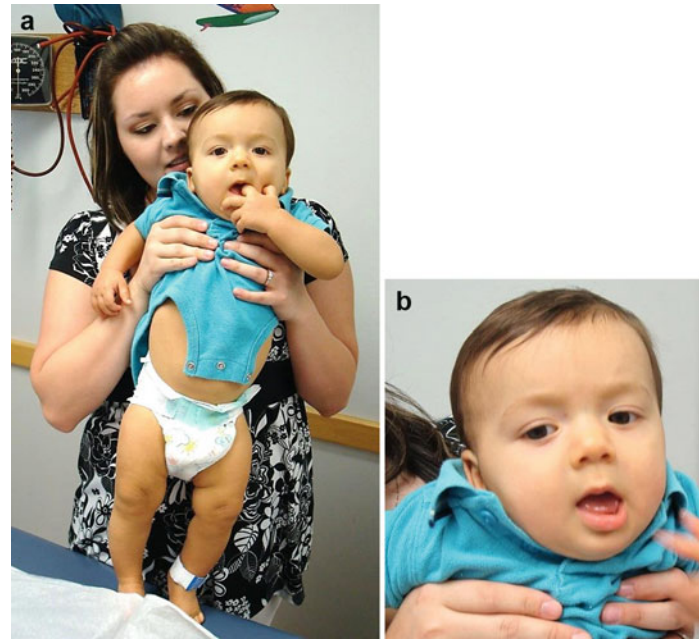

Fig. 1 (**a**, **b**) A 9-month-old boy with nonsyndromic hearing loss

Fig. 2 A 29-year-old man with nonsyndromic hearing loss

Hereditary Hemochromatosis

Contents

Hereditary hemochromatosis (HHC; *HFE* 1) is a common hereditary disorder of iron metabolism and the most common inherited autosomal recessive disorder in Caucasians with a prevalence of 1 in 300 to 1 in 500 individuals. It is characterized by inappropriately high iron absorption resulting in progressive iron overload.

Synonyms and Related Disorders

Hemochromatosis; Neonatal hemochromatosis

Genetics/Basic Defects

1. The human leukocyte antigen (HLA)-linked iron-loading (*HFE*) gene associated with the autosomal recessive disorder known as hereditary hemochromatosis occurs in about 10% of subjects of European descent, most of whom are unaffected heterozygotes. In contrast, the 3–5 per 1,000 who are homozygotes are at risk of developing severe and potentially lethal iron overload, with damage to a number of organs, including the liver, pancreas, heart, joints, and endocrine glands (Bothwell and MacPhail 1998).
2. Cause: result of a single faulty *HFE* gene on chromosome 6p21.3 near the *HLA* complex that codes for a glycoprotein called HFE, which binds to the transferrin receptor and reduces its affinity for iron-bound transferrin, allowing cellular uptake of iron-based transferrin. Other genes, including a second transferrin receptor and the circulating peptide hepcidin, participate in a shared pathway with *HFE* in regulation of iron absorption (Fleming and Sly 2002).
3. Two common mutations (missense):
    1. C282Y:
        1. Accounts for most cases of HHC (Feder et al. 1996).
        2. Homozygotes for C282Y (p.Cys282Tyr) mutation (>80% cases worldwide) are at high risk for HHC.
        3. Heterozygote for C282Y mutation:
            1. Have increased levels of transferrin saturation
            2. Rarely have organ damage
    2. H63D: Homozygotes for H63D (often has a potentiator, such as hepatitis C infection, β-thalassemia trait) are unlikely to develop HHC.

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3. C282Y/H63D (11% present phenotypically): Compound heterozygotes for C282Y/H63D have a milder form of HHC than C282Y homozygotes.
4. Other *HFE* mutations:
   1. Missense mutations:
      1. S65C: the third most common mutation
      2. G93R
      3. I105T
      4. Q127H
      5. R330M
   2. Frameshift mutations:
      1. P160ΔC
      2. V68ΔT
   3. Nonsense mutations
   4. Spice site mutation
5. Clinical expression of the disease:
   1. Homozygotes: affected clinically
   2. Heterozygotes:
      1. Can have minor abnormalities of the parameters that reflect body iron status
      2. Can develop significant iron overload only when other diseases that affect iron metabolism coexist, such as:
         1. Heterozygous β-thalassemia
         2. Hereditary spherocytosis
         3. Sporadic porphyria cutanea tarda
6. Hereditary hemochromatosis not attributable to mutations in *HFE*:
   1. A subgroup of hereditary hemochromatosis indistinguishable from *HFE*-associated HHC.
   2. Does not have mutations in *HFE*.
   3. The disease does not appear to be linked to the HLA complex.
   4. The genetic basis has not been defined.
7. Pathophysiology (Whittington and Kowdley 2002):
   1. Inappropriately high intestinal iron absorption: the most important pathophysiological step in body iron loading
   2. Effects of mutations on iron absorption: central to the understanding of the pathological basis of hereditary hemochromatosis
8. Neonatal hemochromatosis (Feldman and Whitington 2013):
   1. A clinical condition in which severe liver disease in the newborn is accompanied by extrahepatic siderosis.
   2. Gestational alloimmune liver disease (GALD) has been established as the cause of fetal liver injury resulting in nearly all cases of neonatal hemochromatosis.
   3. In GALD, a women is exposed to a fetal antigen that she does not recognize as "self" and subsequently begins to produce IgG antibodies that are directed against fetal hepatocytes.
   4. These antibodies bind to fetal liver antigen and activate the terminal complement cascade resulting in hepatocyte injury and death.
   5. GALD can cause congenital cirrhosis or acute liver failure with and without iron overload and siderosis.
   6. Practitioners should consider GALD in cases of fetal demise, stillbirth, and neonatal acute liver failure.
   7. Identification of infants with GALD is important as treatment is available and effective for subsequent pregnancies.

Clinical Features

1. Variable clinical presentation.
2. Median age at presentation of symptoms:
   1. Fifty-one years in males
   2. Female homozygotes:
      1. Less likely to develop symptomatic disease
      2. Median age: age 50
3. Asymptomatic: abnormal serum iron studies on routine screening.
4. A clinical triad (Andrews 1999):
   1. Glycosuria
   2. Cirrhosis
   3. Hyperpigmentation of the skin
5. Early manifestations:
   1. Often subtle
   2. Vague arthralgias
   3. Fatigue
   4. Lethargy

5. Apathy
6. Weight loss

6. Later manifestations as tissue iron progressively accumulates:
    1. Discoloration of the skin
    2. Hemochromatosis arthropathy (Husar-Memmer et al. 2014):
        1. A common feature of HH.
        2. Due to iron accumulation in joint tissues.
        3. Arthritis with joint swelling most commonly involves:
            1. Metacarpophalangeal (MCP) joints
            2. Proximal interphalangeal joints
            3. Knees
            4. Feet
            5. Wrists
            6. Back
            7. Hips
            8. Neck
        4. Chondrocalcinosis:
            1. Involves the knees and wrists
            2. May be asymptomatic
        5. Symptoms usually do not respond to iron removal.
    3. Liver involvement
        1. Abdominal pain associated with hepatomegaly
        2. Hepatomegaly, the most common physical abnormality
        3. Splenomegaly
        4. Cirrhosis
        5. Portal hypertension:
            1. Ascites
            2. Encephalopathy
        6. Hepatocellular carcinoma in about 30% of cases
    4. Cardiac involvement:
        1. Dilated cardiomyopathy
        2. Arrhythmias
        3. Cardiac failure
    5. Endocrine dysfunction in hereditary hemochromatosis (Pelusi et al. 2016):
        1. Diabetes mellitus
        2. Pituitary hypogonadism:
            1. Decreased libido and impotence (testicular atrophy) in men
            2. Amenorrhea in women
        3. Hypopituitarism or other tropin defects
        4. Thyroid dysfunction
        5. Adrenal dysfunction
        6. Parathyroid defects and osteoporosis

7. Suspect diagnosis from characteristic clinical manifestations:
    1. Classical clinical triad of "bronzed cirrhosis with diabetes" in a middle-aged man:
        1. Diffuse hyperpigmentation (melanoderma), often with a metallic gray or "bronze" rather than a brown discoloration
        2. Hepatomegaly, with the liver markedly enlarged, firm, and sharp to palpation but without signs of hepatocellular insufficiency (no palmar erythema, no spider nevi, no bruises, normal prothrombin time) or of portal hypertension
        3. Diabetes mellitus, often requiring insulin
    2. Presence of cardiomyopathy
    3. Diagnosis at this late stage: considered a diagnostic failure
8. Suspect diagnosis from earlier signs and symptoms:
    1. Sex and age: Both young adults and older women are at risk.
    2. "Rule of three A's":
        1. Asthenia: unexplained chronic fatigue
        2. Arthralgia:
            1. A "painful" handshake: resulting from chronic arthritis of the second and third MCP joints.
            2. Other joints affected especially the knees and wrists.
            3. Can also suffer from pseudogout (pyrophosphate arthropathy).
            4. Arthritis greatly diminishes the quality of life.
        3. Aminotransferase (transaminases) elevation
9. Prognosis of hemochromatosis and most of its complications, including liver cancer, depend on the amount and duration of iron excess (Phatak and Cappuccio 1994; Niederau et al. 1996). Early diagnosis and

therapy largely prevent the adverse consequences of iron overload.

10. Cause of death (Niederau et al. 1985):
    1. Liver failure
    2. Cancer
    3. Congestive heart failure
    4. Arrhythmia
11. Different types of hereditary hemochromatosis (Camaschella and Piperno 1997; Harrison and Bacon 2003; Pietrangelo 2006, 2010; Barton 2013; Bardou-Jacquet and Brissot 2014; Ekanayake et al. 2015; Yun and Vincelette 2015):
    1. Type 1 (*HFE*-related) hereditary hemochromatosis: classic form of hereditary hemochromatosis:
        1. An autosomal recessive disorder with 2–28% penetrance
        2. Common loci:
            1. Caucasian: C282Y, S65C
            2. Worldwide: H63D, IVS5 + 1, G > A
        3. Prevalence:
            1. Most common form worldwide
            2. Varies by race
    2. Type 2 (*HJV*- and *HAMP*- related) hemochromatosis:
        1. An autosomal recessive disease
        2. Type 2A hemochromatosis: caused by mutations of hemojuvelin (*HJV* on 1q21) gene
        3. Type 2B hemochromatosis: caused by mutations of the hepcidin (*HAMP*, on 19q13) gene
        4. Ethnicity: Caucasian or non-Caucasian
        5. Sex: male or female
        6. Onset: 15–20 years
        7. Clinical pictures:
            1. Cardiomegaly.
            2. Central endocrine involvement (hypogonadotropic hypogonadism): impotence, amenorrhea.
            3. Massive iron overload.
            4. Although liver fibrosis is frequent, cardiac and endocrine manifestations are predominant.
    3. Type 3 (*TFR2*-related) hemochromatosis
        1. An autosomal recessive disorder
        2. Caused by mutations in the transferrin receptor 2 (*TFR2*, on 7q22) gene (Joshi et al. 2015)
        3. Ethnicity: Caucasian or non-Caucasian
        4. Sex: male or female
        5. Onset: 30–40 years
        6. Clinical picture:
            1. Cardiomyopathy
            2. Endocrinopathy
            3. Liver disease
            4. Arthropathy: not uncommon
            5. Massive iron overload
            6. Elevated transferrin saturation (TS) and serum ferritin (SF)
    4. Type 4 hemochromatosis (ferroportin disease)
        1. An autosomal dominant disease
        2. Caused by mutations of the ferroportin (*SLC40A1*, on 2q32) gene
        3. More frequent than type 2 or type 3
        4. Type 4A ferroportin disease: caused by loss of the iron export function
        5. Type 4B ferroportin disease (rarer): caused by resistance of ferroportin to hepcidin activity, resulting in an unregulated cellular iron egress
        6. Ethnicity: Caucasian or non-Caucasian
        7. Sex: male or female
        8. Onset: 10–80 years
        9. One patient with unexplained hyperferritinemia
        10. Unexplained elevation of SF and normal TS
12. Other rare iron overload diseases:
    1. Iron-loading anemias (ineffective erythropoiesis, increased iron absorption, blood transfusions):
        1. β-Thalassemia
        2. Congenital dyserythropoietic anemias
        3. Sideroblastic anemia
        4. Pyridoxine-responsive anemia

2. Hypoplastic anemias (blood transfusions):
   1. Aplastic anemia
   2. Myelodysplastic syndromes
   3. Pure red cell aplasia
3. Chronic hemolytic anemias (increased iron absorption):
   1. Spherocytosis
   2. Sickle cell anemia
   3. Pyruvate kinase deficiency
4. Parental iron overload:
   1. Red blood cell transfusion
   2. Iron dextran injections
   3. Long-term hemolysis
5. Ceruloplasmin deficiency (aceruloplasminemia) (decreased ferroxidase activity)
6. A(hypo)transferrinemia: transferrin (Tf/3q21)
7. Sub-Saharan iron overload (increased dietary iron, increased iron absorption)
8. Porphyria cutanea tarda (increased iron absorption)
9. Hepatic disorders:
   1. Chronic viral hepatitis
   2. Alcoholic cirrhosis
   3. Portacaval shunts (increased iron absorption)

Diagnostic Investigations

1. Biochemical testing (Ramrakhiani and Bacon 1998):
   1. The first step in the diagnostic evaluation for hereditary hemochromatosis (HH): involves measurement of fasting transferrin saturation (TS) and serum ferritin levels. These studies are abnormal (high serum ferritin levels) in symptomatic patients.
   2. If the patient being evaluated is young, the iron studies may be normal, even in those who are homozygous for the genetic defect. This relates to the amount of time it takes for patients with the genetic defect and associated increased intestinal iron absorption to develop significant degrees of iron loading.
   3. Thus, as many as 30% of women with HH younger than 30 years of age may not have an elevated TS (Edwards et al. 1988).
   4. Alternatively, serum iron studies (predominantly ferritin) can be abnormal in about 40–50% of patients with chronic viral hepatitis, nonalcoholic steatohepatitis, and alcoholic liver disease, in the absence of HH (Bacon 1997).
   5. Additionally, other inflammatory disorders (e.g., rheumatoid arthritis) and various neoplastic disorders can cause elevated serum ferritin levels. Therefore, TS and serum ferritin levels by themselves cannot be relied on to make a diagnosis of HH.
2. Radiographic features of hemochromatosis arthropathy:
   1. Hook-like osteophytes (MCP joints)
   2. Joint space narrowing
   3. Subchondral cysts
   4. Marginal erosions
   5. Chondrocalcinosis (frequent, wrist, knee; rare, MCP joints, ankle joints)
   6. Femoral head necrosis (rare)
3. MRI of the liver:
   1. The most promising noninvasive technique for identification of HHC. High hepatic iron content causes:
      1. A decrease in signal intensity of the liver
      2. A marked decrease in transverse (T2) relaxation time
   2. Role of magnetic resonance imaging T2 in the evaluation of iron overload early in hereditary hemochromatosis: excessive iron stores in the liver were detected in 39% of patients, showing that iron accumulation begins in the liver (Assis et al. 2015).
4. Liver biopsy to assess histologic hepatic iron stores (Morrison et al. 2003):
   1. Usually not indicated for diagnostic purposes in HFE-HHC.

2. Recommended to C282Y homozygotes with a serum ferritin concentration of >1,000 ng/mL to determine if cirrhosis is present; those with a serum ferritin concentration <1,000 ng/mL need not undergo biopsy.
3. Useful to determine hepatic iron overload, particularly in patients with presumed hemochromatosis who lack the common *HFE* mutations associated with HFE-HHC.

5. Elevated serum iron, transferrin saturation, and ferritin suggest HH, but results can also indicate other forms of hepatocyte injury such as alcoholic or viral hepatitis, or other inflammatory disorders involving the liver (Moyer et al. 2011). In the context of elevated serum iron, transferrin saturation, and ferritin, and after ruling out secondary causes of iron overload, *HFE* gene evaluation is the preferred test to confirm the diagnosis of HH. However, 5–15% of patients with phenotypic HH do not have *HFE* gene mutations. In these cases, MRI evaluation or liver biopsy with iron quantification is indicated.
6. Hormonal and metabolic tests (Pelusi et al. 2016):
   1. Glucose metabolism: glycemia, insulin, and glycated hemoglobin
   2. Pituitary gonadal axis: LH, FSH, testosterone (male), estradiol (female)
   3. Bone metabolism: PTH, serum calcium, phosphate, creatinine, alkaline phosphatase, 25-hydroxy vitamin D plus dual-energy X-ray absorptiometry
7. Molecular genetic testing (Brittenham et al. 2000; Seckington and Powell 2015):
   1. Mutation analysis for the disease-causing alleles in the *HFE* gene (C282Y and H63D):
      1. C282Y/C282Y homozygotes (60–90%)
      2. C282Y/H63D compound heterozygotes (3–8%)
      3. H63D/H63D homozygote (1%)
      4. H63D/? (4%)
      5. C282Y/? (1%)
      6. ?/? (6%)
   2. Testing strategy for a proband:
      1. Mutation analysis warranted in adults with serum transferrin-ion saturation of >45%
      2. Individuals with homozygous C282Y/C282Y or compound heterozygous C282Y/H63D: have genetic makeup to develop HFC-HHC
      3. Individuals who are not C282Y homozygotes:
         1. Generally represent a heterogeneous group.
         2. Many have liver disease unrelated to HFE-HHC or other metabolic syndromes.
         3. Some may have primary iron overload in a pattern identical to HFE-HHC.
         4. The next diagnostic step: perform liver biopsy with assessment of histology and measurement of hepatic iron concentration.
   3. Carrier detection: identification of carriers and noncarriers in at-risk family members is possible provided both *HFE* alleles have been identified in the proband.
   4. Whole-exome sequencing offered complete coverage of target genes and is a fast, cost-effective diagnostic tool for characterization of non-HFE hemochromatosis (Farrell et al. 2015).
8. Screening for HHC (Phatak et al. 1994):
   1. HHC: a prime target for screening because of its high prevalence, morbidity, and mortality, as well as the benefits of early diagnosis and treatment.
   2. Initial screening probe for HHC diagnosis:
      1. Transferrin saturation
      2. Unsaturated iron-binding capacity
   3. Elevation of serum ferritin is common, particularly in Asians, Pacific Islanders, and Africans (Mclaren and Gordeuk 2009).
   4. Generalized population screening is not recommended (Hanson et al. 2001).
   5. The incomplete penetrance of disease means diagnosis cannot be purely based on genetic screening. As such, currently diagnosis relies on a combination of

imaging, biochemical iron, and genetic studies (Ekanayake et al. 2015).

9. Diagnostic workup of neonatal hemochromatosis (Heissat et al. 2015):
    1. In unexplained fetal death or neonatal liver failure, the diagnosis of subsets of NH requires tissue analysis (autopsy) to assess extrahepatic siderosis.
    2. In patients with NH, if mitochondrial respiratory chain disorder is ruled out, NH-GALD is likely.

Genetic Counseling

1. Recurrence risk (Seckington and Powell 2015):
    1. Patient's sib:
        1. Twenty-five percent if both parents are HFE-HHC heterozygotes
        2. Fifty percent if one parent is HFE-HHC heterozygotes and other parent HFE-HHC homozygote
    2. Patient's offspring – 5% risk to be affected due to the high carrier rate for *HFE* mutant alleles in the general population:
        1. The risk that the partner of an individual with HFE-HHC is heterozygous for the C282Y allele is 1/9.
        2. Therefore, the risk to the offspring to be a homozygote for C282Y allele is $1/2 \times 1/9 = 1/18$ (about 5%).
2. Prenatal diagnosis (Seckington and Powell 2015):
    1. Prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing.
    2. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the HFE pathogenic variants have been identified.
3. Management (Phatak and Cappuccio 1994; Tavill 2001; Seckington and Powell 2015):
    1. Early diagnosis and treatment:
        1. Can completely prevent the development of clinical complications
        2. Offer patients a normal life expectancy
    2. Treatment of iron overload:
        1. Periodic phlebotomy:
            1. Goal of therapy: to achieve and maintain a serum ferritin concentration of $\leq$50 ng/mL.
            2. Usual therapy: removal of the excess iron by weekly phlebotomy until the serum ferritin concentration is $\leq$50 ng/mL.
            3. Treatment with weekly phlebotomy frequently results in some clinical improvement in patients with established disease, and if initiated early, organ damage can be prevented and a normal life-span can be expected (Nichols and Bacon 1989).
        2. Dietary management:
            1. Avoid medicinal iron.
            2. Avoid mineral supplements.
            3. Avoid excess vitamin C which increases intestinal absorption of inorganic iron.
            4. Avoid uncooked shellfish or other seafood which can be contaminated with *V. vulnificus* causing sepsis in patients with HHC.
            5. Avoid alcohol consumption for patients with liver involvement.
        3. Iron chelation therapy: not recommended unless the patient has an elevated serum ferritin concentration and concomitant anemia that makes therapeutic phlebotomy impossible
    3. Postnatal treatment, previously based on the use of antioxidants and chelation therapy, has now successfully been replaced by exchange transfusions and intravenous immunoglobulin substitution (Lopriore et al. 2013).
    4. Conventional therapies for diabetes, hepatic failure, and cardiac failure.
    5. Cirrhosis: screen for hepatocellular cancer:
        1. Biannual abdominal ultrasound
        2. Annual serum alpha-fetoprotein testing

6. Orthotopic liver transplantation for end-stage liver disease from decompensated cirrhosis (Salgia and Brown 2015).
7. Surveillance of at-risk asymptomatic adults with C282Y homozygotes:
   1. Monitor serum ferritin concentrations yearly starting in early adulthood.
   2. Initiate therapeutic phlebotomy when serum ferritin concentrations are elevated.
8. Prevention of neonatal hemochromatosis (NH) (Feldman and Whitington 2013):
   1. Once a woman has delivered an infant with NH, the probability that the next pregnancy will be lethally affected is greater than 90% (Whitington and Kelly 2008).
   2. However, recurrence of severe NH can be prevented by treatment with intravenous immunoglobulin starting at 14 weeks' gestation (Lopriore et al. 2013; Whitington and Hibbard 2004).

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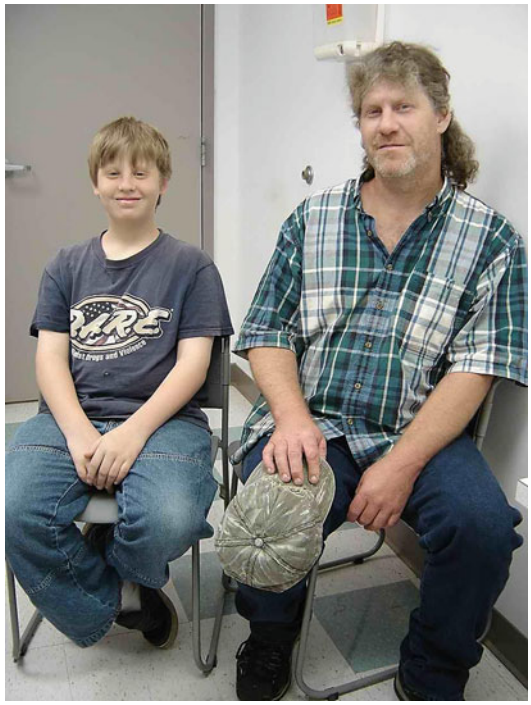

Fig. 1 Father (40-year-old) and son (12-year-old) both carry heterozygous C282Y mutation. H63D and S65C were not detected. The father currently receives periodic phlebotomy with fasting transferrin-iron saturation level of 56% (15–50) and ferritin level of 1,238 ng/mL (20–345). The son is currently asymptomatic. Approximately 3–5% of patients with hereditary hemochromatosis have this genotype. The molecular results do not rule out the possibility of disease-causing mutations in other regions of the *HFE* gene or in other as yet undefined genes

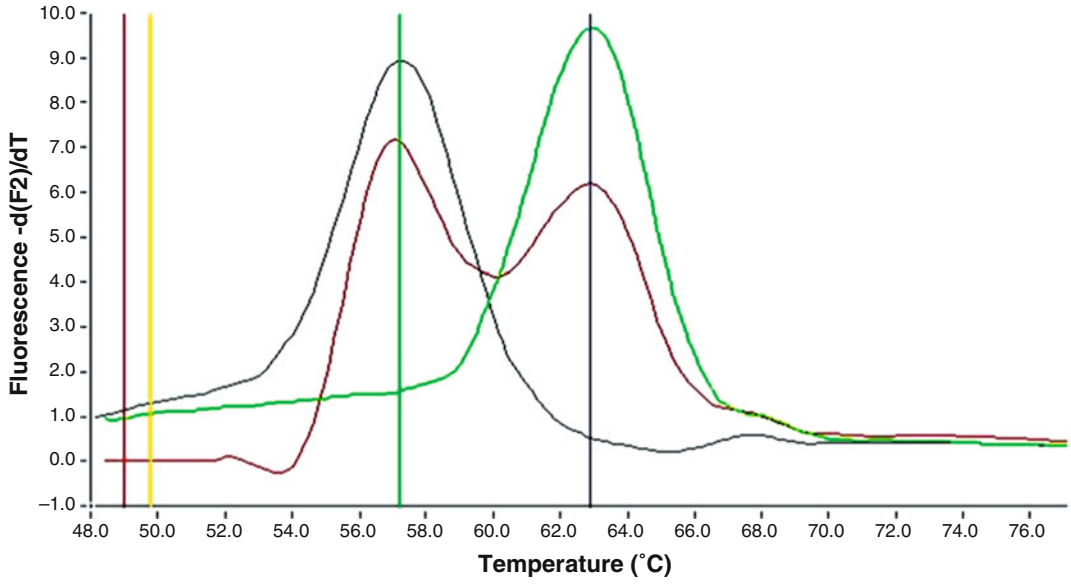

Fig. 2 Real-time PCR of HFE gene in another patient. The patient is homozygous for *C282Y* mutation, demonstrated by the *green line* (melting point (Tm) = 62.89)

Hereditary Multiple Exostoses

Contents

Hereditary multiple exostosis (HME) is a type of skeletal dysplasia characterized by osteochondral growths (osteochondromas) on the periphery of bones, comprised of the bone surrounded by a cap of the cartilage. The estimated prevalence is about 1 in 50,000 Caucasians (Schmale et al. 1994).

Synonyms and Related Disorders

Diaphysis aclasis; Hereditary multiple osteochondromas; Hereditary multiple osteochondromatosis; Multiple cartilaginous exostoses; Multiple hereditary exostoses; (Multiple hereditary) osteochondromatosis

Genetics/Basic Defects

1. Exostoses (Schmale et al. 1994):
    1. Result of dysplasia of the peripheral aspect of the growth plate.
    2. The most common type of benign bone tumors.
    3. Small exostoses may not be discovered because many do not cause symptoms.
    4. Multiple lesions develop in individuals who have a hereditary type.
2. Inheritance:
    1. Autosomal dominant with incomplete penetrance and expressivity skewing (Wicklund et al. 1995; Legeai-Mallet et al. 1997).
    2. About 90% of patients have an affected parent.
    3. About 10% of patients result from a de novo gene mutation.
3. Genetic heterogeneity (Hecht et al. 1997): linkage analysis identified the following three genes associated with hereditary multiple exostoses:
    1. *EXT1* gene:
        1. A ubiquitously expressed gene located on chromosome 8q24.1.
        2. Normal gene product: exostosin 1.
        3. Mutations in *EXT1* are responsible for about half of cases.
    2. *EXT2* gene:
        1. A ubiquitously expressed gene located on chromosome 11p11-p12.
        2. Normal gene product: exostosin 2.
        3. Mutations in *EXT2* are responsible for about one third of cases.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_117

3. *EXT3* gene:
    1. A gene located on chromosome 19p (Le Merrer et al. 1994).
    2. Mutations in *EXT3* are implicated in a minority of cases.
4. These three genotypes may result in different phenotypic expressions of HME and thus explain the variable manifestations of the disease (Carroll et al. 1999).
5. Loss of heterozygosity in the *EXT1* or *EXT2* implicated in causing osteochondromas, which are the most common bone tumors in children, characterized by cartilage-capped, bony excrescences (exostoses) arising from the metaphyseal ends of rapidly growing long bones (Bovée et al. 1996).
6. Deletion of *EXT1* gene and adjacent *TRPS1* gene (a gene located on chromosome 8 proximal to the *EXT1* gene) resulting in Langer-Giedion syndrome (trichorhinophalangeal syndrome, type II) in which multiple exostoses are distinguishing features.
7. EXT genes:
    1. Encode glycosyltransferases.
    2. Catalyze heparin sulfate polymerization.
8. Genotype-phenotype correlations (Pannier and Legeai-Mallet 2008):
    1. More severe disease in individuals with *EXT1* mutations than *EXT2* mutations on the basis of short stature, skeletal deformity (shortened forearm or bowing, knee deformity) and function (elbow, forearm, and knee range of motion) (Francannet et al. 2001; Porter et al. 2004).
    2. The risk of chondrosarcoma may also be higher in individuals with an *EXT1* mutation than in those with an *EXT2* mutation, but *EXT1* mutations are responsible for most cases of HME.

Clinical Features

1. Exostoses (cartilage-capped bony growths):
    1. Bony swellings (bumps) near the growing ends of the long bones: initially painless but later the majority of patients experience pain
    2. Onset during childhood (often asymptomatic)
    3. Sites (Hennekam 1991):
        1. Humerus
        2. Distal end of the femur
        3. Proximal end of the tibia and fibula
        4. Distal ends of the radius
        5. Ribs
        6. Scapula
        7. Ilium
    4. Types:
        1. Pedunculated with a narrow pedicle
        2. Sessile with a broad pedicle
    5. Size and number:
        1. Grow in size and gradually ossify during skeletal development
        2. Ceases with skeletal maturity (when the growth plates close at puberty) after which no new exostoses develop
2. Bowing:
    1. Often occurs without exostoses
    2. Bowing of forearms: ulnar deviation of the wrist secondary to a bowing of the radius and shortening of the ulna
    3. Bowing of lower legs
3. Genu valgum
4. Deformities observed in children (Ham 2013):
    1. Most common deformities:
        1. Disproportionate short stature (40%)
        2. Limb length discrepancies (Gross 1978)
        3. Valgus deformities of the knee and ankle
        4. Asymmetry of the pectoral and pelvic girdles
        5. Bowing of the radius with ulnar subluxation of the carpus
        6. Subluxation of the radial head
        7. Relative shortening of the metatarsals, metacarpals, and phalanges
    2. Less common deformities:
        1. Scoliosis
        2. Coxa valga (Wang et al. 2015)
        3. Acetabular dysplasia
5. Prognosis and complications (Ham 2013):
    1. Normal life span.
    2. Normal intelligence.

3. Cosmetic concern (one of the most common clinical complaints).
4. Mechanical restriction of adjacent joint movements.
5. Adventitious bursa with bursitis.
6. Compression or displacement of the adjacent nerves (22%):
    1. Pain (one of the most common clinical complaints)
    2. Sensory or motor deficits
7. Compression or displacement of the adjacent vessels (11%).
8. Spontaneous hemothorax as a result of rib exostoses (rare) (Castells et al. 1993).
9. Urinary or intestinal obstruction resulting from large pelvic exostoses (rare).
10. Compression of the spinal cord:
    1. Very rare occurrence
    2. Extremely serious complication
11. Slipping of the adjacent tendons.
12. Scapular winging.
13. Fractures at the pedicle.
14. Spinal cord compression.
15. Obstetric problems: complications can occur during delivery due to the aberrant morphology of the pelvis or the presence of osteochondromas on the interior pelvis.
16. Psychosocial problems.
17. Malignant transformation of osteochondroma to osteochondrosarcoma (0.5–5%), the most important complication:
    1. Rapid growth: rare occurrence of a giant costal chondrosarcoma (Acharya et al. 2014; Liu et al. 2013)
    2. Increasing pain
    3. A bulky cartilage cap
18. Morphological classification (based on X-ray and CT images) and malignant transformation (Fan et al. 2014):
    1. Cauliflower-like tumors: exostotic chondrosarcomas were more common in cauliflower-like tumors.
    2. Non-cauliflower-like tumor (pedunculated type, sessile type): benign exostoses were more common in non-cauliflower-like tumors.

6. Differential diagnosis (Pannier and Legeai-Mallet 2008; Kwee et al. 2016):
    1. Metachondromatosis (Kennedy 1983; Bassett and Cowell 1985; Fisher et al. 2013):
        1. An autosomal-dominant disorder, caused by loss of function of the *PTPN11* gene.
        2. Lesions typically occur in hands, feet, femora, tibiae, and the pelvis.
        3. A rare disorder exhibiting, synchronously, both multiple osteochondromas and enchondromas in children.
        4. In contrast to HME, the exostoses of metachondromatosis point toward the joints and frequently regress spontaneously.
        5. Exostoses do not result in the shortening of affected long bones or produce bowing, joint deformity, or subluxation as seen in HME.
    2. Langer-Giedion syndrome:
        1. A contiguous gene deletion syndrome involving *EXT1* and *TRPS1* genes (trichorhinophalangeal syndrome I).
        2. Affected individuals have exostoses, intellectual disability, craniofacial abnormalities (laterally protruding ears, broad nasal bridge and bulbous nose, sparse hair), and digital anomalies (cone-shaped epiphyses).
    3. 11p11.2 deletion syndrome (formerly known as Potocki-Shaffer syndrome) (Wu et al. 2000):
        1. A contiguous gene deletion syndrome involving *EXT2* and *ALX4* (homeobox) genes.
        2. Affected patients have multiple exostoses, an ossification defect of the skull (enlarged parietal foramina), craniofacial dysostosis, and intellectual disability.
    4. Enchondromatosis (Ollier disease) (please see the chapter of "► Enchondromatosis"):
        1. Enchondromas:
            1. Common benign cartilage tumors of the bone

2. Can occur as solitary lesions or as multiple lesions in enchondromatosis, often with unilateral predominance
2. Usually a nonhereditary disorder.
3. The association of hemangiomas is referred to as "Maffucci syndrome."
4. Risk of malignant transformation into chondrosarcomas (20–50%).

5. Dysplasia epiphysealis hemimelica (Trevor disease, tarso-epiphyseal aclasis) (Bovée 2008) (please see the chapter of "► Dysplasia Epiphysealis Hemimelica"):
   1. Cartilaginous overgrowth of a portion of one or more epiphyses
   2. Usually restricted to either medial (most frequent) or lateral side of the limb (hemimelic)
   3. Predominantly affects the lower extremity on one side of the body

Diagnostic Investigations

1. Radiographic features:
   1. Pedunculated or sessile exostoses pointing away from the joint.
   2. The cortex of exostoses continuous with that of the underlying bone.
   3. Exostoses originated in the metaphysis in the long bones and migrate to the diaphysis as growth continues in the epiphysis.
   4. Cartilaginous cap:
      1. Usually radiolucent
      2. The appearance of irregular zones of calcification after puberty
      3. Extensive calcification with irregularities of the cap suggesting the possibility of malignant change
   5. Exostoses prevent normal bone tabulation resulting in metaphyseal widening and growth retardation.
   6. Broad and barrel-shaped metaphyses without normal remodeling.
   7. Wrist:
      1. Shortening of the ulna
      2. Bowing of the radius with subluxations of the inferior radioulnar joint
2. CT and MRI imagings: evaluate spinal cord compression from an osteochondroma (Roach et al. 2009):
   1. The presence of a risk of having a lesion within the spinal canal
   2. Potential occurrence of serious neurologic injury
3. Multidetector CT evaluation (Kwee et al. 2016):
   1. Assessment of emergent complications of HME:
      1. Spinal cord compression
      2. Pneumothorax and hematothorax
      3. Pseudoaneurysms
      4. Fractures
   2. Assessment of non-emergent complications of HME:
      1. Growth disturbances
      2. Chondrosarcoma transformation
      3. Muscular and peripheral nerve involvement
4. MRI imaging: always be the first imaging method due to the absence of radiation and better display of the cartilaginous cap and the relation with the surrounding soft issues (Kwee et al. 2016).
5. Serial technetium bone scans: increased radionucleotide uptake suggests malignancy (Lange et al. 1984; Bouvier et al. 1986).
6. Histology of exostosis:
   1. Core: cancellous bone
   2. Surrounding: cortical bone
   3. Apex: covered with a cap of hyaline cartilage
7. DNA analysis of mutations in the *EXT1*, *EXT2*, and *EXT3* genes available clinically for *EXT1* and *EXT2*:
   1. FISH on metaphase cells.
   2. Genomic microarray analysis.
   3. Screening of the entire coding region.
   4. A combination of sequence analysis and deletion analysis of the entire coding regions of both *EXT1* and *EXT2* detects mutations in 70–95% of affected individuals (Schmale et al. 2013).

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib:
      1. Usually with 50% risk of inheriting the gene alteration, since most probands (about 90%) have a parent with the altered gene and 95% risk of manifesting symptoms (penetrance)
      2. Low risk if both parents are normal
   2. Patient's offspring: 50% risk of inheriting the mutant allele
2. Prenatal diagnosis: available clinically for pregnancies at risk:
   1. Molecular genetic analysis on fetal DNA obtained from amniocentesis or CVS for *EXT1* or *EXT2* mutation, provided the disease-causing allele of an affected family member has been identified prior to prenatal diagnosis
   2. Preimplantation diagnosis using embryonic cells available to couples at 50% risk of having a child with hereditary multiple exostosis, provided the disease-causing mutation of the *EXT1* or *EXT2* gene has been identified in the affected parent
3. Management (Bovée et al. 1996):
   1. Exostoses without clinical problems required no therapy.
   2. Surgical intervention of exostoses:
      1. Indications for surgical excision of exostoses (Peterson 1989):
         1. Painful lesion without bony deformity
         2. Pain due to irritation of the skin, tendons, or nerves
         3. Slowing growth disturbance
         4. Compromise joint motion
         5. Secondary impingement of the tendon, nerve, or vessel
      2. Angular deformities
      3. Improving cosmesis
      4. Either epiphysiodesis of the longer leg or lengthening of the involved leg for leg length discrepancy greater than one inch
      5. Excision of the exostoses and corrective osteotomies for forearm deformity (pain and stiffness of the elbow and wrist are a common cause of disability) (Fogel et al. 1984; Wood et al. 1985; Arms et al. 1997)
   3. Sarcomatous degeneration:
      1. Surgical resection
      2. Adjuvant radiotherapy and chemotherapy for secondary osteosarcoma

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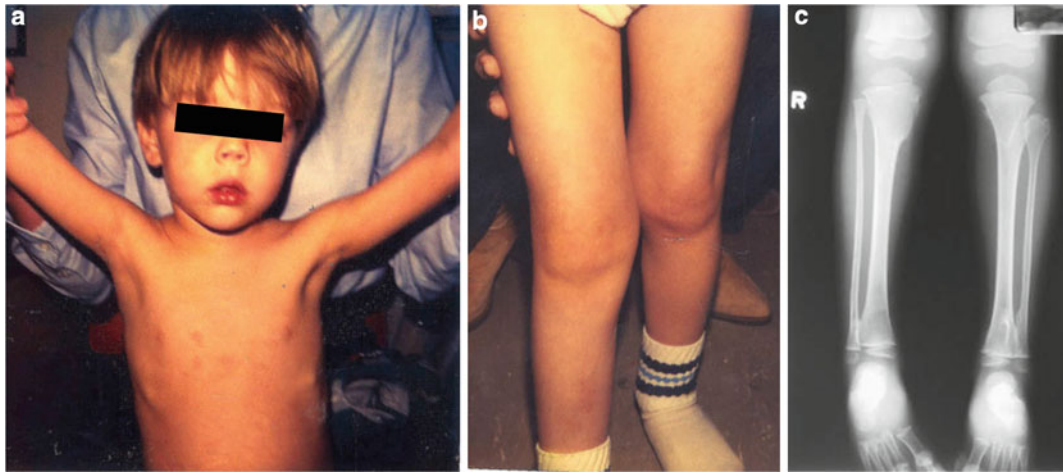

Fig. 1 (**a**–**c**) A boy with hereditary multiple exostoses showing bony growths on both sides of the ribs (**a**) and the lower legs (**b**), illustrated by the radiograph (**c**)

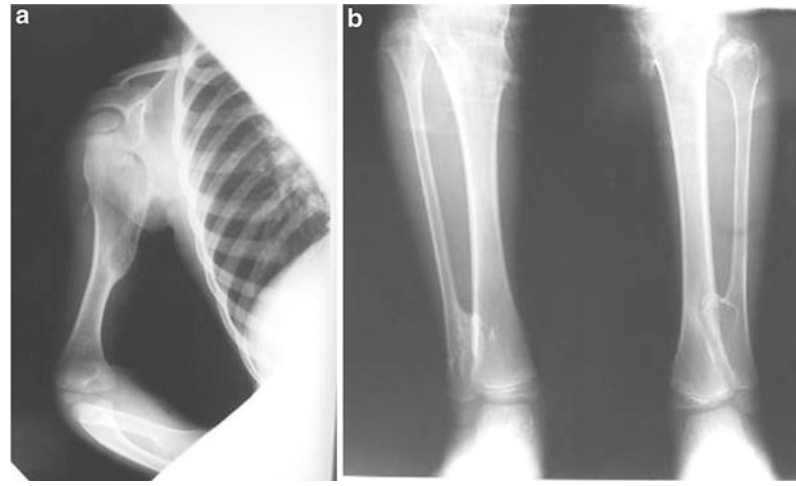

Fig. 2 (**a**, **b**) Radiographs of a 5-year-old boy with hereditary multiple exostoses showing multiple exostoses of the humerus (**a**), radius, tibia, and fibula (**b**)

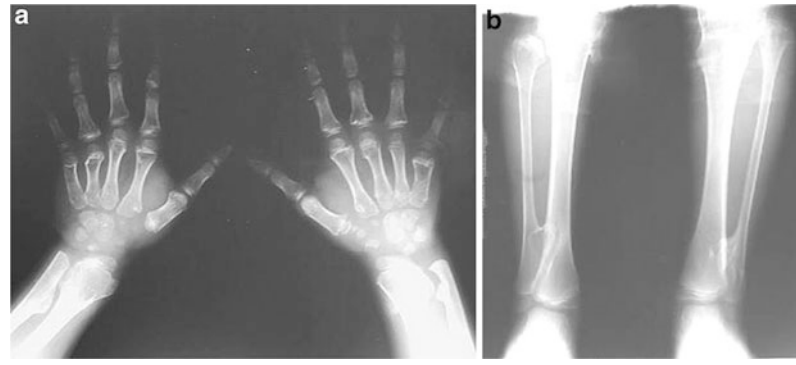

Fig. 3 (**a**, **b**) A 7-year-old boy with hereditary multiple exostoses showing more severe degree of multiple exostoses of the humerus, radius (**a**), tibia, and fibula (**b**)

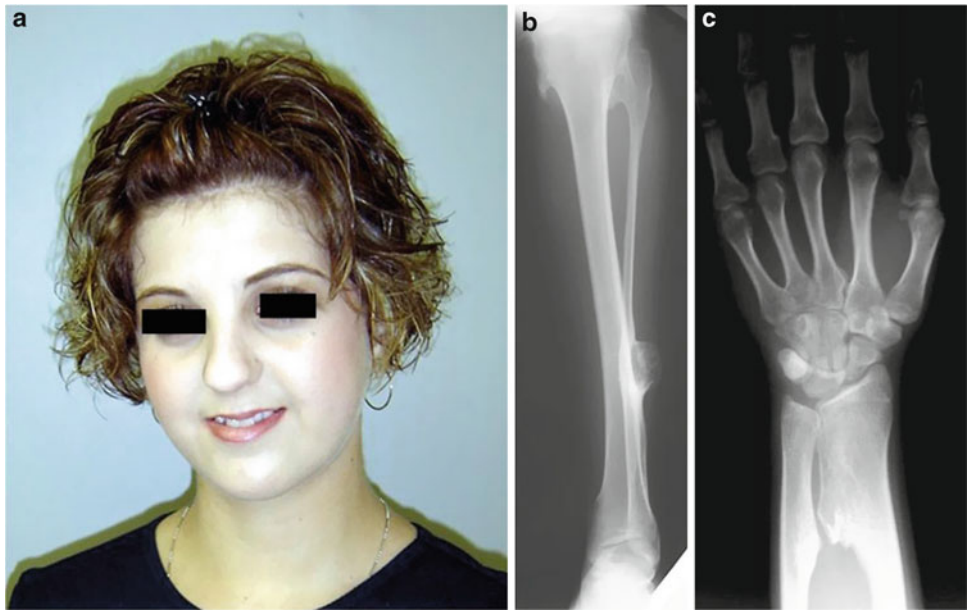

Fig. 4 (**a**–**c**) A 20-year-old female (**a**) with hereditary multiple exostoses showing pedunculated exostosis on the left proximal tibia and fibula, exostosis on the shaft of the left fibula (**b**), and exostoses on the distal radius and ulna (**c**). She was discovered to have multiple exostoses since 1 year of age and has had multiple surgeries to remove multiple tumors from the right femur, left tibia, and left fibula. Currently, she has bumps on the right distal femur, right proximal fibula, right distal tibia, left distal fibula, left distal forearm, right distal phalange of the right fifth finger, and left second toe. Her father is also affected

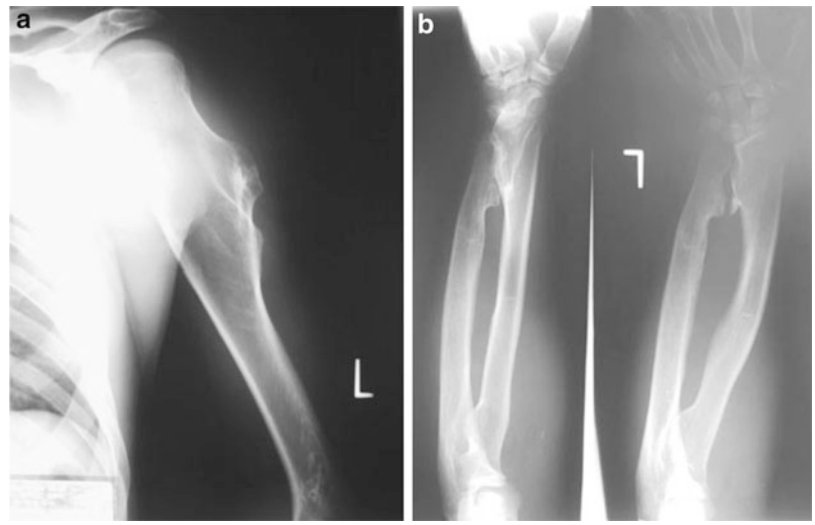

Fig. 5 (**a**, **b**) A 27-year-old male with hereditary multiple exostoses showing exostoses (**a, b**), ulnar shortening, and ulnar carpal drift (**b**)

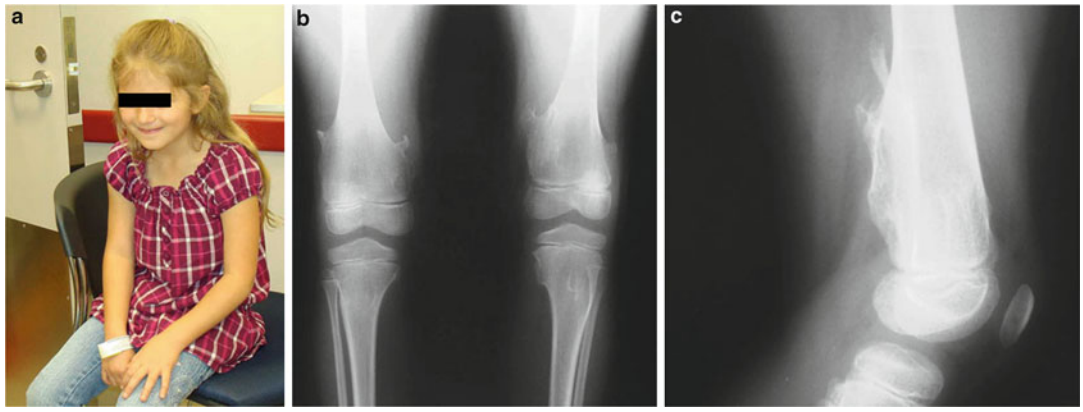

Fig. 6 (**a**–**c**) A 9-year-old girl (**a**) with hereditary multiple exostoses showing typical radiographic features of both distal femurs (**b**)

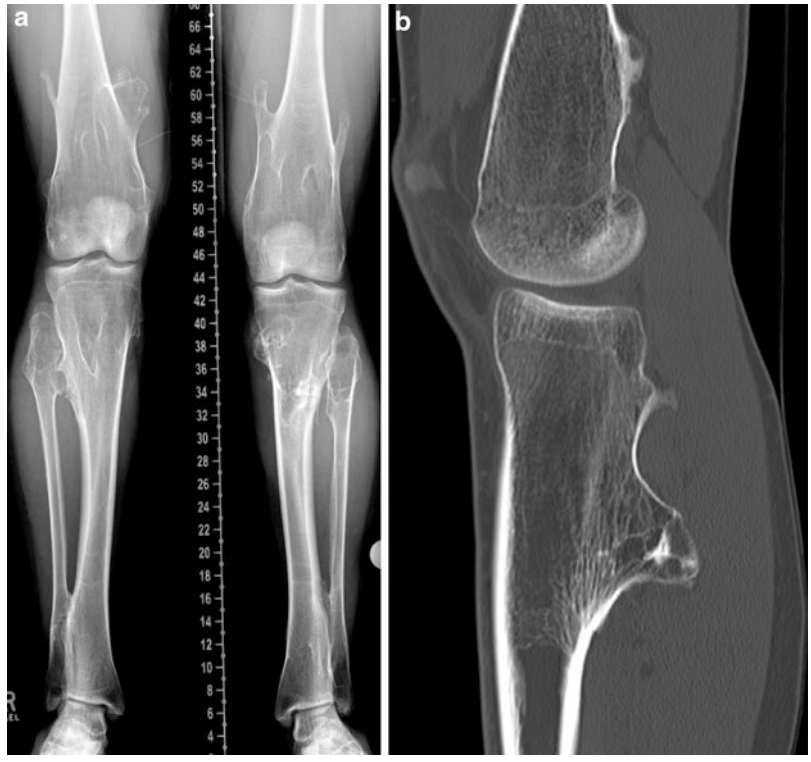

Fig. 7 (**a**, **b**) An 18-year-old male who was diagnosed to have hereditary multiple exostoses at age 3. The mother had a history of bone spur removal at age 11 from the left lower leg. The radiography (**a**) and CT images (**b**) demonstrate multiple exostoses projecting off the proximal (not shown) and distal femora, tibiae, and fibulae. Length discrepancy between the bilateral lower extremities is seen (Courtesy of Dr. Grace Guo)

Hereditary Sensory and Autonomic Neuropathies

Contents

Congenital indifference to pain has been reported since early 1930s (Dearborn 1932; Ford and Wilkins 1938; Boyd and Nie 1949; Winkelmann et al. 1962). Children with underlying peripheral neuropathies have impairment in both the sensory-discriminative and affective-motivational components of pain perception. The majority of them have a type of hereditary sensory and autonomic neuropathy (HSAN). These disorders are characterized by loss of pain sensation and other sensory or autonomic abnormalities (Dyck et al. 1983; Thomas 1993). At present, five types of HSAN have been identified (Axelrod and Hilz 2003; Nagasako et al. 2003; Butler et al. 2006).

Synonyms and Related Disorders

Congenital absence of pain; Congenital general pure analgesia; Congenital insensitivity to pain; Congenital insensitivity to pain with anhidrosis; Congenital pain insensitivity syndrome; Congenital universal indifference to pain; Congenital universal insensitiveness to pain; Hereditary sensory neuropathy type IA (HSN IA); Hereditary sensory radicular neuropathy; HSAN; Inherited autonomic neuropathies; Morvan disease; Riley-Day syndrome (familial dysautonomia)

Genetics/Basic Defects

1. HSAN type 1 (HSAN1)
   1. Inheritance pattern: autosomal dominant
   2. Genetic abnormality: Mutation in *SPTLC1* (serine palmitoyltransferase) gene at locus 9q22.1-q22.3
2. HSAN type 2 (HSAN2)
   1. Inheritance pattern: autosomal recessive
   2. Genetic abnormality: Mutation in *HSN2* (hereditary sensory neuropathy type 2) gene at locus 12p13.33
3. HSAN type 3 (HSAN3)
   1. Inheritance pattern: autosomal recessive
   2. Genetic abnormality: mutation in *IKBKAP* (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein) gene at locus 9q31
4. HSAN type 4 (HSAN4)
   1. Inheritance pattern: autosomal recessive
   2. Genetic abnormality: mutation in *NTRK1* (neurotrophic tyrosine kinase receptor type 1) gene at locus 1q21-q22

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_261

5. HSAN type 5 (HSAN5)
    1. Inheritance pattern: autosomal recessive
    2. Genetic abnormality: mutation in *NGFB* (nerve growth factor B) gene at locus 1p13.2-p11.2 (Capsoni 2014)
6. Unclassified

Clinical Features

1. HSAN type 1 (hereditary sensory radicular neuropathy)
    1. Late onset (second to fourth decade)
    2. Progressive distal sensory loss (pain and thermal sensation)
    3. Loss of distal reflexes/distal muscle wasting
    4. Numbness or distal pain predominantly affecting the distal lower extremities
    5. Intermittent lancinating pains occurring in some kinships
    6. Usually no autonomic dysfunction
    7. Intelligence may be mildly impaired
    8. Hearing loss (deafness)
    9. Ataxic gait
    10. Severe ulceration of extremities
    11. Painless injuries
    12. Stress fractures
    13. Osteomyelities
2. HSAN type 2 (Morvan disease)
    1. Onset in early infancy
    2. A rare disorder
    3. Nonprogressive
    4. Global distal sensory loss/minimal weakness (hypotonia)
    5. Delayed milestones
    6. Self-mutilation
    7. Usually no autonomic dysfunction
3. HSAN type 3 (Riley-Day syndrome; familial dysautonomia)
    1. Onset at birth
    2. Progressive
    3. Ashkenazi Jewish disease
    4. Earliest signs
        1. Feeding difficulties due to poor oral coordination
        2. Hypotonia
        3. Frequent gastroesophageal reflux leading to aspiration
    5. Profound autonomic dysfunction
        1. Absence of tears (alacrima) with emotional crying: one of the cardinal features of the disorder.
        2. Protracted episodes of nausea and vomiting triggered by emotional or physical stress and even arousal from sleep. These episodes, termed the "dysautonomic crisis," are usually associated with a constellation of signs including agitation, tachycardia, and hypertension.
        3. Vasomotor and cardiovascular perturbations manifest as erythematous skin blotching and hyperhydrosis with excitation or even eating.
    6. Loss of pain and thermal sensation
    7. Absent deep tendon reflexes
    8. Absent fungiform papillae on the tongue
    9. Normal sweat response
4. HSAN type 4 (congenital insensitivity to pain with anhidrosis)
    1. Onset in infancy
    2. Commonest HSAN
    3. Profound insensitivity to pain
    4. Decreased or absent thermal sensation
    5. Deep tendon reflexes usually intact
    6. Absent or markedly decreased sweating (anhidrosis): cardinal feature
    7. Episodic fever and extreme hyperpyrexia: usually the earliest sign of the disorder
    8. Severe learning disability
    9. Self-mutilation
    10. Auto-amputation
    11. Osteomyelitis
    12. Corneal scarring
5. HSAN type 5 (congenital insensitivity to pain)
    1. Onset in infancy
    2. Only a few cases described in the literature
    3. Profound insensitivity to pain
    4. Painless burns (Aguayo et al. 1971)
    5. Finger and toe mutilations (Van Epps and Kerr 1940)
    6. Tactile, vibratory, and thermal sensation usually intact
    7. Deep tendon reflexes intact

8. Usually no autonomic dysfunction
9. Intelligence may be mildly impaired
10. Hearing loss (deafness)
11. Severe ulceration of extremities
12. Joint injuries (Swanson 1963)
13. Painless injuries/fractures

Diagnostic Investigations

1. Radiological studies
   1. Radiographic features (Zhang and Haga 2014)
      1. Fractures
      2. Joint dislocations
      3. Osteomyelitis/arthritis
      4. Charcot joints
   2. Magnetic resonance imagings: useful when bone infections or necrosis are suspected (Auer-Grumbach 2008)
2. Peripheral nerve abnormality
   1. HSAN type 1
      1. Severe loss of small myelinated and unmyelinated fibers
      2. Moderate loss of large unmyelinated fibers
   2. HSAN type 2
      1. Severe loss of myelinated fibers
      2. Some loss of unmyelinated fibers
   3. HSAN type 3
      1. Total absence of large diameter myelinated neurons
      2. Severe loss of unmyelinated fibers
   4. HSAN type 4
      1. Virtual absence of unmyelinated fibers
      2. Reduction of small myelinated fibers
   5. HSAN type 5
      1. Severe reduction of unmyelinated fibers
      2. May be moderate loss of thin myelinated fibers
3. Molecular genetic studies
   1. HSAN 1
      1. Sequence analysis of *SPTLC1* for HSAN 1A
      2. Sequence analysis of *SPTLC2* for HSAN 1C
   2. HSAN 2
      1. *WNK1* (type HSAN 2A)
      2. *FAM134B* (type HSAN 2B)
      3. *KIF1A* (type HSAN 2C)
   3. HSAN 3: target mutation analysis and sequence analysis of *IKBKAP*
   4. HSAN 4: sequence analysis of *CIPA*
   5. HSAN 5: sequence analysis of *NGF*

Genetic Counseling

1. Recurrence risk.
   1. Patient's sib
      1. Autosomal recessive: 25%
      2. Autosomal dominant: not increased unless one of the parents is affected
   2. Patient's offspring:
      1. Autosomal recessive: recurrence risk not increased unless the spouse is a carrier or affected
      2. Autosomal dominant: a 50% risk
2. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15–18 weeks of gestation or chorionic villus sampling at approximately 10–12 weeks of gestation. Both disease-causing alleles (autosomal recessive) must be identified in the family before prenatal testing can be performed.
3. Preimplantation genetic diagnosis may be an option for some families in which the disease-causing mutations have been identified.
4. Management.
   1. Symptomatic management for feeding problems, GE reflux, aspiration pneumonia, hypertension, orthostatic hypotension, and corneal ulcerations
   2. Treatment of self-injurious behavior (Kuhn et al. 2008)
      1. Pharmacological interventions: little evidence in support of the efficacy
         (a) Anticonvulsants
         (b) Antipsychotics
      2. Behavior intervention (a simplified habit reversal treatment)
   3. Training in the care of the sensory-impaired limb: important

1. Self-examination especially of the feet for any signs of trauma
2. Prevent callous formation in neuropathic skin
3. Cleaning and protection of wounds on neuropathic limbs in combination with antiseptic treatment to eradicate infections help prevent osteomyelitis and amputations
4. Administration of bisphosphonates and vitamin D: beneficial to painless fracture in HSAN 1 (Marik et al. 2012)

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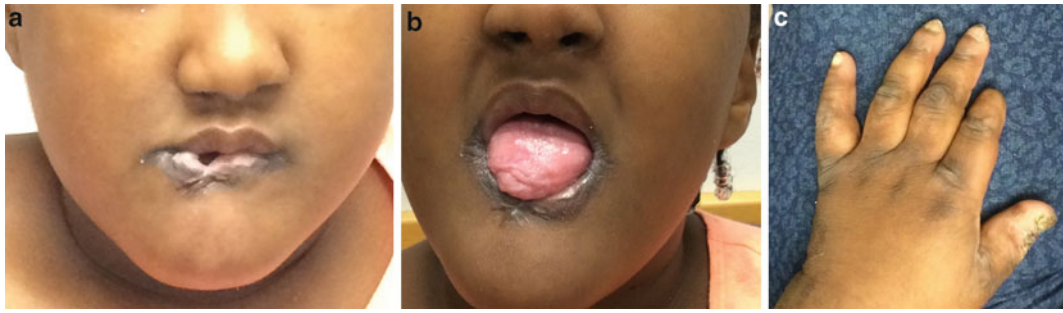

Fig. 1 (**a**–**c**) The patient is a 7-year-old African American girl who was followed for congenital insensitivity to pain, developmental delay, hypotonia, mild to moderate sensorineural hearing loss, strabismus, and myopia. She perspires. She had significant damages to her hands, feet, and face because of her insensitivity to pain. Past history showed that she did not cry when she got her immunizations. She had osteomyelitis at 1 year of age in her left heel after a bout of cellulitis. She also had a history of fracturing her tibia/fibula by jumping down. She had surgeries for strabismus, tongue injuries secondary to repeat bitings, and central corneal opacification and scarring secondary to repeat scratching of the eyes. The pictures here show bitten lower lip (**a**), tongue (**b**), and damaged finger (**c**). EMG and nerve conduction studies were normal. Oligonucleotide array CGH analysis was normal (Courtesy of Dr. Susonne Ursin)

Hereditary Spastic Paraplegia

Contents

The hereditary spastic paraplegia (HSP) are inherited disorders in which the primary neurological syndrome is bilateral, approximately symmetrical, lower-extremity spastic weakness, often accompanied by urinary urgency (Fink 2003; Figs. 1 and 2)

Synonyms and Related Disorders

Allan–Herndon–Dudley syndrome; Cerebral palsy; Crash syndrome; Familial spastic paraplegia; Gareis–Mason syndrome; Kjellin syndrome; Mast syndrome; MASA syndrome; Pelizeaus–Merzbacher disease; Silver syndrome; Spastic quadriplegia/tetraplegia; Strumpell disease; Troyer syndrome; X-linked hydrocephalus

Genetics/Basic Defects

1. Genetic types of HSP (Fink 1997, 2002, 2003, 2013; Online Mendelian Inheritance in Man (OMIM))
    1. Autosomal dominant, autosomal recessive, and X-linked HSP are each genetically heterogeneous
    2. Twenty genetic types of HSP defined by genetic linkage analysis
    3. HSP loci are designated SPG ("spastic paraplegia") 1–21 in order of their discovery
2. Autosomal dominant HSP
    1. SPG3A (OMIM 182600) (14q22.1)
        1. Caused by mutation in the atlastin gene
        2. Symptoms usually begin in early childhood, often nonprogressive (Strumpell disease)
    2. SPG4 (OMIM 182601) (2p22.3)
        1. Caused by mutation in the spastin gene
        2. Most common type of dominantly inherited HSP (45%)
        3. May be associated with dementia
    3. SPG6 (OMIM 600363) (15q11.2)
        1. Caused by mutation in the nonimprinted gene in Prader–Willi syndrome/Angelman syndrome chromosome region-1 gene (*NIPA1*)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Prototypical late-adolescent, early-adult onset, slowly progressive uncomplicated HSP. Rarely complicated by epilepsy or variable peripheral neuropathy

4. SPG8 (OMIM 603563) (8q24.13)
   1. Caused by mutation in the KIAA0196 gene
   2. Symptoms begin in adulthood, often severe
   3. Progressive lower-limb spasticity and hyperreflexia resulting in difficulty walking
   4. Other features: upper limb spasticity, impaired vibration sense in the distal lower limbs, and urinary urgency or incontinence (de Bot et al. 2013)
5. SPG10 (OMIM 604187) (12q13.3)
   1. Caused by mutation in the kinesin-5A gene
   2. Associated with distal muscle wasting
6. SPG12 (OMIM 604805) (19q13.32)
   1. Caused by mutation in the reticulon 2 gene (*RTN2*)
   2. Lower-limb spasticity and hyperreflexia, resulting in walking difficulties, with some patients having urinary symptoms and distal sensory impairment (Montenegro et al. 2012)
7. SPG13 (OMIM 605280) (2q33.1)
   1. Caused by mutation in the mitochondrial chaperonin HSP60 gene
   2. Lower-limb spasticity/weakness, hyperreflexia, extensor plantar responses, pyramidal signs, decreased vibratory sense in the lower limbs, and urinary urgency/incontinence
8. SPG17 (OMIM 270985) (11q12.3)
   1. Caused by mutation in the BSCL gene
   2. Spastic paraplegia with amyotrophy of hands and feet (Silver syndrome) (Silver 1966)
9. SPG31 (OMIM 610250) (2p11.2)
   1. Caused by mutation in the receptor expression–enhancing protein-1 gene (*REEP1*)
   2. Onset: most in first or second decade
10. SPG33 (OMIM 610244) (10q24.2)
    1. Caused by mutation in the zinc finger FYVE domain–containing protein-27 gene (*ZFYVE27*)
    2. Lower-limb spasticity/weakness, spastic gait, hyperreflexia, extensor plantar responses, ankle clonus
11. SPG42 (OMIM 612539) (3q25.31)
    1. Caused by mutation in the solute carrier family 33 (acetyl-CoA transporter), member 1 gene (*SLC33A1*)
    2. Varied age of onset with increased lower-limb tone, hyperreflexia, lower-limb muscle weakness/atrophy, extensor plantar responses, and pes cavus in Chinese (Lin et al. 2008)
12. SPG61 (OMIM 615685) (16p12.3)
    1. Caused by mutation in the ARL6IP1 gene
    2. Spastic paraplegia with polysensory and motor neuropathy and loss of terminal digits due to acropathy (Novarino et al. 2014)

3. Autosomal recessive HSP
   1. SPG5A (OMIM 270800) (8q12.3)
      1. Caused by mutation in the cytochrome P450, family 7, subfamily b, polypeptide 1 gene (*CYP7B1*)
      2. Some patients with pure spastic paraplegia affecting gait, whereas others with complicated phenotype with additional manifestations including optic atrophy or cerebellar ataxia (Arnoldi et al. 2012)
   2. SPG7 (OMIM 607259) (16q24.3)
      1. Caused by mutation in the paraplegin gene (*PGN*)
      2. Variably associated with mitochondrial abnormalities on skeletal muscle biopsy and dysarthria, dysphagia, optic disc pallor, axonal neuropathy, and evidence of "vascular lesions," cerebellar or cerebral atrophy on cranial MRI
   3. SPG11 (OMIM 604360) (15q21.1)
      1. Caused by mutation in the spatacsin gene

2. Perhaps the most common autosomal recessive form of HSP (50%)
3. Variably associated with thin corpus callosum, mental retardation, upper extremity weakness, dysarthria, and nystagmus
4. Symptoms begin in the first or second decades

4. SPG15 (OMIM 270700) (14q24.1)
   1. Caused by mutation in the gene encoding spastizin (*ZFYVE26*)
   2. Progressive spasticity affecting the lower limbs associated with retinal degeneration, pigmental maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration (Kjellin syndrome) (Goizet et al. 2009)
5. SPG18 (OMIM 611225) (8p11.3)
   1. Caused by mutation in the endoplasmic reticulum lipid raft–associated protein 2 gene (*ERLIN2*)
   2. Spastic paraplegia complicated by mental retardation and thin corpus callosum. Also juvenile primary lateral sclerosis
6. SPG20 (OMIM 275900) (13q13.3)
   1. Caused by mutation in the gene encoding spartin (*SPG20*)
   2. Spastic paraplegia associated with distal muscle wasting (Troyer syndrome)
7. SPG21 (OMIM 248900) (15q22.31)
   1. Caused by mutation in the gene encoding the 33-kD acidic cluster protein (ACP33)
   2. Progressive spastic paraparesis associated in more advanced cases with cognitive decline, dementia, other neurological abnormalities, and brain imaging showing thinning of the corpus callosum (Simpson et al. 2003)
   3. Also called Mast syndrome
8. SPG26 (OMIM 609195) (12p11.1-q14)
   1. Caused by mutation in the beta-1,4-*N*-acetylgalactosaminyltransferase 1 gene (*B4GALNT1*)
   2. Onset in the first two decades of life of gait abnormalities due to lower-limb spasticity and muscle weakness with upper limb involvement in some patients
   3. Additional features: intellectual disability, peripheral neuropathy, dysarthria, cerebellar signs, extrapyramidal signs, and cortical atrophy (Boukhris et al. 2013)
9. SPG 28 (OMIM 609340) (14q22.1)
   1. Caused by mutation in the DDHD1 gene
   2. Early-onset, slowly progressive lower-limb spasticity resulting in walking difficulties, with some patients having distal sensory impairment (Tesson et al. 2012)
10. SPG 30 (OMIM 610357) (2q37.3)
    1. Caused by mutation in the kinesin family member 1A gene (*KIF1A*)
    2. Onset in the first and second decades of unsteady spastic gait and hyperreflexia of the lower limbs (Erlich et al. 2011)
11. SPG35 (OMIM 612319) (16q23.1)
    1. Caused by mutation in the gene encoding fatty acid 2-hydroxylase (*FA2H*)
    2. Childhood onset of gait difficulties due to progressive spastic paraparesis, dysarthria, and mild cognitive decline associated with leukodystrophy on brain imaging
    3. Other variable neurological features: dystonia, optic atrophy, and seizures (Dick et al. 2010)
    4. Phenotypic spectrum of disorders referred as fatty acid hydrolase–associated neurodegeneration (Kruer et al. 2010)
12. SPG39 (OMIM 612020) (19p13.2)
    1. Uncomplicated HSP
    2. Caused by mutation in the patatin-like phospholipase domain–containing protein 6 gene (*PNPLA6*)
    3. Progressive spastic paraplegia associated with distal upper- and lower-

extremity wasting (Rainier et al. 2008)

13. SPG43 (OMIM 615043) (19q12)
    1. Caused by mutation in the chromosome 19 open reading frame 12 gene (*C19ORF12*)
    2. Progressive spastic paraplegia with atrophy of intrinsic hand muscles and dysarthria
14. SPG44 (OMIM 613206) (1q42.13)
    1. Caused by mutation in the gap junction protein, gamma-2 gene (GJC2)
    2. Lower-/upper-limb spasticity, spastic gait, hyperreflexia, extensor plantar responses, dysarthria, intentional tremor, dysmetria, cerebellar ataxia, hypomyelinating leukoencephalopathy, and thin corpus callosum (Orthmann-Murphy et al. 2009)
15. SPG45 (OMIM 613162) (10q24.3-25.1)
    1. Caused by mutation in the 5-prime nucleotidase cytosolic II gene (NT5C2)
    2. Onset in the first 2 years of life with lower-limb spasticity, spastic gait, hyperreflexia, mental retardation, and brain MRI features of dysplastic/thin corpus callosum and white-matter changes (Novarino et al. 2014)
16. SPG46 (OMIM 614409) (9p13.3)
    1. Caused by mutation in the beta acid glucosidase 2 gene (*GBA2*)
    2. Onset: childhood with slowly progressive spastic paraplegia and cerebellar signs
    3. Some patients with cognitive impairment, cataracts, and cerebral, cerebellar, and corpus callosum atrophy (Boukhris et al. 2010; Martin et al. 2013)
17. SPG47 (OMIM 614066) (1p13.2)
    1. Caused by mutation in the adapter-related protein complex 4, beta-1 subunit gene (*AP4B1*)
    2. Neonatal hypotonia progressing to hypertonia and spasticity and severe mental retardation with poor or absent speech development (Abou Jamra et al. 2011)
18. SPG48 (OMIM 613647) (7p22.1)
    1. Caused by mutation in the KIAA0415 gene
    2. Progressive spastic paraplegia associated with urinary incontinence in two adult French sibs (Slabicki et al. 2010)
19. SPG49 (OMIM 615031) (14q32.31)
    1. Caused by mutation in the tectonin beta-propeller repeat-containing protein 2 gene (*TECPR2*)
    2. Onset of spastic paraplegia in the first decade associated with delayed psychomotor development, mental retardation, dysmorphic features, thin corpus callosum on MRI, and episodes of central apnea, which may be fatal (Oz-Levi et al. 2012)
20. SPG50 (OMIM 612936) (7q22.1)
    1. Caused by mutation in the adapter-related protein complex 4, MU-1 subunit gene (*AP4M1*)
    2. Neonatal hypotonia progressing to hypertonia, spastic quadriplegia, severe mental retardation with poor or absent speech development, dysmorphic features, and abnormal brain MRI (ventriculomegaly, white-matter abnormalities and variable cerebral atrophy) (Verkerk et al. 2009)
21. SPG51 (OMIM 613744) (15q21.2)
    1. Caused by mutation in the adapter-related protein complex 4, epsilon-1 subunit gene (*AP4E1*)
    2. Neonatal hypotonia progressing to hypertonia and spastic quadriplegia/tetraplegia and severe mental retardation, poor or absent speech development, dysmorphic features, and abnormal brain MRI (enlarged ventricles, cortical and cerebellar atrophy, and diffuse white-matter loss) (Moreno-De-Luca et al. 2011)

22. SPG52 (OMIM 614067) (14q12)
    1. Caused by mutation in the adapter-related protein complex 4, sigma-1 subunit (*AP4S1*)
    2. Neonatal hypotonia progressing to hypertonia, spastic quadriplegia, severe mental retardation with poor or absent speech development, dysmorphic features, shy character, and short stature (Abou Jamra et al. 2011)
23. SPG53 (OMIM 614898) (8p22)
    1. Caused by mutation in the homologue of the yeast vacuolar protein sorting 37 gene (*VPS37A*)
    2. Onset in infancy of delayed motor development progressing to upper- and lower-limb spasticity with impaired walking and mild-to-moderate cognitive impairment (Zivony-Elboum et al. 2012)
24. SPG54 (OMIM 615033) (8p11.23)
    1. Caused by mutation in the DDHD domain-containing protein 2 gene (*DDHD2*)
    2. Psychomotor delay, cognitive impairment, progressive spasticity (onset before age 2 years), thin corpus callosum, periventricular white-matter abnormalities.
    3. Additional clinical features: foot contractures, dysarthria, dysphagia, strabismus, optic hypoplasia
25. SPG55 (OMIM 615035) (12q24.31)
    1. Caused by mutation in the chromosome 12 open reading frame 65 gene (*C12ORF65*)
    2. Spastic paraplegia associated with distal muscle atrophy/weakness, predominantly affecting the lower limbs, optic atrophy, hyperreflexia, steppage gait, difficulty walking, extensor plantar responses, axonal neuropathy, distal sensory impairment, and hypoplastic corpus callosum in some patients (Shimazaki et al. 2012; Spiegel et al. 2014)
26. SPG56 (OMIM 615030) (4q25)
    1. Caused by mutation in the cytochrome P450, family 2, subfamily U, polypeptide 1 gene (*CYP2U1*)
    2. Early-onset progressive lower-limb spasticity resulting in walking difficulties and often affected upper limbs (Tesson et al. 2012)
27. SPG57 (OMIM 615658) (3q12.2)
    1. Caused by mutation in the TRK-fused gene (*TFG*)
    2. Severe spasticity affecting lower limbs with inability to walk, hyperreflexia, extensor plantar responses, muscle weakness/atrophy affecting upper and lower limbs due to an axonal demyelinating sensorimotor neuropathy, and optic atrophy (Beetz et al. 2013)
28. SPG63 (OMIM 615686) (1p13.3)
    1. Caused by mutation in the AMPD2 gene
    2. Delayed walking and a scissors gait, followed by hypertonia, hyperreflexia, and MRI showing periventricular deep white-matter changes in the corpus callosum (Novarino et al. 2014)
29. SPG64 (OMIM 615683) (10q24.1)
    1. Caused by mutation in the ENTPD1 gene
    2. Childhood onset with unsteady gait with areflexia/hyperreflexia, dysarthria, and spasticity (Novarino et al. 2014)
30. SPG72 (OMIM 615625) (5q31.2)
    1. Caused by mutation in the receptor expression–enhancing protein 2 gene (*REEP2*)
    2. Spastic paraplegia with difficulty walking and stiff legs associated with hyperreflexia and extensor plantar responses in early childhood (Esteves et al. 2014)
    3. Autosomal recessive form has been described

4. X-linked HSP
    1. SPG1 (OMIM 303350) (Xq28)

1. Caused by mutation in the gene encoding the L1 cell adhesion molecule (LICAM)
2. Mutations in this gene also cause MASA syndrome and X-linked recessive hydrocephalus (Crash syndrome) (OMIM 303350)
3. Some forms of HSP with progressive spasticity occurs in isolation
4. Others with progressive spasticity with other neurologic features including mental retardation, and variably, hydrocephalus, aphasia, and adducted/clapsed thumbs
5. Also called Gareis-Mason syndrome

2. SPG2 (OMIM 312920) (Xq22.2)
   1. Caused by mutation in the myelin proteolipid protein gene (*PLP1*)
   2. X-linked recessive inheritance
   3. Allelic to Pelizaeus-Merzbacher disease
   4. Progressive spasticity occurs in isolation or occurs with other neurologic features, variably associated with MRI evidence of CNS white matter abnormality
   5. Mutations in this gene also cause Pelizeaus-Merzbacher disease (OMIM 312080)
3. SPG22 (OMIM
   1. Caused by mutation in the monocarboxylate transporter 8 gene (*MCT8*)
   2. Also called Allan-Herndon-Dudley syndrome (X-linked dominant)
   3. Congenital onset with neck muscle hypotonia in infancy, mental retardation, dysarthria, ataxia, spastic paraplegia, abnormal facies

Clinical Features

1. Variable onset of symptoms, rate of progression and degree of disability between genetic types of HSP (Fink and Hedera 1999; Fink 2003), as well as within individual families in which all subjects have precisely the same HSP gene mutation
   1. Initial symptoms: tumbling and tripping due to lower-extremity stiffness and weakness with age of onset at any age from infancy to senescence
   2. Later symptoms
      1. Marked lower-extremity spastic weakness
      2. Requiring cane, walker, or wheelchair
2. Correlation of age of onset and progression of the disease
   1. In general, HSP symptoms beginning in early childhood may not show significant worsening even over many years.
   2. In contrast, HSP symptoms beginning after adolescence typically worsen insidiously
   3. Urinary urgency is very common, and although usually occurring after many years, it may occasionally be the presenting symptom of HSP
   4. In uncomplicated HSP
      1. Spastic weakness: confined to the lower extremities
      2. Normal strength and dexterity of the upper extremities, speech, and swallowing remain normal
3. Classification of HSP (Harding 1983)
   1. Uncomplicated HSP
      1. Neurological findings confined to the lower extremities
         1. Spastic weakness
         2. Hyperreflexia
         3. Extensor plantar responses
         4. Mildly impaired vibratory sensation in the distal lower extremities
      2. Normal strength and dexterity of the upper extremities, speech, and swallowing remain normal
   2. Complicated HSP
      1. Signs of uncomplicated HSP plus
      2. Other neurological or systemic impairments not attributed to coexisting disorders
         1. Cataracts
         2. Motor neuropathy

3. Mental retardation
4. Muscle wasting

4. Diagnosis of HSP
   1. Typical symptoms of gait disturbance often associated with urinary urgency
      1. Childhood onset, essentially non-progressive spastic diplegia
      2. Childhood-through-adulthood onset of insidiously progressive spastic weakness in the legs
   2. Neurological findings of corticospinal tract deficits
      1. Lower extremities
         1. Spasticity
         2. Weakness
         3. Hyperreflexia
         4. Extensor plantar responses
      2. Upper extremities
         1. Brisk but not pathological reflexes
         2. Normal muscle tone
   3. Family history of similar disorder
   4. Exclusion of alternate disorders such as
      1. Multiple sclerosis
      2. Leukodystrophy
      3. Structural abnormalities involving the brain and spinal cord
      4. Dopa-responsive dystonia
5. Differential diagnosis of spastic paraplegia with additional abnormalities on MRI of the brain (de Bot et al. 2010)
   1. Leukoencephalopathy
      1. Many neurometabolic and other hereditary white-matter disorders with characteristic MRI pattern like Krabbe disease, Alexander disease, X-linked adrenoleukodystrophy, vanishing white matter; inflammatory disorders like multiple sclerosis, acute disseminated encephalomyelitis, and neuromyelitis optica
      2. HSPs: SPG4 (some), SPG11, SPG15, SPG21
   2. Thin corpus callosum
      1. Thin corpus callosum + epilepsy, Andermann syndrome (agenesis of the corpus callosum with peripheral neuropathy) (OMIM 218000)
      2. HSPs: SPG1, SPG4 (some), SPG11, SPG15, SPG21, SPG32
   3. Cerebral atrophy
      1. Cerebellar ataxia
      2. HSPs: SPG7
6. Differential diagnosis of spastic paraplegia with additional clinical features (de Bot et al. 2010)
   1. Mental retardation
      1. Many neurometabolic or neurogenetic disorders; sometimes recognizable based on MRI abnormalities or further additional features
      2. HSPs: SPG1, SPG2, SPG11, SPG14, SPG15, SPG16, SPG20, SPG21, SPG23, SPG27, SPG32, SPG35
   2. Dysmorphisms
      1. Andermann syndrome, hydrocephalus due to congenital stenosis of aqueduct of Sylvius
      2. HSPs: SPG1, SPG23
   3. Optic atrophy
      1. Cobalamin C disease, biotinidase deficiency, cerebral folate deficiency, SPOAN (spastic paraplegia, optic atrophy, and neuropathy), ARSACS (autosomal recessive spastic ataxia of Charlevoix-Saguenay), type III 3-methylglutaconic aciduria
      2. HSPs: SPG7
   4. Retinopathy
      1. Cobalamin C disease, Sjögren–Larsson syndrome, homocarnosinosis, abetalipoproteinemia
      2. HSPs: SPG15
   5. Cataract
      1. Cerebrotendinous xanthomatosis, α-methyl-CoA racemase deficiency
      2. HSPs: SPG9
   6. Hearing loss/deafness
      1. Biotinidase deficiency, cerebral folate deficiency
      2. HSPs: SPG29
   7. Neuropathy/amyotrophy
      1. dHMN (distal hereditary motor neuropathy), HMSN (hereditary motor and sensory neuropathy) V,

cerebrotendinous xanthomatosis, cobalamin C disease, MTHFR (5,10-methylenetetrahydrofolate) deficiency, metachromatic leukodystrophy, Krabbe disease, adrenomyeloneuropathy, polyglucosan body disease, α-methyl-CoA racemase deficiency, biotinidase deficiency, abetalipoproteinemia (posterior column), homocysteine remethylation defects, SPOAN, ARSACS, Andermann syndrome
2. HSPs: SPG7, SPG9, SPG10, SPG11, SPG14, SPG17, SPG20, SPG27, SPG38, SPG39

8. Cerebellar ataxia
   1. Atypical Friedreich ataxia, cerebrotendinous xanthomatosis, triple H (hyperornithinemia-hyperammonemia-homocitrullinuria) syndrome, cerebral folate deficiency, metachromatic leukodystrophy, SAX (spastic ataxia) 1, SAX2, ARSACS, ARSAL (autosomal recessive spastic ataxia with leukoencephalopathy), Type III 3-methylglutaconic aciduria, Alexander disease
   2. HSPs: SPG7, SPG15, SPG20, SPG21, SPG27
9. Extrapyramidal signs/diurnal fluctuations
   1. Dopamine synthesis defects and cerebral folate deficiency (dystonia), amyotrophic dystonic paraplegia (dystonia), polyglucosan body disease, phenylketonuria and cerebrotendinous xanthomatosis (parkinsonism), dopa-responsive dystonia (diurnal fluctuations)
   2. HSPs: SPG21, SPG23 (tremor)
10. Epilepsy
    1. Dopamine synthesis defects, α-methyl-CoA racemase deficiency, triple H syndrome, metachromatic leukodystrophy, cerebrotendinous xanthomatosis, arginase deficiency, cerebral folate deficiency, thin corpus callosum + epilepsy, Alexander disease
    2. HSPs: SPG2, SPG35
11. Cutaneous signs
    1. Cerebrotendinous xanthomatosis (xanthomas), biotinidase deficiency (alopecia, dermatitis), Sjögren–Larsson (ichthyosis), adrenoleukodystrophy/adrenomyeloneuropathy (melanoderma)
    2. HSPs: SPG23 (pigmentary abnormalities)
12. Episodes of confusion, nausea/vomiting, or diarrhea
    1. Cobalamin C disease, MTHFR deficiency, triple H, arginase deficiency, cerebrotendinous xanthomatosis (chronic diarrhea), adrenal insufficiency (adrenomyeloneuropathy, adrenoleukodystrophy), abetalipoproteinemia (diarrhea), homocysteine remethylation defects (confusion)
    2. HSPs: SPG9 (gastroesophageal reflux), SPG29 (hiatus hernia, hyperbilirubinemia)

Diagnostic Investigations

1. MRI (Fink 2006)
   1. Important to exclude alternative disorders including multiple sclerosis, leukodystrophies, and structural abnormalities affecting the brain or spinal cord
   2. Uncomplicated HSP: normal in conventional brain MRI
   3. Severe forms of complicated HSP: brain MRI may reveal syndrome-specific abnormalities such as thin corpus callosum in SPG11, cerebral or cerebellar abnormalities in SPG7, and hydrocephalus in SPG1
   4. MRI of the spinal cord: may be entirely normal or show atrophy, particularly involving the thoracic spinal cord
2. Electromyography (EMG)/nerve conduction studies (NCSs) (Fink 2006)

1. Uncomplicated HSP: usually normal
2. Complicated forms of HSP (e.g., SPG10, SPG14, SPG15, and SPG26): associated with peripheral neuropathy and evidence of lower motor neuron involvement

3. Muscle biopsy in some subjects with SPG7 (due to mutations in the mitochondrial metalloprotease paraplegin) shows ragged red fibers and cytochrome oxidase C negative fibers (DeMichele et al. 1998)
4. Neuropathologic studies in uncomplicated HSP (Behan and Maia 1974)
   1. Axonal degeneration of selected motor (corticospinal tracts) and sensory (dorsal column fibers) within the spinal cord, particularly prominent in the distal aspects of these fibers
   2. Anterior horn cells are generally preserved
5. Molecular genetic analysis: uncomplicated, complicated, and full panel gene tests for HSP are clinically available at Invitae, San Francisco, CA (www.invitae.com)

Genetic Counseling

1. Recurrence risk (Fink 2006; Finsterer et al. 2012)
   1. Patient's sib
      1. Autosomal dominant inheritance
         1. Over 90% of the affected individuals have an affected parent, depending on the penetrance, proportion of de novo mutations, and germinal mosaicism
         2. Each child of an affected individual has a 50% chance of inheriting the mutation
      2. Autosomal recessive inheritance: Each sibling of an affected patient has a 25% chance of being affected, a 50% risk of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier
      3. X-linked recessive inheritance
         1. Mother is a carrier: 50% of brothers are affected and 50% of sisters are carriers
         2. Mother is not a carrier: low recurrence risk but still exists since the risk of germline mosaicism in mothers is not known
      4. X-linked dominant inheritance
         1. A carrier mother: a 50% risk of transmitting the disease-causing mutation with each pregnancy. Sons who inherit the mutation will be affected. Daughters who inherit the mutation will be carriers and may or may not be affected
         2. A noncarrier mother: recurrence risk to sibs low but not zero since the risk of germline mosaicism in mothers is not known
   2. Patient's offspring
      1. Autosomal dominant inheritance: 50%
      2. Autosomal recessive inheritance: not increased unless the spouse is a carrier
      3. X-linked recessive inheritance
         1. No sons will inherit the mutant allele and therefore will not be affected
         2. All daughters will be carriers
      4. X-linked dominant inheritance
         1. All the daughters of an affected male inherit the mutation but may or may not have symptoms
         2. None of his sons will be affected
   3. Frequency of spontaneous mutations for dominantly inherited HSP: 12%
   4. Genetic penetrance
      1. Uncomplicated HSPs: age-dependent and high penetrance (70–85% for SPG4)
      2. Incomplete penetrance: reported in SPG4, SPG8, and SPG3A
      3. Extent of clinical variability
      4. Genetic anticipation (affected individuals in succeeding generations may be more severely affected and develop symptoms at an earlier age): reported in a minority of SPG3A
2. Prenatal diagnosis for pregnancies at risk is offered by specialized laboratories providing custom prenatal diagnosis to families in which the disease-causing mutation has been identified

3. Management: presently limited to symptomatic reduction of muscle spasticity (Fink 2003)
    1. Exercise/daily physical therapy
        1. Maintain and improve muscle flexibility and range of motion (stretching exercises)
        2. Improve muscle strength (resistance exercise)
        3. Maintain walking reflexes (walking on a slowly moving treadmill with arm supports or walking in a swimming pool)
        4. Improve cardiovascular fitness
        5. Ankle-foot orthotic devices: often useful to reduce toe dragging
    2. Medications
        1. Lioresal (oral or intrathecal)
        2. Tizanidine
        3. Dantrolene
        4. Oxybutynin (helpful in reducing urinary urgency)

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Fig. 1 This 8-year-old boy was noted to have unstable gait with frequent falls, and weakness on the upper extremities. On examination, he had ankle clonuses, brisk deep tendon reflexes (DTR), weak grasp, and occasional tip-toe walking. He was receiving special education. Chromosome analysis (46, XY), Fragile X analysis, and brain MRI were normal. The 7-year-old brother had similar but milder symptoms. The father is similarly affected

Fig. 2 This 4-year-old girl was evaluated for spastic legs with onset since 3 month of age. On examination, she was noted to have brisk DTR, ankle clonuses, tight Achilles tendon, and tip toe walking. Her mother had spastic legs with brisk DTR, ankle clonuses, and some loss of sensation in her toes. The maternal grandmother had a history of leg weakness and bladder problems with onset in her 30s

Herlyn-Werner-Wunderlich Syndrome

Contents

Herlyn-Werner-Wunderlich syndrome (HWWS) (Herlyn and Werner 1971; Wunderlich 1976) is a rare Müllerian anomaly consisting of a didelphic uterus, a hemivaginal septum, and an ipsilateral renal agenesis. The diagnosis should be suspected in adolescent females with a pelvic mass and an ipsilateral renal agenesis.

Synonyms and Related Disorders

Blind hemivagina with ipsilateral renal agenesis; Obstructed hemivagina; Septate uterus; Uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis

Genetics/Basic Defects

1. Anatomical defect is caused by a failure of lateral fusion of Müllerian ducts (didelphic/septate uterus and double vagina) combined with a failure of vertical fusion between the Müllerian duct and the urogenital sinus (hemivaginal septum) ipsilateral to the side of the renal agenesis.
2. Various types of uterine anomalies secondary to nondevelopment or failure of fusion of the distal segments of the Müllerian ducts (Troiano and McCarthy 2004).
    1. Hypoplasia/agenesis of the uterus
    2. Unicornuate uterus (approximately 20%)
    3. Didelphic uterus (approximately 5%)
    4. Bicornuate uterus (approximately 10%)
    5. Septate uterus: the most common Müllerian duct anomaly (approximately 55%)
    6. Arcuate uterus
3. Various types of vaginal anomalies secondary to the different embryological origins of the upper two-thirds of the vagina (originates from the Müllerian ducts of mesodermal origin) and the lower third of the vagina (originates from the urogenital sinus of endodermal origin): the anomaly may exist alone or in association with Müllerian anomalies.
    1. Hypoplasia/aplasia
    2. Duplication
    3. Septa
4. Close interrelationship between the urinary and reproductive systems during embryogenesis may explain the coexistence of urinary and reproductive tract abnormalities.
5. Specific association of a didelphic uterus, an obstructed hemivagina, and an ipsilateral renal

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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agenesis is a rare malformation concomitantly involving both Müllerian and Wolffian ducts.
6. Mode of inheritance: unclear but Wiersma et al. (1976) had reported mother and daughter with uterus bicornis bicollis with partial vaginal septum and unilateral hematocolpos with ipsilateral renal agenesis, suggesting a possible sex-limited autosomal dominant inheritance.

Clinical Features

1. Presenting symptoms (Vercellini et al. 2007; Rana et al. 2008; Bhoil et al. 2016): the median age of presentation is 13 years. The condition is usually discovered at puberty shortly after menarche. The diagnosis is generally made only if the suspicion of the existence of this syndrome is raised.
    1. Abdominal pelvic mass due to hemihematocolpos resulting from retained long-standing, partially clotted menstrual blood in the obstructed hemivagina.
    2. Recurrent and progressive pelvic pain.
    3. Dysmenorrhea (painful menstruation).
    4. Foul-smelling discharge.
    5. Menstrual bleeding.
    6. Menstrual irregularity.
    7. Intra-abdominal abscess.
    8. Fever and vomiting can be the presenting symptoms.
    9. If not treated, complications leading to infertility, endometriosis, pelvic adhesions, and pyosalpinx or pyocolpos may present in the late phase with a high miscarriage rate.
2. A didelphic uterus (Heinonen 1982, 2000; Zurawin et al. 2004; Vercellini et al. 2007)
    1. Characterized by two uterine bodies and two cervices
    2. The presence of a longitudinal vaginal septum in the majority of cases
3. Consequences of blood stasis and retrograde menstruation in the obstructed system
    1. Hematocolpos (a dilated hemivagina)
    2. Hematometra (a dilated uterine cavity)
    3. Hematosalpinx (bleeding/dilated fallopian tube)
4. Other vaginal anomalies
    1. Imperforate hymen variants
    2. Vaginal atresia
    3. Duplicated vagina
    4. Fused labia
5. Ipsilateral renal agenesis (Rock and Jones 1980)
6. Occasional gastrointestinal tract malformations
    1. Esophageal atresia
    2. Imperforate anus
7. Natural history if untreated
    1. Endometriosis
    2. Pelvic adhesions
    3. Pyosalpinx
    4. Pyocolpos
8. Unusual dichotomy in reproductive function
    1. Fertility not compromised with high spontaneous abortion rate (40%)
    2. No obstetric difficulties when a pregnancy is carried to term (Rana et al. 2008)

Diagnostic Investigations

1. Abdominal examination finding of a suprapubic mass with tenderness to palpation.
2. Pelvic and/or rectal examination findings of a paravaginal cystic mass.
3. Abdominal and pelvic imagings (Gholoum et al. 2006; Madureira et al. 2006; Orazi et al. 2007):
    1. Ultrasonography allows the correct diagnosis by showing uterovaginal duplication, hematocolpos, pyocolpos, or hematometrocolpos and the absence of the ipsilateral kidney.
    2. CT scan: limited due to radiation exposure and limited soft-tissue resolution.
    3. Magnetic resonance imaging provides more detailed information regarding uterine morphology, the continuity with each vaginal channel (obstructed and nonobstructed), and the bloody nature of the contents.
4. Laparoscopy:
    1. The gold standard for diagnosis
    2. Has the added benefit of performing therapeutic drainage of hematometra/

hematocolpos, vaginal septotomy, and marsupialization (Gholoum et al. 2006)

5. Unilateral renal agenesis can be diagnosed prenatally. Female fetuses or neonates with renal malformations or multidysplastic kidneys need to be screened for genital malformations and to look for an obstructed Müllerian system. The uterine anomaly can be better detected in the neonatal period because the uterus is still under maternal hormonal stimulation and is characterized by a prominent myometrium and an echogenic endometrium. It is advisable that follow-up ultrasonographic examination of these asymptomatic patients be performed until the end of puberty.

Genetic Counseling

1. Recurrence risk: possible sex-limited autosomal dominant inheritance
    1. Patient's sib: recurrence risk not increased in female sibs unless the mother is affected
    2. Patient's offspring: a 50% risk for female offspring
2. Prenatal diagnosis: Uterus didelphys with blind hemivagina and ipsilateral renal agenesis (Herlyn-Werner-Wunderlich syndrome) suspected on the presence of hydrocolpos on prenatal sonography (Han et al. 2013).
3. Management
    1. Operative management:
        1. Vaginal septectomy with marsupialization and drainage of hematocolpos/hematometrocolpos to provide relief of pain and prevent further complications: a preferred surgical approach with a good long-term outcome.
        2. Salpingectomy for pyosalpinx if needed.
        3. One-fifth of patients with HWWS were susceptible to pelvic endometriosis, and all of the ovarian endometriotic cysts were ipsilateral to the vaginal septum. Pelvic endometriosis in adolescents appeared to be related to obstructed genital abnormality.
        4. Vaginal septum resection should be the first step in treatment and surgery has an important role in the treatment of endometriosis and pelvic adhesion (Tong et al. 2014).
    2. Errors in the surgical management can occur when the diagnosis is not suspected, and laparotomy to explore and resect the intra-abdominal mass is performed.
    3. Hemihysterectomy with or without salpingo-oophorectomy is rarely indicated and should be avoided to provide the best chance for a successful reproductive outcome.
    4. Postoperative considerations:
        1. To achieve the goal of normal sexual relations and successful reproductive outcomes
        2. Vaginal adenosis in the previously obstructed vagina

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Fig. 1 A 13-year-old female was evaluated for vaginal bleeding and lower abdominal pain. Abdominal ultrasonography showed a very unusual appearance of the uterus with two horns which converge to form one lower uterine segment which then go into a prominent cervix where there was a large amount of fluid (blood) within the cervix and vagina

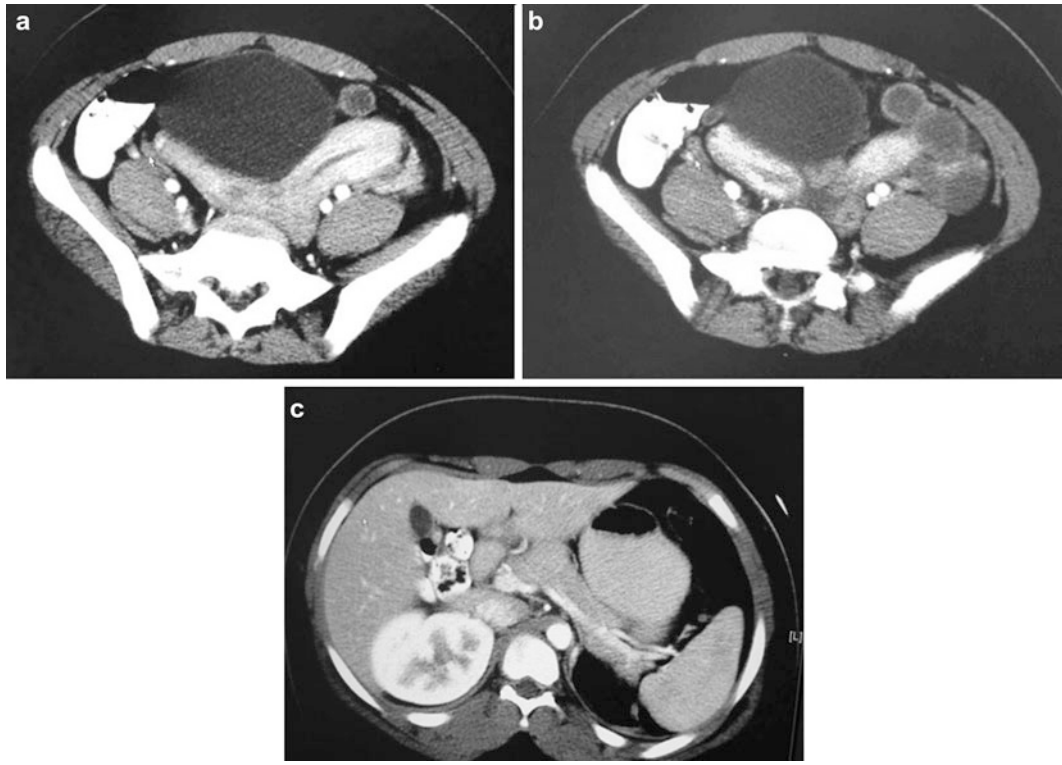

Fig. 2 (**a**–**c**) CT scan of the abdomen and pelvis showed congenital uterine anomaly likely a didelphic uterus, the absence of left kidney, and the presence of hypertrophic right kidney

Holoprosencephaly

Contents

Holoprosencephaly (HPE) is a heterogeneous entity of CNS anomalies caused by the impaired midline cleavage of the embryonic forebrain. The incidence is estimated to be 1 in 16,000 live births and observed in 1 of 250 spontaneous abortions (Roessler and Muenke 2001).

Synonyms and Related Disorders

Arhinencephaly; Cebocephaly; Ethmocephaly; Holoprosencephaly (alobar, lobar, semilobar); Holoprosencephaly facies syndrome; Premaxillary agenesis

Genetics/Basic Defects

1. Isolated and sporadic in most cases.
2. Genetically heterogeneous (Nanni et al. 2000), involving at least 12 loci on 11 chromosomes (Wallis and Muenke 2000). There are at least five putative loci for HPE:
    1. *HPE1*.
        1. Map locus: 21q22.3
        2. Familial alobar holoprosencephaly
    2. *HPE2* (*SIX3*).
        1. Map locus: 2p21 (Muenke et al. 1989)
        2. Chromosome 2 form of holoprosencephaly, including midline cleft syndrome and DeMyer sequence
        3. Caused by mutations in the homeobox-containing *SIX3* gene (Wallis et al. 1999)
    3. *HPE3* on 7q36-qter (Gurrieri et al. 1993), characterized as the locus containing the human *sonic hedgehog* gene (*SHH*).
        1. Either loss-of-function mutation or disruption of one of the *sonic hedgehog* alleles at 7q36 (haploinsufficiency) shown to cause variable phenotype of holoprosencephaly.
        2. A broad spectrum of holoprosencephaly present in patients with de novo 7q36 deletions (Frints et al. 1998) or with autosomal dominant holoprosencephaly having a linkage on 7q36.
        3. 7q deletion syndrome without typical holoprosencephaly in some patients.
        4. Interaction of partial trisomy 3p and partial monosomy 7q: invariably associated with severe forms of holoprosencephaly

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and facial dysmorphism. This delineates an autosomal imbalance syndrome or a dosage effect involving distal 3p duplication/terminal 7q deletion and dysmorphogenesis of the forebrain and midface.

4. *HPE*4 (TG-interacting factor, *TGIF*) on 18p11.3. Mutations of *TGIF* have been associated with holoprosencephaly and premaxillary agenesis.
5. *HPE5* (*ZIC2*) on 13q32 (Brown et al. 1998).

3. SHH signaling pathway or the Nodal/TGF pathway (Roessler et al. 1996; Cohen 2006; Bertolacini et al. 2010):
   1. *SHH* is the major gene implicated in holoprosencephaly (12.7 % of HPE cases: 50% of overall point mutations and 38% of overall large deletions) (Dubourg et al. 2004).
   2. *ZIC2* is the second HPE gene by order of involvement (9.2 % of HPE cases: 31% of overall point mutations and 38% of overall large deletions).
   3. Point mutations and large deletions in *SIX3* represent 3% and 1% of HPE cases, respectively. They are generally found in severe phenotypes (Pasquier et al. 2005).
   4. Mutations in *TGIF* account for 1% of studied cases and large deletions for nearly 1% (Gripp et al. 1998, 2000).
4. *GLI2* mutations (Rahimov et al. 2006): nucleotide change and diverse phenotype:
   1. 451A → G (Arg151Gly): holoprosencephaly-like phenotype
   2. 3,677C → T (Pro1226Leu): lobar HPE
   3. 1,809C → T (Pro604Ser)
      1. Anophthalmos
      2. Branchial arch anomalies
      3. CNS anomalies
   4. 3,348G → A (Met1116Ile)
      1. Heminasal aplasia
      2. Orbital anomalies
5. *FAST1* (forkhead activin signal transducer 1) mutations: *FAST1* is the first human gene with mutations causing both midline defects (holoprosencephaly) and lateral defects (anomalies of cardiac looping) (Ouspenskaia et al. 2002).
6. Other known HPE-associated genes:
   1. *PTCH*.
      1. Patched mutations in humans result in haploinsufficiency.
      2. A few of such mutations cause holoprosencephaly.
      3. Common in nevoid basal cell carcinoma syndrome and in isolated basal cell carcinomas.
   2. *DHCR7*.
      1. Mutations resulting in reduced serum cholesterol and accumulation of 7-dehydrocholesterol in autosomal recessive Smith-Lemli-Opitz syndrome.
      2. Four percent of cases with Smith-Lemli-Opitz syndrome have holoprosencephaly.
   3. *DISP1*: Loss-of-function mutations may be associated with normal brain structure and development but facial features usually seen in conjunction with frank HPE (Roessler et al. 2009).
   4. *NODAL*: Mutations may result in HPE but are more commonly associated with cardiac and laterality defects (Roessler et al. 2009).
   5. *FOXH1* (part of the NODAL signaling pathway): Mutations may result in HPE or cardiac defects (Roessler et al. 2008).
   6. *FGF*8: A loss-of-function mutation has been described in three members of one family with a range of classic HPE-spectrum features (Araúz et al. 2010).
   7. *TDGF1*: *TDGF1* encodes a membrane-associated protein that serves as a coreceptor for Nodal signaling (de la Cruz et al. 2002).
   8. *NOG*: Mutations in the coding region of *NOG* are rare and play at most an uncommon role in human HPE (Srivastava et al. 2012).
   9. *STIL*: Homozygous mutation causes holoprosencephaly and microcephaly in two siblings (Mouden et al. 2015).
   10. *GAS1: GAS1* is a positive regulator of SHH; mutations may result in the full

spectrum of HPE. The functional effects of all reported variants have not been confirmed (Ribeiro et al. 2010; Pineda-Alvarez et al. 2012).

11. *DLL1*: Deletions (and a single variant) implicate the NOTCH signaling pathway in the pathogenesis of HPE (Dupé et al. 2011).
12. *CDON*: *CDON* is a SHH coreceptor; mutations may result in a small proportion of HPE (Bae et al. 2011).

7. Subtypes of holoprosencephaly and the range of possible craniofacial features (Blaas et al. 2002; Hahn and Plawner 2004):
    1. Alobar holoprosencephaly: The most severe form characterized by complete or nearly complete lack of separation of the cerebral hemispheres with a single midline forebrain ventricle (monoventricle), which often communicates with a dorsal cyst. The interhemispheric fissure and corpus callosum are completely absent.
        1. Cyclopia (a single eye or a partially divided eye in a single orbit with or without proboscis above the eye)
        2. Ethmocephaly (extreme ocular hypotelorism with proboscis located between the eyes)
        3. Cebocephaly (ocular hypotelorism with a single-nostril nose)
        4. Premaxillary agenesis (ocular hypotelorism with median cleft lip and palate)
        5. Bilateral cleft lip
        6. Ocular hypotelorism only
        7. Anophthalmia or microphthalmia
        8. Relatively normal facial appearance
    2. Semilobar holoprosencephaly: There is a failure of separation of the anterior hemispheres, whereas some portion of the posterior hemispheres manifests separation. The frontal horns of the lateral ventricle are absent, but posterior horns are present. The corpus callosum is absent anteriorly, but the splenium of the corpus callosum is present.
        1. Bilateral cleft lip with median process representing the philtrum-premaxilla anlage
        2. Flat nasal bridge
        3. Absent nasal septum
        4. Flat nasal tip
        5. Midline cleft lip and/or palate
        6. Ocular hypotelorism
        7. Flat nose
        8. Anophthalmia/microphthalmia
        9. Relatively normal facial appearance
    3. Lobar holoprosencephaly: The mildest form, the cerebral hemispheres are fairly well separated, whereas only the most rostral/ventral aspects are nonseparated. The splenium and body of the corpus callosum are present, although the genu may be poorly developed. Rudimentary formation of the frontal horns may be present.
        1. Bilateral cleft lip with median process
        2. Ocular hypotelorism
        3. Flat nose
        4. Relatively normal facial appearance
    4. Middle interhemispheric variant or syntelencephaly: In contrast to classic HPE, there is failure of separation of the posterior frontal and parietal lobes, whereas the poles of the frontal and occipital lobes are well separated (Barkovich and Quint 1993; Simon et al. 2002).
    5. Septopreoptic type: Nonseparation is restricted to the septal and/or preoptic regions and was described in small case series (Hahn et al. 2010).
8. Causes: (Cohen 1982, 1989a, b; Vance et al. 1998; Muenke et al. 2000; Bendavid et al. 2010; Solomon et al. 2013)
    1. Detectable chromosome abnormalities (24–45 %):
        1. Numerical chromosomal abnormalities:
            1. Trisomy 13 (most common)
            2. Trisomy 18
            3. Triploidy
            4. Mosaic trisomy 9
        2. Structural chromosomal abnormalities: reported in virtually all chromosomes. The most frequent ones are as follows:
            1. Involving 13q [del(13q), r(13), dup (13q)]
            2. Del(18p)
            3. Del(7)(q36) (20%)
            4. Dup(3)(p24-pter) (10%)

5. Del(2)(p21)
6. Del(21)(q22.3)
7. Del(22q11)
8. i(18q) (Bangma et al. 2011)
9. Partial monosomy 14q

2. Monogenic holoprosencephaly (18–25 %):
   1. Autosomal dominant
      1. Pallister-Hall syndrome
      2. Rubinstein-Taybi syndrome
      3. Kallmann syndrome
      4. Martin syndrome (with club foot and spinal anomalies)
      5. Steinfeld syndrome (with congenital heart disease, absent gallbladder, renal dysplasia, and radial defects)
      6. Ectrodactyly and hypertelorism
   2. Autosomal recessive
      1. Meckel-Gruber syndrome
      2. Smith-Lemli-Opitz syndrome
      3. Pseudotrisomy 13 syndrome
      4. XK aprosencephaly syndrome
      5. Heterotaxy and holoprosencephaly
      6. Genoa syndrome (with craniosynostosis)
      7. Lambotte syndrome (with microcephaly, prenatal growth retardation, and hypertelorism)
      8. Hydrolethalus syndrome (with hydrocephalus, polydactyly, and other anomalies)
      9. Facial clefts and brachial amelia
   3. X-linked recessive (holoprosencephaly with fetal hypokinesia/akinesia)
3. Agnathia-otocephaly (10%)
4. Frontonasal dysplasia (6.7 %)
5. Sirenomelia association
6. Holoprosencephaly, ectopia cordis, and embryonal neoplasms

9. Nongenetic risk factors (Muenke and Beachy 2000; Cohen and Shiotas 2002; Johnson and Rasmussen 2010):
   1. Maternal diabetes
      1. One to 2% of newborn infants of diabetic mothers develop holoprosen-cephaly.
      2. The most commonly studied with the strongest association of the risk factor.
   2. Salicylates use, respiratory and sexually transmitted infections, and use of assisted reproductive technologies: identified in epidemiologic studies as possibly associated with increased risk of HPE
   3. Quality of diet and use of multivitamin supplements: associated with a decreased risk
   4. Retinoic acid
      1. CNS anomalies, particularly hydrocephalus
      2. Holoprosencephaly
   5. Ethyl alcohol
      1. Holoprosencephaly/arhinencephaly
      2. Agnathic cyclopia
      3. Midline cerebral dysgenesis with hypothalamic-pituitary dysfunction
      4. Hydrocephalus
      5. Agenesis of the corpus callosum and anterior commissure
   6. Estrogen/progestin
   7. Anticonvulsants
   8. Low-calorie weight reduction diets
   9. Prenatal infections
      1. Cytomegalovirus
      2. Rubella
      3. Toxoplasma
   10. Poverty
   11. Previous pregnancy loss

Clinical Features

1. Variable expression, ranging from a small brain with a single cerebral ventricle and cyclopia to clinically unaffected carriers in familial holoprosencephaly.
2. Face (DeMyer et al. 1964; Cohen and Sulik 1992; Blaas et al. 2002): Holoprosencephaly is often associated with distinct facial appearance (holoprosencephaly facies syndrome). The face predicts the brain approximately 80% of the time. In decreasing order of severity:
   1. Absence of eye(s) (the most severe form)
   2. Cyclopia
      1. The most severe dysmorphism
      2. A median monophthalmia (a single midline eye)

3. Synophthalmia (fusion of two eyes in a single midline orbit)
4. Anophthalmia
5. Presence of a single median orbit (sine qua non for the diagnosis)
6. Without or with proboscis (single or double protruding from the glabella, just above the median eye)
7. Complete arhinia with no nose, no nasal bones
8. Degree of facial dysmorphism strongly correlated with the severity of brain malformation (facial and the oculo-orbital phenotype reflects the underlying central nervous system pathology)

3. Ethmocephaly
   1. Rarest type
   2. Close-set eyes (ocular hypotelorism) located in two separate orbits
   3. A median proboscis between the two eyes as a rudimentary tubelike nose
   4. Hypoplastic or absent median facial bones
4. Cebocephaly
   1. Close-set eyes (ocular hypotelorism) into separate orbits
   2. A nose with a single nostril
   3. No cleft lip
5. Premaxillary agenesis
   1. Close-set eyes (ocular hypotelorism)
   2. Median cleft lip and palate

3. Eyes.
   1. Anophthalmia
   2. Microphthalmia
   3. Cyclopia
   4. Fused eyes
   5. Coloboma
   6. Hypotelorism
   7. Bulging eyes
   8. Other eye malformations
      1. Fused lids
      2. Optic disk hypoplasia
      3. Cataract
4. Nose.
   1. Proboscis
   2. Arhinia with or without proboscis
   3. Flat nose
      1. With proboscis
      2. Absent or nonpatent nares
      3. Other malformations
5. Mouth.
   1. Median cleft lip
   2. Bilateral cleft lip
   3. Unilateral cleft lip
   4. Cleft palate alone
   5. Cleft lip with cleft palate
   6. Cleft lip alone
   7. Cleft uvula
   8. Microstomia
   9. Macrostomia
   10. Agnathia
   11. Micrognathia
6. Ear.
   1. Fused ears
   2. Other ear malformations
7. Neurodevelopmental deficits.
   1. Hoarse or "barking" voice and high-pitched crying
   2. Major feeding problems with choking spells
   3. Common growth delay
   4. Seizures
   5. Spasticity or floppy muscle tone
   6. Brainstem dysfunction with irregular breathing and heart rate and erratic body temperature control
   7. Profound developmental delay with very limited expressive language and minimal attainment of motor skills
   8. Behavioral problems
8. Endocrine disorders.
   1. Occasional diabetes insipidus with episodes of dehydration
   2. Rare panhypopituitarism
9. Presence of microforms of holoprosencephaly in relatives of patients with holoprosencephaly.
   1. Microcephaly
   2. Single central maxillary incisor (Berry et al. 1984)
   3. Ocular hypotelorism
   4. Anosmia/hyposmia secondary to absent olfactory tracts and bulbs
   5. Iris coloboma
   6. Absent superior labial frenulum
   7. Midface hypoplasia
   8. Congenital nasal pyriform aperture stenosis
   9. Developmental delay

10. Holoprosencephaly-agnathia spectrum (Kauvar et al. 2010).
    1. Holoprosencephaly, the most common developmental disorder of the human forebrain, is occasionally associated with the spectrum of agnathia or virtual absence of the mandible.
    2. This condition results in a constellation of structural cerebral and craniofacial abnormalities.
    3. The majority of these patients are female and have the most severe forms of HPE, with cyclopia present more frequently than is usually observed in cohorts of patients with HPE. Also, many patients have additional clinical findings not typical in patients with classic HPE, particularly situs abnormalities.
11. Prognosis.
    1. Infants born with cyclopia, ethmocephaly, and cebocephaly: virtually, all die within a week of birth.
    2. Infants born with premaxillary agenesis, unilateral or bilateral cleft lip, or more normal facies.
        1. Half of the patients die before 4–5 months.
        2. Twenty to 30% of the patients live to 1 year of age. Longer survival is possible to at least 11 years.
    3. Cases diagnosed in utero will have an extremely poor neurologic development after birth.
    4. Causes of death (Barr and Cohen 1999) most often due to brainstem malfunction (unable to control the respiration and heart rate) aggravated by infections and other stresses.

Diagnostic Investigations

1. Laboratory (Hahn and Plawner 2004).
    1. Electrolytes and osmolarity
    2. Cortisol, ACTH, TSH, free T4, IGF1
2. Radiographs for bony and spine abnormalities.
3. Neuroimaging assessment of holoprosencephaly (MRI/CT of the brain) (Hahn and Plawner 2004).
    1. Deep gray nuclei abnormalities (nonseparation)
        1. Thalamic nuclei (degree of nonseparation and orientation)
        2. Caudate nuclei
        3. Lentiform nuclei
        4. Hypothalamus
        5. Pituitary (normal or abnormal based on location, morphology, and signal intensity)
        6. Mesencephalon
    2. Ventricular system
        1. Presence of a monoventricle
        2. Presence of dorsal cyst
        3. Aqueductal abnormalities
        4. Hydrocephalus
    3. Cerebral cortex
        1. Gyral and sulcal abnormalities (thickness and numbers)
        2. Subcortical heterotopias
        3. Sylvian fissure abnormalities
        4. White matter maturation Delayed or appropriate
    4. White matter maturation
    5. Other malformations
        1. Dandy-Walker malformation
        2. Encephalocele
        3. Myelomeningocele
4. Electrophysiology for seizures.
5. Cytogenetic analysis (Berry et al. 1990; Bendavid et al. 2009, 2010).
    1. An essential diagnostic tool.
    2. Initially, karyotype approach led to the identification of several recurrent chromosomal anomalies predicting different HPE loci.
6. Molecular genetic diagnoses.
    1. Subsequently, several genes were isolated from these critical HPE regions, but point mutations and deletions in these genes were found only in 25% of the genetic cases.
    2. In order to identify other HPE genes, a more accurate investigation of the genome in HPE patients was necessary: If HPE is isolated and nonsyndromic, including sporadic

cases, the study of the four major genes involved in the disease should be undertaken.

3. To date, high-resolution cytogenetic techniques such as subtelomeric multiplex ligation-dependent probe amplification (MLPA) and microarray-based comparative genomic hybridization (array CGH) have enhanced chromosomal aberration analysis.
    1. A systematic search for gains or losses in the subtelomeres by MLPA
        1. Leads to identification of 4% more anomalies.
        2. Rearrangements, deletions, or duplications must be verified by FISH on the karyotype of the proband and parents, so the identification of a cryptic-balanced translocation in a parent can change the approach to genetic counseling.
    2. Array-CGH analysis
        1. A part of the molecular diagnosis algorithm to help clinicians get more disease markers for difficult HPE genetic counseling (Pineda-Alvarez et al. 2010)
        2. Indicates a high prevalence of genomic rearrangements in HPE (Bendavid et al. 2009)
        3. Detects a high frequency of submicroscopic anomalies with a yield of 25%, especially in severe forms and in fetuses
        4. Helpful in identification of unbalanced anomalies, as MLPA for subtelomeres, and leading secondarily to identification of parental cryptic-balanced translocations by FISH (Bendavid et al. 2009)
        5. Would allow identification of new HPE loci

7. Necropsy and anatomical classification (Demyer and Zeman 1963; Delezoide et al. 1990; Dubourg et al. 2007): Holoprosencephaly is generally classified into three major types and one milder subtype. The distinction among the following three types is not always clear.
    1. Alobar holoprosencephaly
        1. The most severe form
        2. Complete failure of brain tissue to develop into the normal right and left cerebral hemispheres
        3. The brain consisting of a single fused cerebral hemisphere located in the frontal region
        4. Total absence of interhemispheric fissure and falx cerebri
        5. The brain surface is smooth with sparse convolutional markings
        6. A single dilated ventricle communicating with a large dorsal cyst
        7. Absence of the third ventricle, neurohypophysis, and olfactory bulbs and tracts
        8. Absence of corpus callosum
        9. Fused thalami and basal ganglia
        10. Migrational anomalies often present
    2. Semilobar holoprosencephaly
        1. The less severe form.
        2. Rudimentary cerebral lobes. Only partial separation into two cerebral hemispheres; the hemispheres are not separated across the midline in the front part of the brain.
        3. A single ventricle.
        4. Olfactory bulbs and corpus callosum are usually absent.
        5. Partial presence of the septum pellucidum and corpus callosum pending on the severity.
    3. Lobar holoprosencephaly
        1. The least severe form
        2. Well-formed cerebral lobes that may be of normal size
        3. Virtual complete separation of the cerebral hemispheres
        4. Various degree of rostral and basilar nonseparation
        5. Absent, hypoplastic, or normal olfactory bulbs and tracts and corpus callosum
        6. Gray matter heterotopias and other associated migrational anomalies
    4. Middle interhemispheric variant or syntelencephaly
        1. Failure of separation of the posterior frontal and parietal lobes

2. Callosal genu and splenium normally formed
3. Absence of corpus callosum
4. Hypothalamus and lentiform nuclei normally separated
5. Heterotopic gray matter

Genetic Counseling

1. Based on a rigorous clinical evaluation exploring family history, environmental factors, and associated features (Mercier et al. 2010)
2. Recurrence risk: depending on the basis for the actual condition (Blaas et al. 2002)
    1. Patient's sib
        1. Empirical estimate of 20% for holoprosencephaly, 15% for a microform, and 15% for normal phenotype.
        2. Increased recurrence risk depending on the type of Mendelian inheritance (autosomal recessive and dominant conditions with holoprosencephaly). Existence of incomplete penetrance or an incomplete form or microform of holoprosencephaly makes the interpretation of familial occurrence difficult.
        3. Fifty percent recurrence risk of having affected siblings with variable clinical symptoms and severity if a parent is affected with holoprosencephaly.
        4. Germline mosaicism in which apparently unaffected parents with negative family history having more than one affected child.
        5. Sibs of a child with a numeric chromosome abnormality have a slightly increased risk of having a similar chromosome abnormality (depending on the specific abnormality and the age of the mother) with a similar or different phenotype.
        6. Increased in a case where a parent carries a chromosome translocation or other chromosome rearrangement.
    2. Patient's offspring
        1. Severe cases of prosencephaly: not surviving to reproductive age
        2. Individuals with mild form or microform holoprosencephaly (with a gene mutation for the autosomal dominant nonsyndromic holoprosencephaly): 50% recurrence risk of having an affected child
3. Prenatal diagnosis
    1. Prenatal ultrasonography (Nyberg et al. 1987; Lai et al. 2000) can detect CNS and facial abnormalities of severe HPE as early as the first trimester, but is less sensitive for the detection of milder forms of HPE, such as lobar HPE.
        1. General characteristics
            1. Polyhydramnios
            2. Ocular hypotelorism
            3. Cleft lip/palate
            4. Arhinia
            5. Cyclopia and proboscis: identifiable at the beginning of the ninth week of gestation by 2-D and 3-D ultrasonography
            6. Absence of central falx
            7. Demonstration of a single rudimentary cerebral ventricle
        2. Alobar holoprosencephaly
            1. Single ventricle
            2. Presence or absence of dorsal sac
            3. Fused thalami
            4. Absence of cavum septum pellucidum
        3. Semilobar holoprosencephaly
            1. Single ventricle with rudimentary occipital horns
            2. Presence or absence of dorsal sac
            3. Fused thalami
            4. Absence of cavum septum pellucidum
        4. Lobar holoprosencephaly (Pilu et al. 1992)
            1. Almost divided ventricles except at frontal horns of lateral ventricles
            2. Some enlargement of lateral ventricle

3. Flat roof of frontal horns in microtonal view
4. Wide communication between the frontal horns and the inferior third ventricles
5. Absence of dorsal sac
6. Divided thalami
7. Absence of cavum septum pellucidum

2. In utero helical CT 3D imaging: diagnosed agnathia-holoprosencephaly at 23 weeks of gestation (Ebina et al. 2001)
3. Fetal MRI provides better characterization of brain malformations, but only later in the third trimester of pregnancy (Hahn and Barnes 2010; Mercier et al. 2010).
4. Cytogenetic analysis from CVS or amniocytes (Chen et al. 1992, 1996, 1999, 2001).
   1. Parent with a balanced chromosomal rearrangement
   2. Fetus with multiple anomalies including holoprosencephaly from prenatal ultrasonography
5. Prenatal diagnosis by molecular analysis on fetal DNA obtained from amniocentesis or CVS for the disease-causing mutation previously identified in the proband.
   1. Sequence analysis or deletion/duplication analysis
      1. *SIX3*-related holoprosencephaly
      2. *SHH*-related holoprosencephaly
      3. *TGIF*-related holoprosencephaly (Chen et al. 2002)
      4. *ZIC2*-related holoprosencephaly
      5. *GLI2*-related holoprosencephaly
      6. *PTCH1*-related holoprosencephaly
      7. *TRAPPC10*-related holoprosencephaly
      8. *ZIC2*-related holoprosencephaly
   2. Pallister-Hall syndrome: mutation analysis for mutation panel GLI3 (2023delG and 2012delG)
   3. Rubinstein-Taybi syndrome: FISH analysis of the deletion of the *CREBBP* gene on chromosome 16 (16p13.3)
   4. Smith-Lemli-Opitz syndrome
      1. Detection of two disease-causing mutations in the *DHCR7* gene previously identified in the proband
      2. Abnormal concentration of 7-dehydrocholesterol levels
6. Preimplantation genetic diagnosis.
   1. May be available for families in which the disease-causing mutation has been identified
   2. Reported for sonic hedgehog mutation causing familial holoprosencephaly (Verlinsky et al. 2003)

4. Management
   1. Care for common medical problems (Levy et al. 2010).
      1. Hydrocephalus.
      2. Seizures.
      3. Motor impairment.
      4. Oromotor dysfunction with risk of poor nutrition and aspiration.
      5. Chronic lung disease.
      6. Gastroesophageal reflux.
      7. Constipation.
      8. Hypothalamic dysfunction with disturbed sleep-wake cycles and temperature dysregulation.
      9. Endocrine dysfunction: Diabetes insipidus in particular is found in about 70% of children with classic HPE.
   2. Treatment strategies based on the types of brain malformations and associated anomalies
      1. Lethal entity: no specific treatment available
      2. Nonlethal entity
         1. Ventriculoperitoneal shunt for hydrocephalus
         2. Cleft lip and palate repair if indicated
         3. Monitoring of fluid and electrolyte intake in patients with diabetes insipidus
         4. Hormone replacement therapy for pituitary dysfunction
   3. Supportive
      1. Multidisciplinary team approach
      2. Support and counseling of the parents
      3. Seizure management

4. Gastrostomy tube placement and fundoplication for gastroesophageal reflux and vomiting

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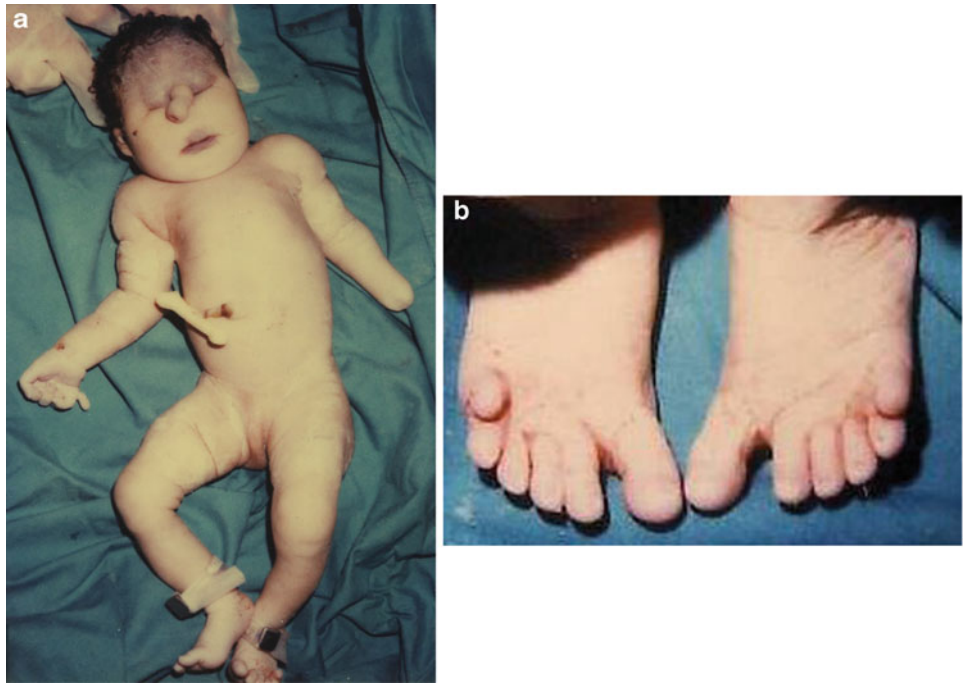

Fig. 1 (**a**, **b**) A neonate with trisomy 13 showing ethmocephaly, transverse reduction of the left forearm, and polydactyly of the right hand and both feet

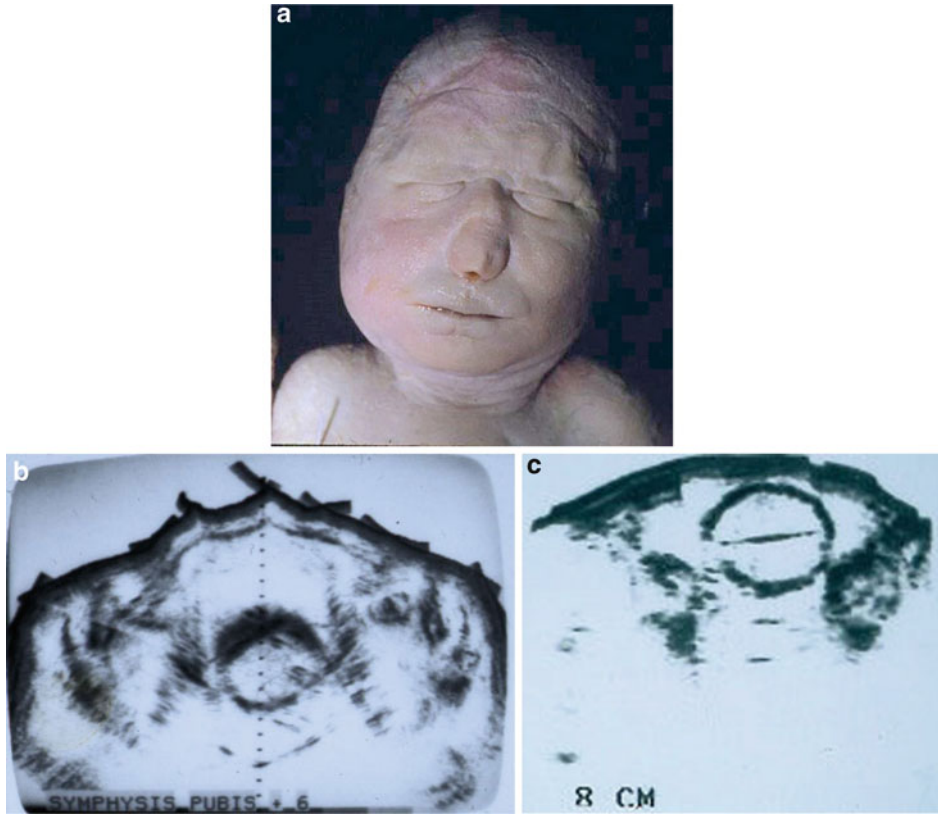

Fig. 2 (**a**–**c**) A neonate with trisomy 18 showing cebocephaly. The prenatal ultrasound showed fetal scalp edema, microcephaly, and holoprosencephaly (a normal brain ultrasound at the same gestation is illustrated here)

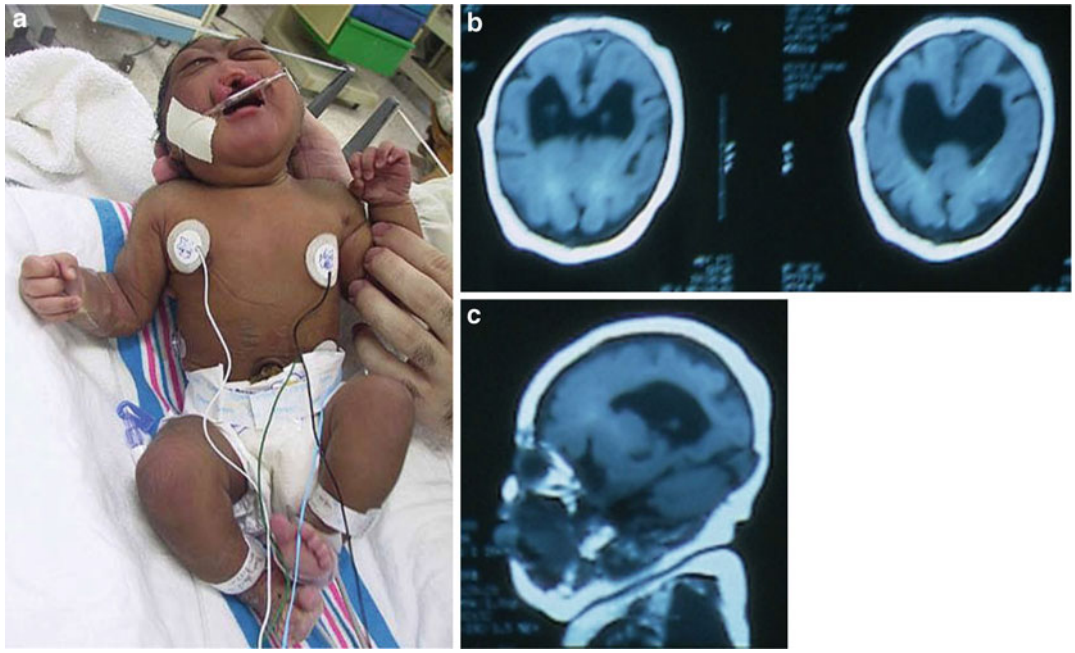

Fig. 3 (**a**–**c**) A neonate with semilobar holoprosencephaly illustrated by MRI of the brain

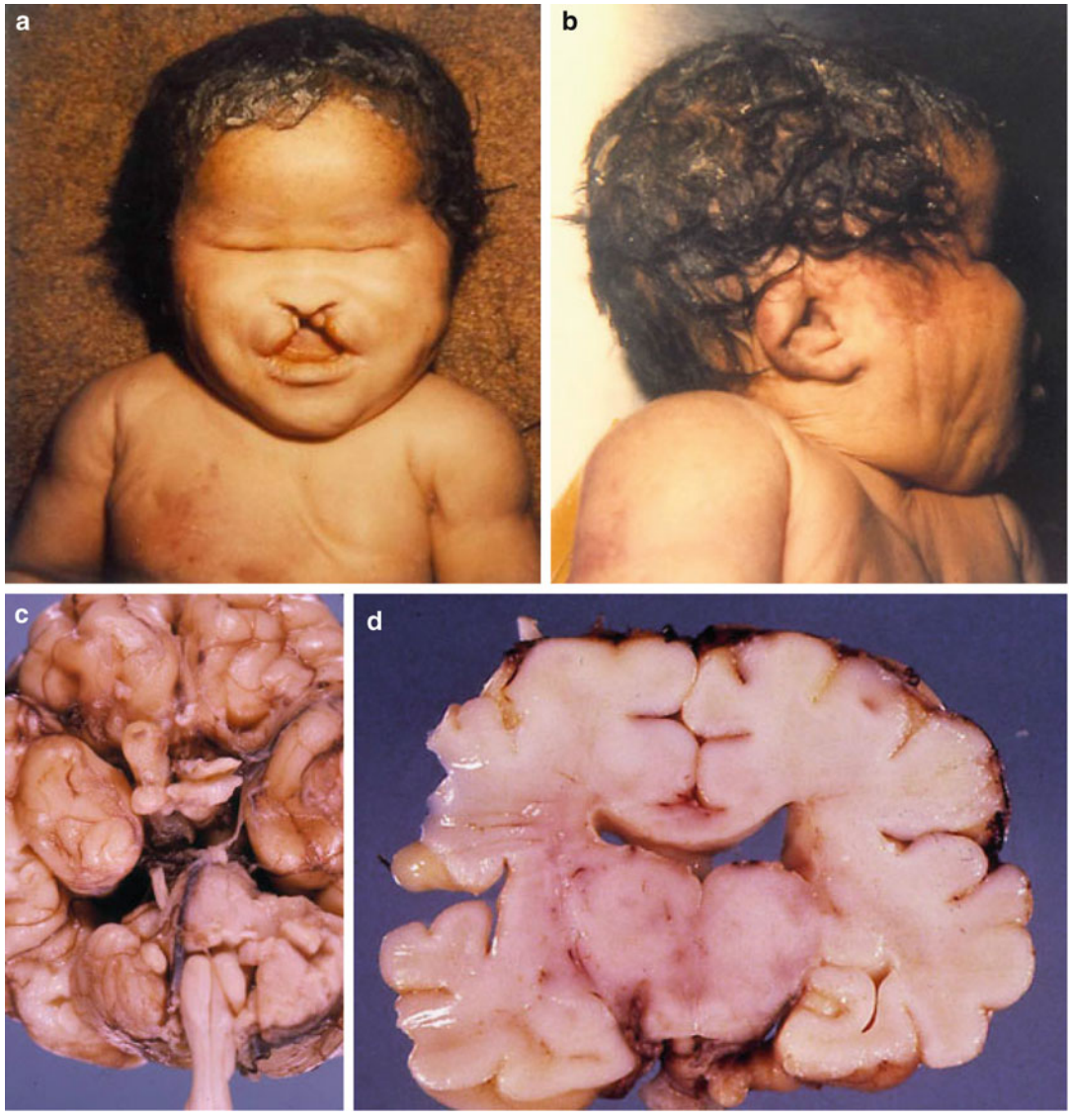

Fig. 4 (**a**–**d**) Front and lateral views of an infant with arhinencephaly. The postmortem brain showed absence of olfactory tract and sulci and septum pellucidum and fused thalami

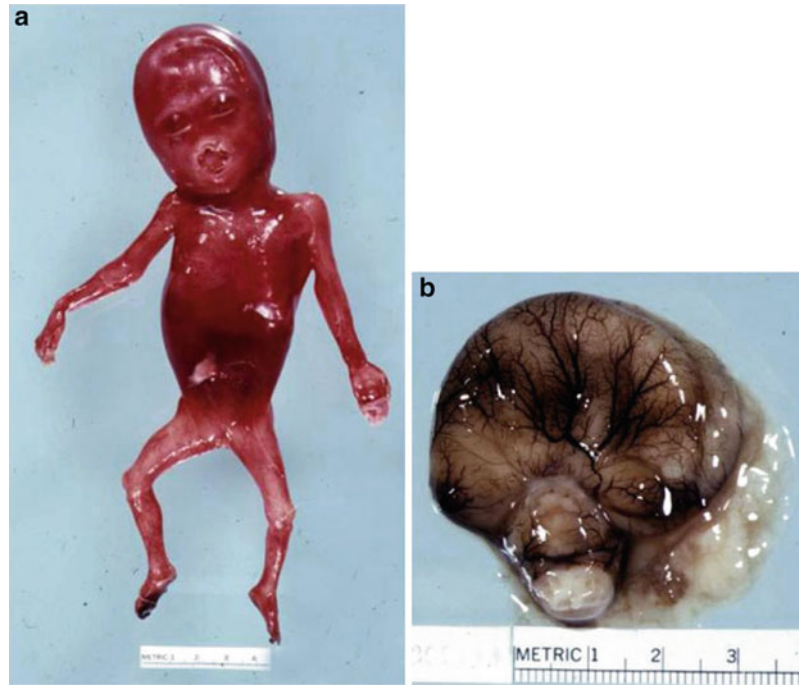

Fig. 5 (**a**, **b**) A fetus with premaxillary agenesis showing facial dysmorphism, including hypotelorism, absence of nose, median cleft lip and palate, and low-set ears. In addition, the fetus had 13 pairs of ribs and absence of uterus and left kidney. The pregnancy was terminated at 17 weeks of gestation because of alobar holoprosencephaly detected by ultrasonography. The postmortem brain showed alobar prosencephaly with a cerebral vesicle. Gyri were not developed

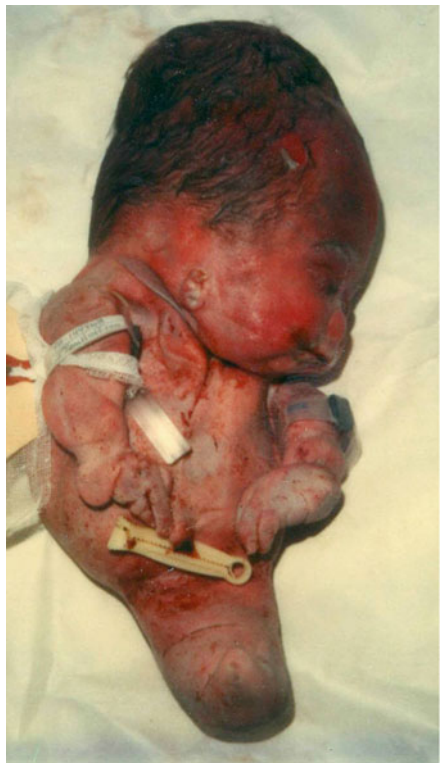

Fig. 6 A newborn with sirenomelia associated with holoprosencephaly

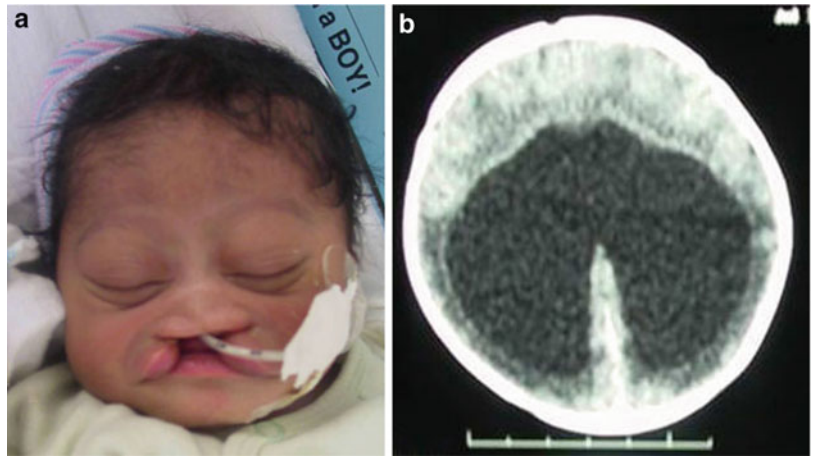

Fig. 7 (**a**, **b**) A neonate with premaxillary agenesis and holoprosencephaly illustrated by MRI of the brain

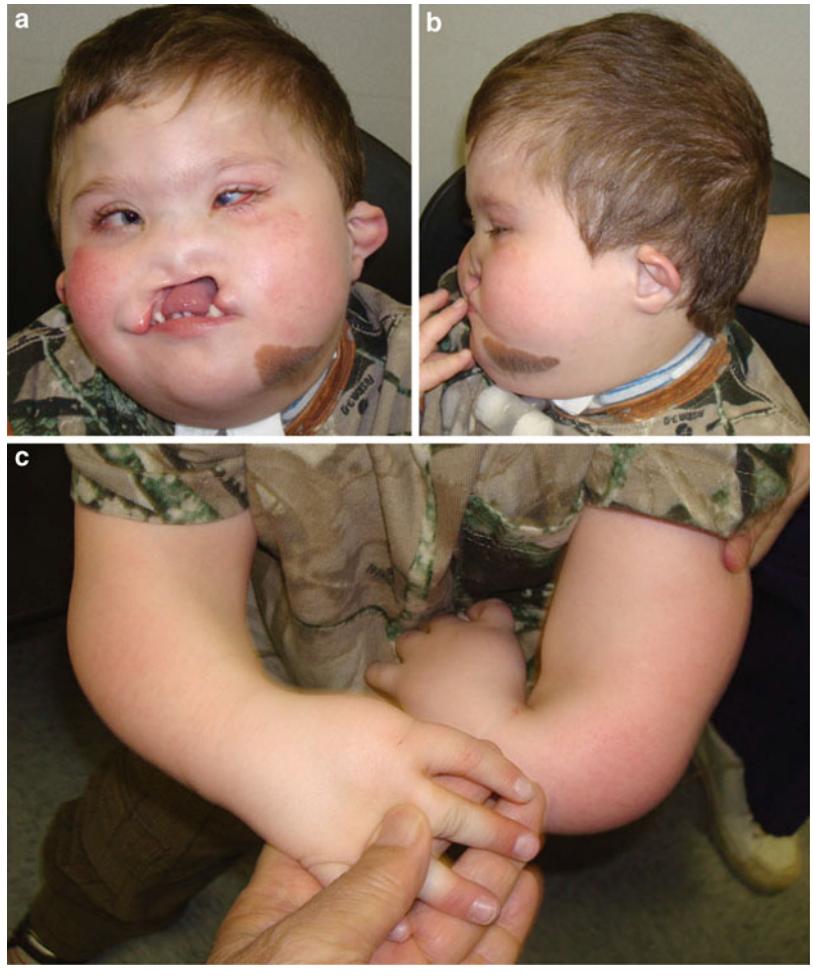

Fig. 8 (**a**–**c**) A child with premaxillary agenesis and upper limb defects

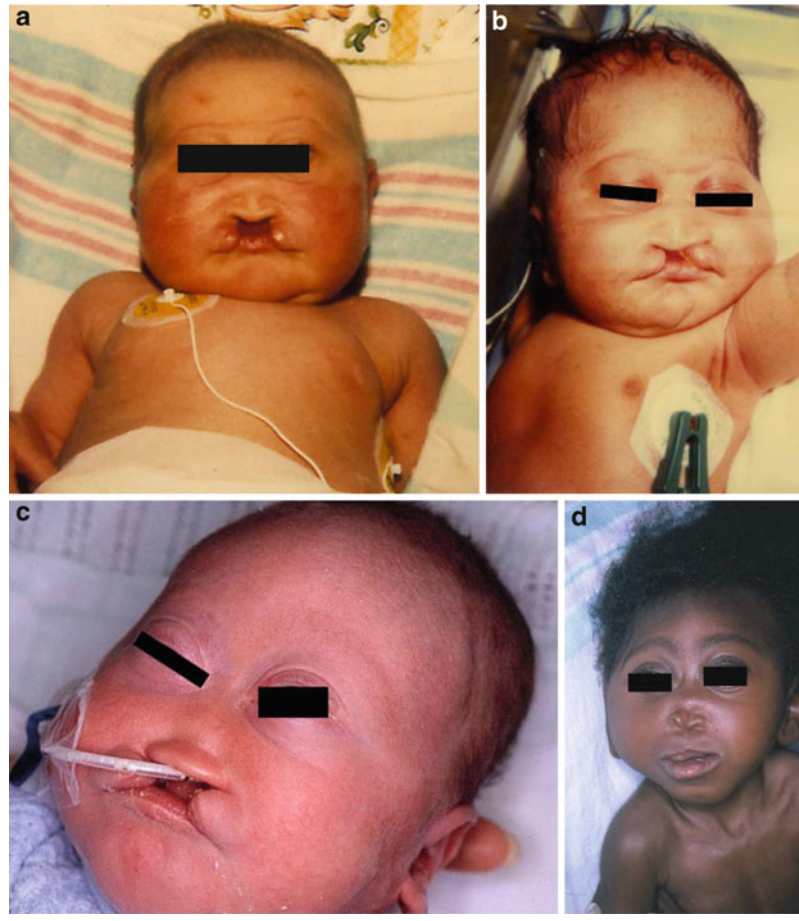

Fig. 9 (**a**–**d**) Four infants with premaxillary agenesis

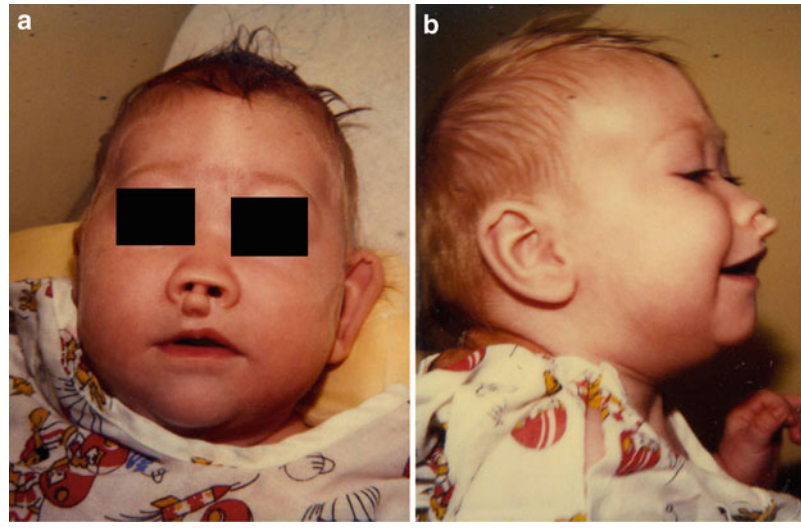

Fig. 10 (**a**, **b**) An infant with hypotelorism and duplicated nose

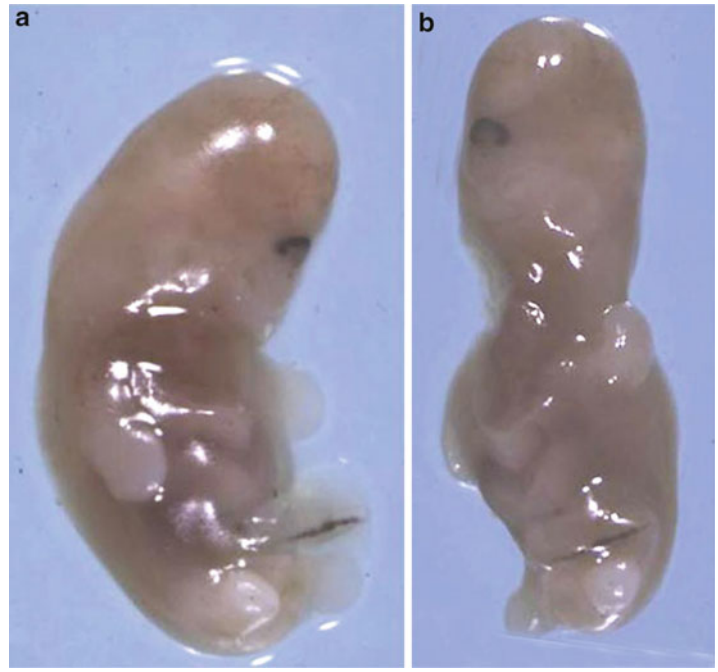

Fig. 11 (**a**, **b**) An aborted embryo with cyclopia

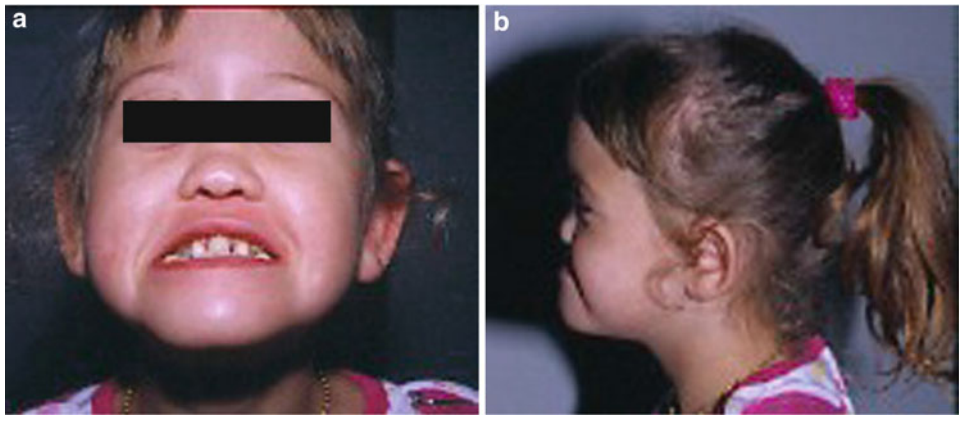

Fig. 12 (**a**, **b**) A girl with mild hypotelorism, antimongoloid slant, and a central incisor

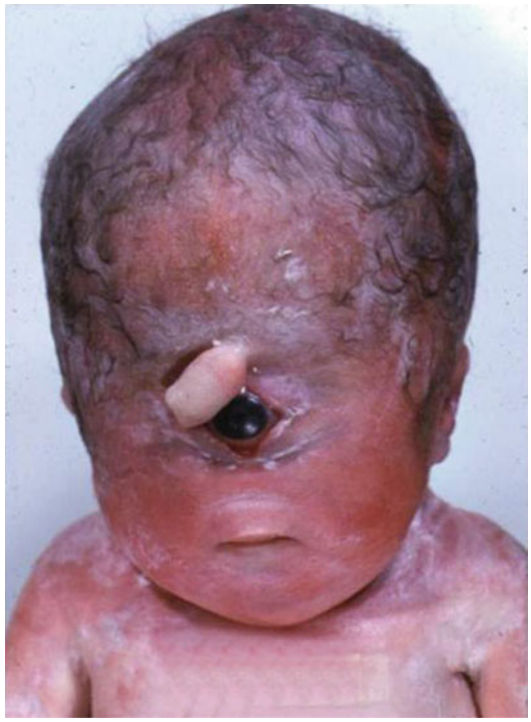

Fig. 13 A neonate with cyclopia. The infant had holoprosencephaly (arhinencephaly), agenesis of olfactory and optic nerves, agenesis of pituitary, cor biloculare, left diaphragmatic hernia, bilobar spleen, agenesis of adrenal glands, and absence of right umbilical artery

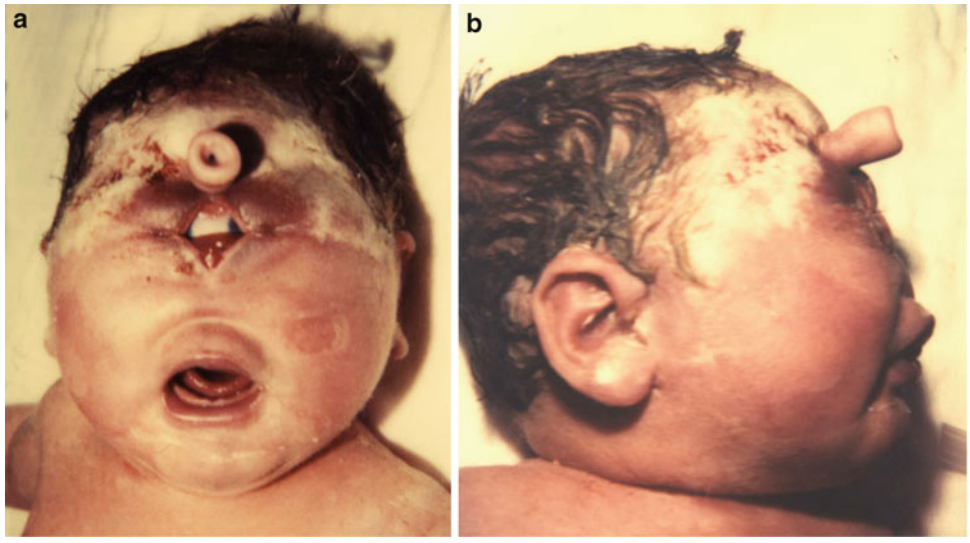

Fig. 14 (**a**, **b**) Another neonate with cyclopia

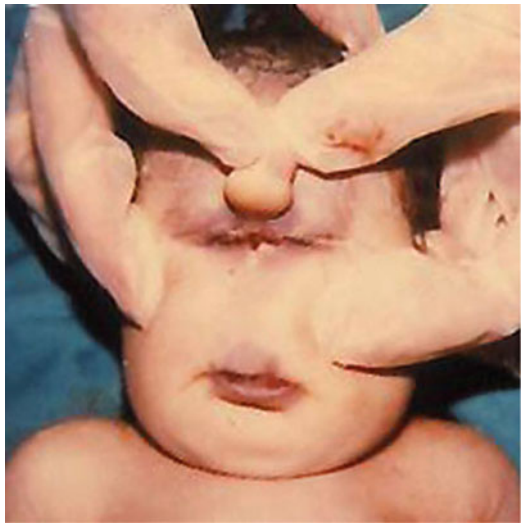

Fig. 15 An infant with ethmocephaly

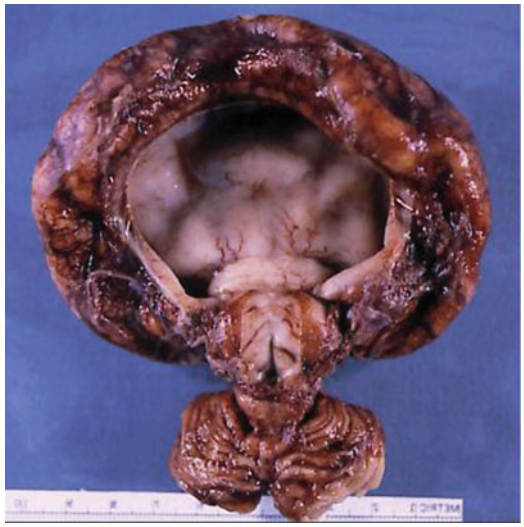

Fig. 16 Postmortem brain with holoprosencephaly (dorsal view) showing a dilated single ventricle. The large dorsal cyst was ruptured during dissection, and the remnants of the membranous cyst wall are vaguely visible at the margins of the ventricle, especially on the right side

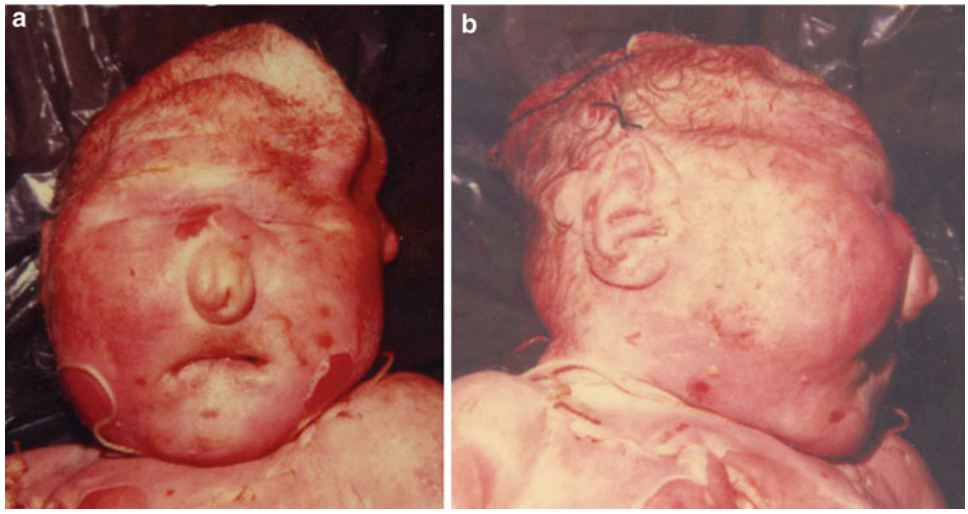

Fig. 17 (**a**, **b**) A neonate with cebocephaly

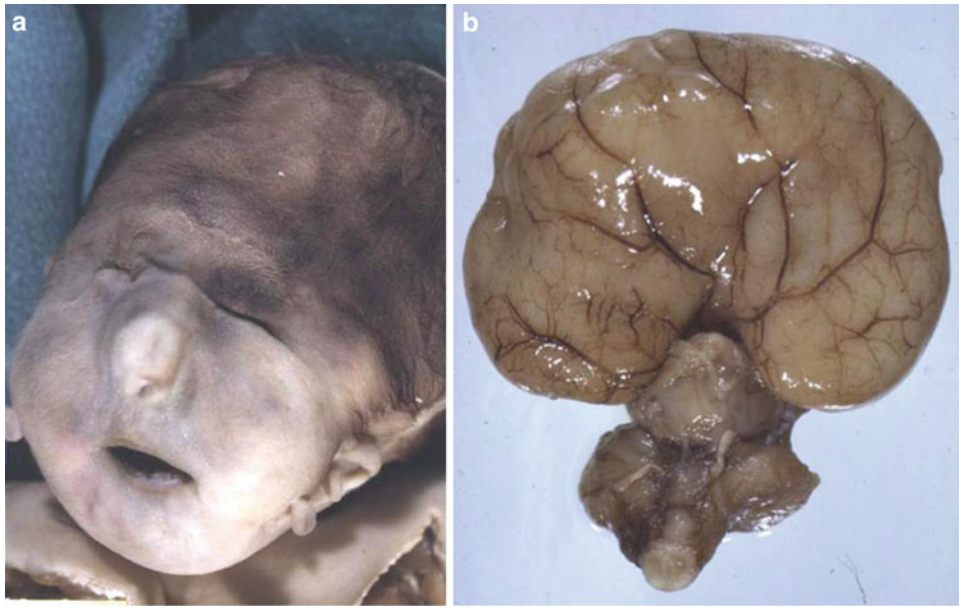

Fig. 18 (**a**, **b**) A premature neonate with cebocephaly. The infant had anophthalmia; bilateral nasal atresia; alobar holoprosencephaly (*ventral view*) with a 4.5 × 5.5 × 6.0 cm dorsal cyst (not shown), atresia of left external auditory canal with hypoplastic malformed auricle; agenesis of left lung; left kidney and left ureter; hypoplasia of left posterior cranial fossa and left cerebellum; multiple skin tags; hemivertebrae; and absence of right umbilical artery

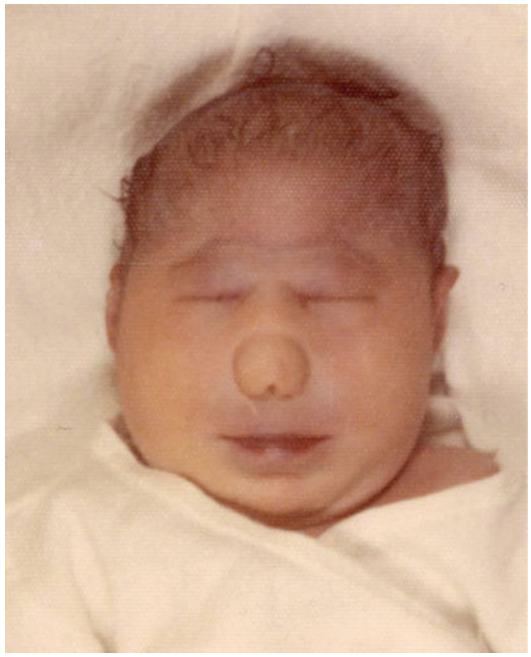

Fig. 19 A neonate with cebocephaly and 48, XXY, +13

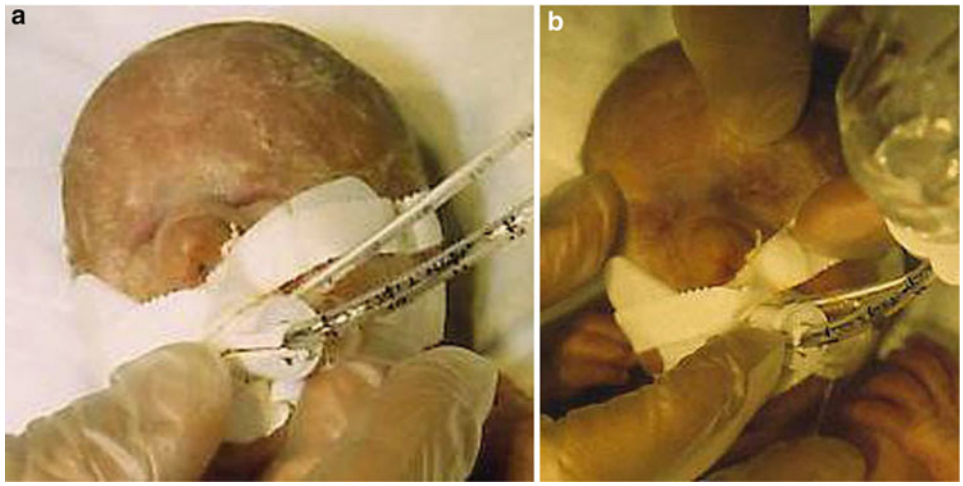

Fig. 20 (**a**, **b**) A newborn with trisomy 13 showing ocular hypotelorism and extreme microphthalmia

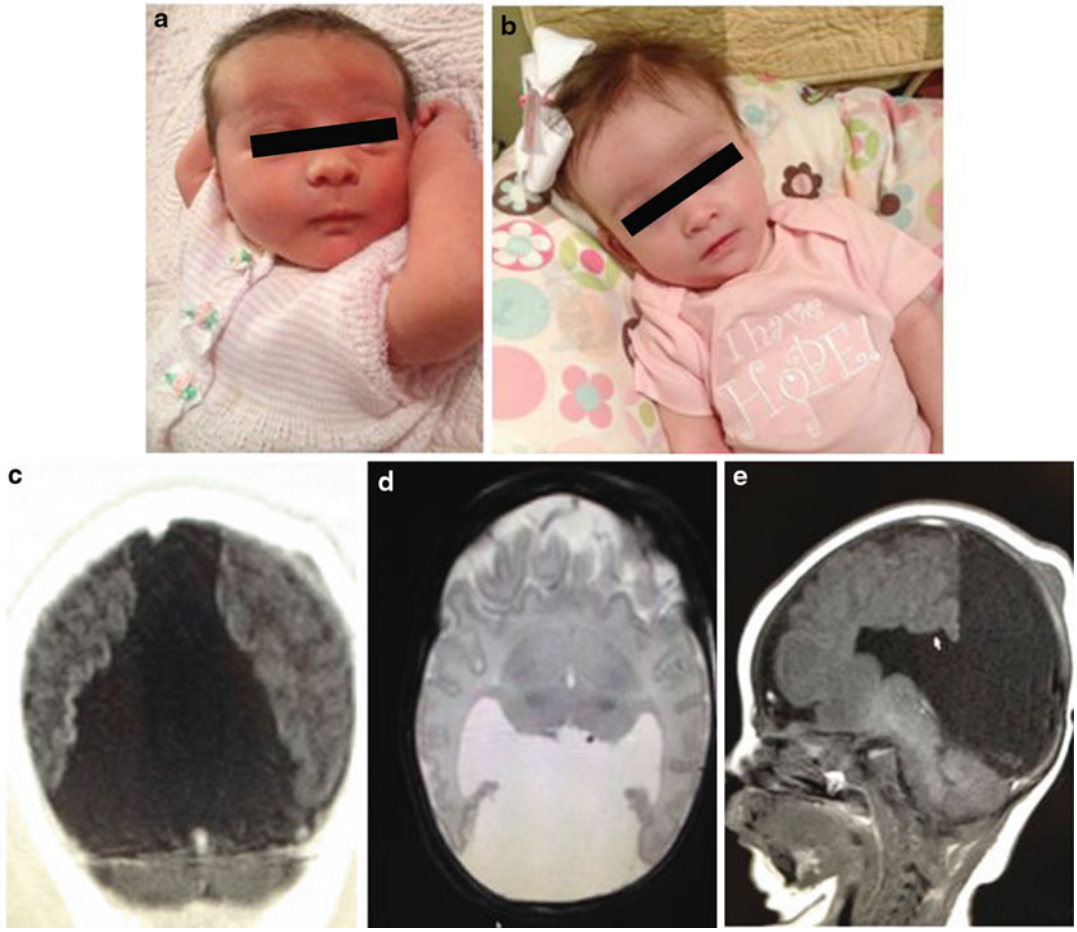

Fig. 21 (**a**–**e**) This female infant was evaluated at 4 weeks of age (**a**) and 18 months of age (**b**) for holoprosencephaly. Prenatal ultrasound examination at 17 weeks of gestation showed significant cerebral fluid accumulation in the fetal brain, a single ventricle of the brain, and a normal midface. A repeat ultrasound examination at 20 weeks of gestation showed a small head, abnormal intracerebral architecture, fused thalami, a large ventricle, and evidence of significant hydrocephalus. The baby was born at 36 weeks of gestation. The baby surprisingly looked normal despite the prenatal ultrasound findings of holoprosencephaly. The MRI of the brain (**c**–**e**) at birth showed dysgenesis of the corpus callosum, fusion of the posterior ventricle with absence of the septum pellucidum, interhemispheric fusion of the frontal lobe, enlarged cystic area over the posterior parieto-occipital region, partial formation of the frontal falx but bilateral Sylvian fissures communicated at the vertex, and severe hypoplasia of frontal lobe. These MRI findings are compatible with the diagnosis of semilobar holoprosencephaly. Molecular study (GeneDx) identified that the newborn was heterozygous for the C > A nucleotide substitution in exon 1 of the *ZIC2* gene, resulting in the replacement of a histidine codon (CAC) with a glutamine codon (CAA) at amino acid position 286 (c.858C > A or p.His286Gln)(H286Q). The presence of H286Q is considered a disease-causing mutation, and its presence is consistent with the diagnosis in this patient. No mutations were identified in the *SHH*, *SIX3*, or *TGIF* genes by sequencing

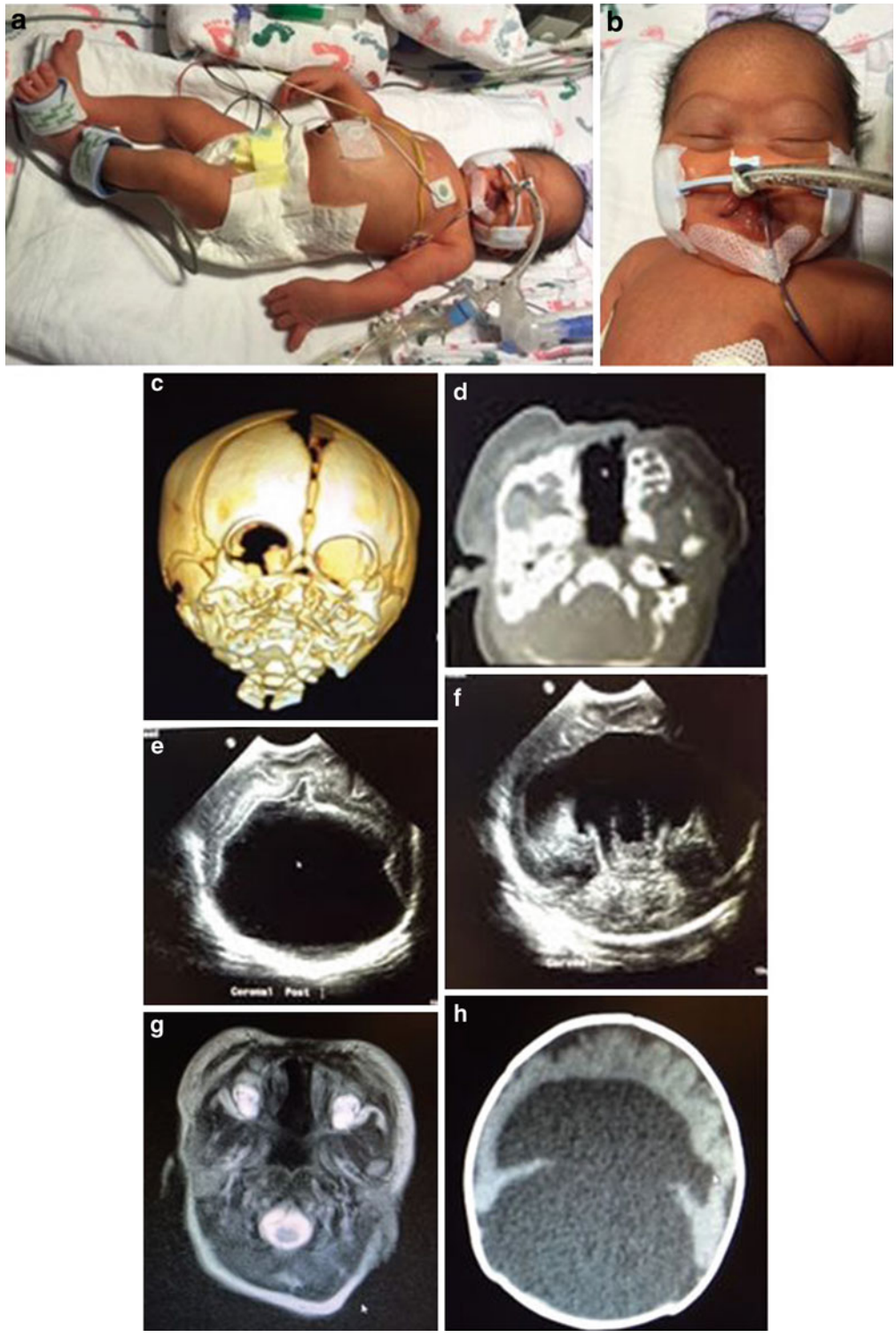

Fig. 22 **(a–h)** This baby girl was delivered at 36 6/7 weeks of gestation via cesarean section. Holoprosencephaly was diagnosed by prenatal ultrasound. Prenatal laboratories were unremarkable. Chromosome analysis of amniotic fluid revealed normal 46, XX. The chromosome microarray analysis was normal. At birth, the

Fig. 22 (continued) baby was noted to have ocular hypotelorism, depressed nasal bridge, and median cleft lip and palate (**a**, **b**). CT of the facial bones (**c**, **d**) revealed absence of the soft palate with a single cavity for the mouth and nasopharynx. There was essentially absence of the anterior maxilla and absence of the soft palate with a unicavity of the mouth and nasopharynx. CT of the brain (**e**, **f**) revealed a single ventricle with a large dorsal cyst and a pancaking of the residual cortex anteriorly. The basal ganglia regions were fused as are the thalami. The falx and the corpus callosum were absent. Multiplanar/multipulse sequence MRI of the brain (**g**, **h**) showed absence of anterior and posterior falx, a monoventricle along with fusion of both thalami, and absence of the corpus callosum. Hypogenesis/agenesis of the nasal cavity and nasal bones with cleft palate was present. The CT and MRI findings are consistent with alobar holoprosencephaly (Courtesy of Dr. Lea Bonifacio)

Holt-Oram Syndrome

Contents

In 1960, Holt and Oram (1960) described a family in which nine members in four generations were affected by skeletal abnormalities of the upper limbs, cardiac malformations, and arrhythmias. The prevalence is about 1 in 100,000 live births. About 40–85% of cases are due to fresh mutation.

Synonyms and Related Disorders

Atrial digital dysplasia; Heart-hand syndrome

Genetics/Basic Defects

1. An autosomal dominant disorder (Holmes 1965; Massumi and Nutter 1966):
   1. Complete penetrance (Gladstone and Sybert 1982)
   2. Widely variable expression (Gall et al. 1966; Kaufman et al. 1974; Letts et al. 1976; Smith et al. 1979)
2. Holt-Oram syndrome frequently linked to the gene *TBX5*, which is mapped to 12q24.1 (Terrett et al. 1994).
3. TBX5: essential for heart development (Horb and Thomsen 1999).
4. Caused by mutations in the *TBX5* gene, a member of the T-box family that encodes a transcription factor (Basson et al. 1997; Li et al. 1997; Akrami et al. 2001; Huang 2002; Fan et al. 2003):
   1. Mutations predicted to create null alleles cause substantial abnormalities in both the limb and heart.
   2. Nonsense mutations of *TBX5* produce distinct phenotypes (Basson et al. 1999):
      1. One class of missense mutations: causes significant cardiac malformations but only minor skeletal abnormalities.
      2. Other class of nonsense mutations: causes extensive upper limb malformations but few significant cardiac abnormalities.
      3. Several novel missense mutations in *TBX5* lead to functional haploinsufficiency and result in a reduced transcriptional activation of target genes, which is likely central to the pathogenesis of Holt-Oram syndrome (Boogerd et al. 2010).
5. Chamber-specific cardiac expression of Tbx5 and heart defects in Holt-Oram syndrome: provides an embryologic basis for the prevalence

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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of atrial septal defects (ostium primum and secundum), ventricular muscular septal defects, and left-sided malformations (endocardial cushion defects, hypoplastic left heart, and aberrant trabeculation), observed in patients with Holt-Oram syndrome (Bruneau et al. 1999).

6. Intrafamilial variations of the malformations: suggest that genetic background or modifier genes play an important role in the phenotypic expression of Holt-Oram syndrome (Huang 2002).
7. Sporadic cases may represent a de novo germline mutation in *TBX5* (Basson 2014).
8. T-box genes in human disorders (Packham and Brook 2003):
    1. Holt-Oram syndrome/TBX5
    2. Ulnar-mammary syndrome/TBX3
    3. DiGeorge syndrome/TBX1
    4. ACTH deficiency/TBX19
    5. Cleft palate with ankyloglossia/TBX22
9. Hand-heart syndromes (syndromes with frequent association of congenital cardiac and upper limb malformations): genetically heterogeneous (Basson et al. 1995):
    1. Holt-Oram syndrome: the most common form
    2. Heart-hand syndrome type II (Tabatznik syndrome)
        1. Hypoplastic deltoids
        2. Skeletal anomalies in the humeri, radii, ulnae, and thenar bones
        3. Brachydactyly type D
        4. Congenital cardiac arrhythmias (junctional rhythms and atrial fibrillation)
    3. Heart-hand syndrome type III
        1. Cardiac conduction defects (intraventricular delays and sick sinus syndrome)
        2. Skeletal malformations limited to the hands and feet (brachydactyly type C)
    4. Autosomal dominant "partial phenocopy" conditions
        1. Familial atrial septal defects with conduction disease occurring without limb deformities
        2. Familial limb malformations occurring without cardiac defects

Clinical Features

1. Preaxial radial ray abnormalities of the upper limb(s) (Ashby et al. 1969; Hurst et al. 1991; Basson et al. 1994; Newbury-Ecob et al. 1996; Venugopalan 2015)
    1. Almost always present
    2. Unilateral or bilateral
    3. Symmetric or asymmetric (left side more affected than the right side)
    4. Severe (phocomelia) to mild phenotype due to aplasia, hypoplasia, fusion, or anomalous development of involved bones
    5. Thumbs
        1. Aplasia
        2. Hypoplasia
        3. Triphalangeal
        4. Syndactyly
        5. Long
        6. Normal
    6. Fingers
        1. Clinodactyly
        2. Brachydactyly
        3. Hypoplasia
        4. Absent
        5. Syndactyly
        6. Normal
    7. Radial bones
        1. Hypoplasia
        2. Aplasia
    8. Ulnar
        1. Hypoplasia
        2. Aplasia
    9. Carpal bones
        1. Deformed
        2. Extra
    10. Thenar bones: hypoplastic thenar eminence
    11. Humerus
        1. Hypoplasia
        2. Abnormal head
        3. Aplasia
        4. Normal
    12. Clavicles
        1. Hypoplasia
        2. Prominent acromioclavicular joint
        3. Normal

13. Thorax
    1. Pectus excavatum
    2. Hypoplasia pectoralis major
14. Limited supination
15. Limited extension of the elbow

2. Cardiac anomaly (75% of cases) (Ashby et al. 1969; Sletten and Pierpont 1996; Basson 2014)
    1. Structural defects
        1. Atrial septal defect (most common type, usually of secundum variety)
        2. Ventricular septal defect
        3. Pulmonary stenosis (including peripheral arterial)
        4. Mitral valve prolapse
        5. Complex cardiac malformations (tetralogy of Fallot, hypoplastic left heart, endocardial cushion defects, truncus arteriosus)
    2. Cardiac conduction defects
        1. Paroxysmal tachycardia
        2. Prolonged PR interval (ECG)
        3. Wandering atrial pacemaker
        4. Atrial ectopics
        5. Sinus bradycardia
        6. Syncope
        7. Sinus arrest
        8. Atrioventricular block
        9. Atrial fibrillation
3. Mild to no symptoms in children and young adult
    1. Recurrent respiratory infections
    2. Failure to thrive
4. Older adults
    1. Congestive heart failure
    2. Supraventricular arrhythmia, especially atrial fibrillation
5. Differential diagnosis (Huang 2002)
    1. Fanconi anemia syndrome
        1. Multiple congenital anomalies consisting of malformations of the thumbs, forearms, and heart
        2. Progressive bone marrow failure with pancytopenia, typically in the first decade
        3. An increased risk for myelodysplasia or acute myelogenous leukemia
        4. Diagnosis based on detection of chromosomal breakage or rearrangement in the presence of diepoxybutane or mitomycin C
    2. Thrombocytopenia-absent radius
        1. Both radii always absent.
        2. Thumbs always present.
        3. Occasional phocomelia.
        4. Possible involvement of lower limbs:
            1. Club foot
            2. Knee instability
        5. Thrombocytopenia:
            1. Present in infancy
            2. Generally improves with time
        6. Heart defect can be present.
    3. Heart-hand syndrome II (Tabatznik) (Silengo et al. 1990)
        1. Type D brachydactyly (shortening of the distal phalanx of the thumb with or without shortening of the fourth and fifth metacarpals)
        2. Sloping shoulders
        3. Short upper limbs
        4. Bowing of the distal radii
        5. Absence of the styloid process of the ulna
        6. Supraventricular tachycardia
        7. Possible mild mental retardation and mild facial dysmorphism
    4. Heart-hand syndrome III
        1. Type C brachydactyly (shortening of the middle phalanges)
        2. An accessory wedged-shaped ossicles on the proximal phalanx of the index fingers
        3. Sick sinus syndrome
    5. Okihiro syndrome
        1. Duane syndrome
            1. A congenital eye movement disorder resulting from abnormal development of cranial nerve VI
            2. Absence of abduction of the globe
            3. Narrowing of the palpebral fissure on adduction of the globe
        2. Upper extremity reduction defects
        3. Cardiac malformations
    6. Long-thumb brachydactyly syndrome
        1. Elongation of the thumb distal to the proximal interphalangeal joint
        2. Often associated with index finger brachydactyly and clinodactyly

3. Narrow shoulders
4. Secondary short clavicles
5. Pectus excavatum
6. Occasional rhizomelic limb shortening
7. Frequent with cardiac conductive defect

7. VACTERL association
   1. Radial defect usually unilateral
   2. Accompanied by other malformations such as imperforate anus and tracheoesophageal fistula and congenital heart defect

Diagnostic Investigations

1. Radiography (Poznanski et al. 1970)
   1. Phocomelia of the upper limbs
   2. Shortened humeri
   3. Shortened forearms
      1. Aplasia/hypoplasia of the radius
      2. Hypoplastic ulna
      3. Radioulnar synostosis
      4. Humeral-ulnar synostosis
   4. Thumbs
      1. Absent thumbs
      2. Triphalangeal thumbs
      3. Clinodactyly
      4. Syndactyly
      5. Absent first metacarpals
      6. Hypoplastic thenar eminences
   5. First metacarpals
      1. Absent
      2. Hypoplastic
   6. Fifth fingers
      1. Short middle phalanx
      2. Clinodactyly
   7. Carpal bones
      1. Deformed
      2. Extra carpals
      3. Fused
      4. Irregular
      5. Delayed formation
   8. Shoulders
      1. Deformed scapula and/or clavicle
      2. Deformed head of the humerus
      3. Accessory bones
   9. Deformed sternum
2. Echocardiography for structural cardiac defects
3. Electrocardiography for cardiac conduction defects (Bossert et al. 2002)
   1. Sinus arrest
   2. Various degrees of atrioventricular block
   3. Right bundle branch block
   4. Sinus node dysfunction
   5. Wandering pacemaker
   6. Bradycardia
   7. Atrial fibrillation/flutter
   8. Supraventricular tachycardia and WPW syndrome
   9. Premature ventricular complexes
4. Karyotyping: helps map the breakpoints within the critical area of 12q (Venugopalan 2015)
5. Molecular genetic testing of *TBX5* by sequencing of entire coding region or mutation scanning

Genetic Counseling

1. Recurrence risk
   1. Probands
      1. Sixty to seventy percent have an affected parent
      2. Thirty to forty percent have a de novo mutation
   2. Patient's sib: not increased unless a parent is affected in which case, there is 50% recurrence risk
   3. Patient's offspring: 50%
2. Prenatal diagnosis
   1. Ultrasonography of Holt-Oram syndrome (Brons et al. 1988; Tongsong and Chanprapaph 2000) for fetuses at risk involving severe anomalies by demonstrating cardiac defect associated with upper limb defects, especially the radial ray defects
   2. Molecular genetic testing of *TBX5* of fetal DNA obtained from amniocentesis or CVS, provided the disease-causing mutation has been identified in the family
   3. Preimplantation genetic diagnosis
      1. May be available for families in which the disease-causing mutation has been identified

   2. Reported for Glu69ter *TBX5* mutation causing Holt-Oram syndrome (McDermott et al. 2005)
3. Management
   1. A permanent pacemaker for advanced heart block
   2. Surgery for severe cardiac defect
   3. Prostheses for children with severe limb shortening
   4. Orthopedic management of severe limb defects

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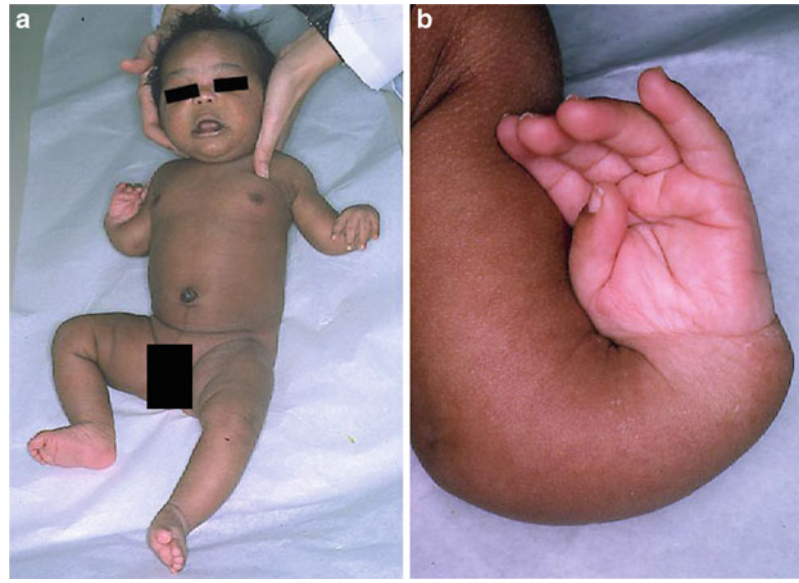

Fig. 1 (**a**, **b**) An infant with Holt-Oram syndrome showing club hands and fingerlike thumbs

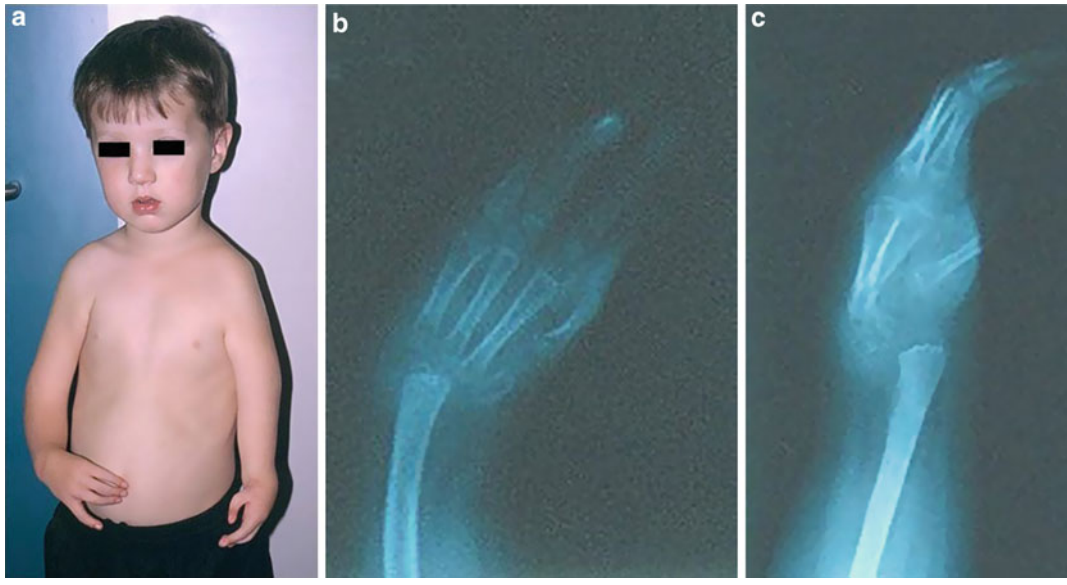

Fig. 2 (**a**–**c**) A child with Holt-Oram syndrome showing bilateral club hands, absent radius, and absent thumbs, demonstrated by radiographs

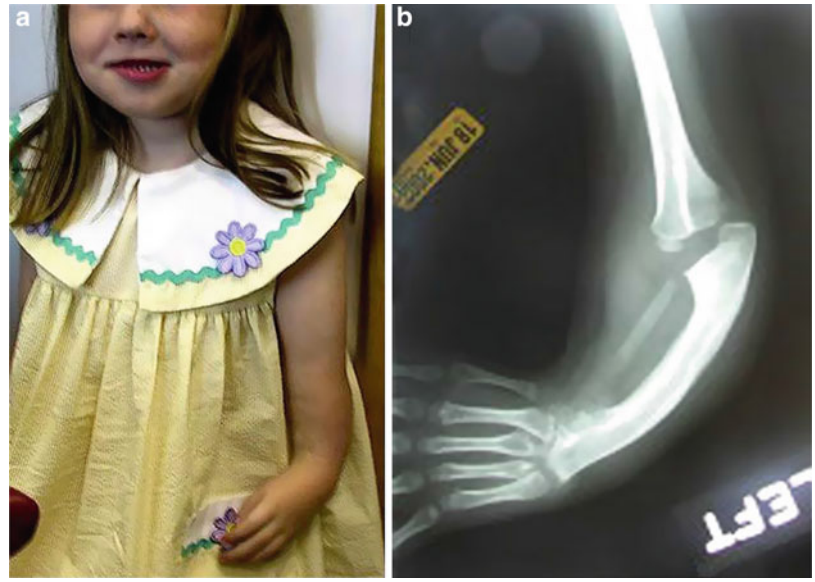

Fig. 3 (**a**, **b**) A child with Holt-Oram syndrome showing left club hand and hypoplastic radius, illustrated by radiography

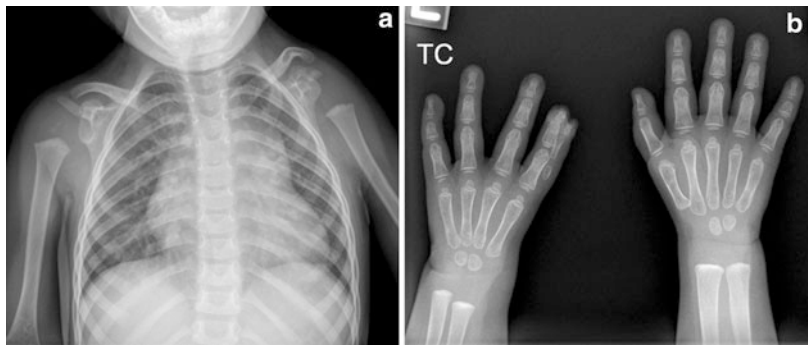

Fig. 4 (**a**, **b**) This 2-year-old girl with a history of Holt-Oram syndrome was evaluated. Chest X-ray (**a**) demonstrates dysplastic left glenoid with dysplastic appearance of the far lateral aspect of the left clavicle. Cardiac silhouette is mildly enlarged with prominent pulmonary vascularity and the normal left aortic arch is not seen. Findings are suggestive of cardiovascular anomaly. The X-ray of bilateral hands (**b**) demonstrates an abnormal left hand with findings suggestive of absence of the thumb, although with supernumerary bony and soft tissue along the margins of the second digit involving the phalanges. No accessory metacarpal was identified (Courtesy of Dr. Grace Guo)

Huntington Disease

Contents

Huntington disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, typically characterized by a movement disorder, affecting middle-aged adults. It is the most frequent cause of genetic chorea with reported prevalence rates in North America and Europe ranging from 3 to 7 per 100,000 (Cardoso et al. 2006).

Synonyms and Related Disorders

Huntington chorea

Genetics/Basic Defects

1. Caused by a mutation in the *IT15* gene, which is a 210-kb gene located near the tip of the short arm of chromosome 4 (4p16.3), resulting in the N-terminal region of huntingtin protein (Htt) (The Huntington's Disease Collaborative Research Group 1993; Cardoso 2009; Harris et al. 2009).
2. "Biallelic mutations" or "compound heterozygosity" are more accurate descriptive terms than "homozygosity" when there are two nonidentical expanded huntingtin (HTT) alleles (Uhlmann et al. 2015).
3. Patients with Huntington disease have an expanded and unstable trinucleotide CAG (cytosine-adenine-guanine) repeat in the *IT15* gene within exon 1 (Rubinsztein et al. 1996). Huntington disease is, therefore, considered one of the trinucleotide repeat disorders (Myers 2004).
    1. Normal CAG repeat length in the *HD* gene: 26 or lower.
    2. Expansions of 40 or more cause HD with complete penetrance.
    3. Individuals with 36–39 repeats may also develop HD but penetrance is incomplete (Rubinsztein et al. 1996).
    4. A CAG repeat range between 27 and 35: considered normal allele with particular risk for expansion into the HD range in the paternal germline (Ranen et al. 1995; Laccone et al. 1999)
    5. The number of CAG repeats
        1. Has significant implications for age at onset, disease severity, and stability of the gene between generations.
        2. Presence of a robust inverse correlation between the number of polyglutamine repeats and the age at disease onset so

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that longer repeat lengths are associated with earlier onset of Huntington disease (Shelbourne et al. 2007).
3. The number of CAG repeats, however, is not an absolute prediction of disease onset.

4. The nature of the genetic defect in the *HD* gene (Myers et al. 1998) explains many of the genetic features of the disorder, including:
1. The variability in age at onset
2. The tendency for juvenile disease to be inherited from fathers
1. Merritt et al. (1969) first observed that a disproportionate number of cases with onset before the age of 21 had inherited the *HD* gene from affected fathers.
2. The observation of earlier ages at onset in successive generations, termed "anticipation," is seen in several of the trinucleotide repeat disorders including HD.
3. Meiotic instability of the *HD* repeat in paternal transmission explains the observation of anticipation in HD.
3. The sporadic appearance of new mutations to HD

5. Pathophysiology (Roze et al. 2008)
1. The expanded polyglutamine repeat alters the normal functions of Htt.
2. The mutated protein, Exp-Htt, is itself toxic.
3. Htt interacts with an array of proteins in neuronal cells.
4. One important characteristic of Huntington disease is the particular vulnerability of a particular brain region, the caudate-putamen, despite similar expression of the mutated protein in other brain areas.

6. Potential pathways for pathogenesis of Huntington's disease (Frank 2014)
1. Neuronal aggregates
1. Neuronal intracytoplasmic and intranuclear inclusions containing mutant huntingtin, truncated N-terminal mutant and wild-type fragment, and chaperones and components of the proteolytic pathway are characteristic of HD neuropathology.
2. Accumulation of mutant protein aggregates may be a result of impairment of the ubiquitin–proteosome pathway.
3. Autophagic mechanisms are implicated in the clearance of protein aggregates.
2. Transcriptional dysregulation
1. Aberrant nuclear localization of mutant toxic huntingtin fragments and their association with transcription factors.
2. Dysregulation related to entrapment of transcriptional factors in protein aggregates.
3. Excitotoxicity: Excitotoxic neuron death in HD could result from a combination of increased glutamate and glutamate agonist release from cortical afferents.
4. Mitochondrial dysfunction and altered energy metabolism.
1. Selective inhibitors of complex II of the mitochondrial electron transport chain, 3-nitropropionic acid, and malonate cause selective striatal neuronal loss similar to that seen in patients with HD.
2. Multitude of bioenergetic defects has been reported in patients with HD.
5. Changes in axonal transport and synaptic dysfunction.
6. Normal huntingtin plays a role in axonal trafficking.
7. Disruption of axonal transport contributes to pathologic process in HD.

Clinical Features

1. A triad of HD (Cardoso 2009; Harris et al. 2009; Bordelon 2013)
1. Movement disorder (Leigh et al. 1983; Carella et al. 1993; Jankovic and Ashizawa 1995; Reuter et al. 2000; Tan et al. 2000)
1. Full spectrum of motor impairment
1. Eye movement abnormalities
2. Parkinsonian features
3. Dystonia (particularly in juvenile HD)
4. Myoclonus

5. Tics
6. Ataxia
7. Dysarthria
8. Dysphagia
9. Spasticity with hyperreflexia and extensor plantar responses

2. Chorea: often superseded by dystonia or akineto-rigid parkinsonian features with progressing illness
3. Dystonia: found in more than 90% of patients with HD in one study (Louis et al. 1999) although rarely it becomes as prominent as in idiopathic dystonias
4. Rigidity
5. Bradykinesia (slowness of movement)

2. Cognitive decline
   1. Universally go through cognitive decline, mental slowing, impaired problem-solving abilities, and other signs of a frontal dysexecutive syndrome, and they eventually become demented. These patients present with the prototype of so-called subcortical dementia (Lawrence et al. 1996; Kirkwood et al. 2001; Ho et al. 2003).
   2. Cognitive decline also heralds the juvenile onset of HD (Ribai et al. 2007).
   3. Asymptomatic carriers of the HD gene have decreased phonemic fluency (Larsson et al. 2008).
3. Behavioral changes
   1. Universal and may occasionally antedate motor manifestations
   2. Major depression is common, diagnosed in more than 40% of subjects, and responsible for increased suicide rates in HD
   3. Broad spectrum of behavioral abnormalities (Caine and Shoulson 1983; Mendez 1994; Schoenfeld et al. 1984; Shiwach 1994; Rosenblatt and Leroi 2000; Rosenblatt et al. 2003; Guttman et al. 2003)
      1. Depression.
      2. Anxiety or panic attacks.
      3. Obsessive-compulsive symptoms.
      4. Manic features.
      5. Psychosis.
      6. Irritability and aggressive behavior.
      7. Sexual disinhibition.
      8. Apathy.
      9. In presymptomatic HD, significantly more psychiatric symptoms (specially depression, anxiety, and obsessive-compulsiveness) were reported than for the controls (Duffin et al. 2007).
      10. Similarly, psychiatric difficulties are indicators of juvenile HD onset (Ribai et al. 2007).

2. End-stage HD
   1. Relentlessly progressive course with death occurring 15–20 years after symptom onset with particularly rapid progression in the juvenile Westphal variant.
   2. Typically rigid and akinetic, demented, and mute.
   3. Immobility and dysphagia often lead to aspiration pneumonia, the most common cause of death in these patients (Marshall 2004; Sorensen and Fenger 1992; Lanska et al. 1988).
3. Differential diagnosis
   1. Choreoacanthocytosis: the most likely disorder to be confused
      1. Dementia
      2. Involuntary movements
      3. Caudate atrophy
      4. Abnormal red blood cell morphology
      5. Neuropathy
      6. Seizures
      7. Myopathy
      8. Elevated creatine phosphokinase
      9. Self-mutilation
      10. An unusual eating dystonia
   2. Different causes of chorea
      1. Genetic causes of chorea syndromes (Gövert and Schneider 2013)
         1. Huntington disease
         2. Huntington disease-like (HDL) illnesses (HDL1, HDL2, HDL4)
         3. Chorea-acanthocytosis (Levine-Critchley syndrome)
         4. McLeod syndrome

5. Wilson disease (Hepatolenticular degeneration)
6. Benign hereditary chorea (Thyroid-lung syndrome)
7. Spinocerebellar atrophy types 2, 3, 17
8. Dentatorubropallidoluysian degeneration (DRPLA)
9. Ataxia-telangiectasia
10. Ataxia associated with oculomotor apraxia
11. Neuroferritinopathy (Haw River syndrome, Naito-Oyanagi disease)
12. Pantothenate kinase-associated degeneration
13. Leigh disease and other mitochondriopathy
14. Lesch-Nyhan disease
15. Creutzfeldt-Jakob disease
16. Neuronal ceroid lipofuscinosis
17. Glutaric aciduria
18. Polycythemia vera
19. Celiac disease

2. Immunologic causes
   1. Sydenham chorea
   2. Systemic lupus erythematosus
   3. Antiphospholipid antibody syndrome
3. Drug-induced chorea
   1. Amantadine
   2. CNS stimulants (amphetamines, methylphenidate, cyproheptadine)
   3. Anticholinergics
   4. Anticonvulsants (carbamazepine, phenytoin)
   5. Carbon monoxide
   6. Cocaine
   7. Dopamine agonists
   8. Dopamine-receptor blockers
   9. Estrogens
   10. Ethanol
   11. Levodopa
   12. Levofloxacin
   13. Lithium
   14. Sympathomimetics
   15. Theophylline
   16. Tricyclic antidepressants
   17. Carbamazepine
   18. Drugs that cause tardive dyskinesia
   19. Withdrawal emergent syndrome
4. Infections
   1. AIDS-related (toxoplasmosis, progressive multifocal leukoencephalopathy, HIV encephalitis)
   2. Bacteria (diphtheria, scarlet fever, whooping cough)
   3. Encephalitis (B19 parvovirus, Japanese encephalitis, measles, mumps, West Nile river encephalitis, others)
   4. Parasites (neurocysticercosis)
   5. Protozoan (malaria, syphilis)
5. Endocrine-metabolic dysfunction
   1. Adrenal insufficiency
   2. Hyper/hypocalcemia
   3. Hyper/hypoglycemia
   4. Hypomagnesemia
   5. Hypernatremia
   6. Liver failure
6. Vascular
   1. Postpump chorea (cardiac surgery)
   2. Stroke
   3. Subdural hematoma
7. Miscellaneous
   1. Anoxic encephalopathy
   2. Cerebral palsy
   3. Kernicterus
   4. Multiple sclerosis
   5. Normal maturation (less than 12 months old)
   6. Nutritional (e.g., B12 deficiency)
   7. Posttraumatic (brain injury)
   8. Chorea gravidarum hyperthyroidism
   9. External pallidal atrophy
   10. Pick disease
   11. Paraneoplastic syndromes
   12. Acute disseminated encephalomyelopathy
   13. Multiple system atrophy

Diagnostic Investigations

1. A confirmed family history of Huntington disease combined with clinical manifestations: sufficient for diagnosis (Harris et al. 2009)

2. Neuroimaging (MRI and CT)
    1. Severe atrophy of the caudate nucleus in moderately disabled patients
    2. May be relatively normal in patients in the early stages
3. Pet scan: Atrophy of the caudate nucleus can be detected in a presymptomatic state by the finding of head of caudate hypometabolism
4. Neuropathological features
    1. Neuronal loss and gliosis in the cortex and striatum, particularly the caudate nucleus: the most prominent neuropathologic features (Roth et al. 2005).
    2. Neuronal injury occurs initially in the caudate tail, in the medial paraventricular caudate, and in the dorsal part of the putamen.
    3. Further neuronal loss and an increase in astrocytes can be observed in widespread cortical and subcortical regions as the neurodegenerative process progresses.
    4. Pathologic observation of affected striatum shows loss of GABAergic spiny projection neurons with preservation of the aspiny interneurons and large aspiny acetylcholinesterase-positive neurons.
    5. A decrease of important neurotransmitters and neuropeptides, such as γ-aminobutyric acid (GABA), calbindin, enkephalin, and substance P, as a result of selective loss of the medium spiny neurons
5. Three main types of genetic testing of HD
    1. To confirm or rule out disease
    2. Presymptomatic testing to determine the carrier status of an individual at genetic risk for inheriting the disease
        1. To assist in making decisions about marriage, procreation, or career.
        2. The emotional impact of the result can be difficult to anticipate and can evoke substantial adverse emotional reactions (Taylor and Myers 1997; Almqvist et al. 1999).
        3. Appropriate pretest counseling is important to assist the at-risk individual in considering the risks and benefits of genetic testing for diseases such as HD for which available treatment does not justify testing.
    3. Prenatal testing to determine the carrier status of a fetus
6. Other laboratory testings (Singer 2012)
    1. Complete blood count
    2. Creatine phosphokinase
    3. Peripheral smear for acanthocytes
    4. Comprehensive metabolic panel
    5. Ceruloplasmin level
    6. Measurement of thyroxine (T4) and triiodothyronine (T3)
    7. B12 tests
    8. Antinuclear antibody sedimentation rate
    9. Lupus anticoagulant-anticardiolipin antibodies
    10. Antistreptolysin O (ASO) titer
    11. Anti-DNase-B titer

Genetic Counseling

1. Recurrence risk (Warby et al. 2014)
    1. Patient's sib
        1. A 50% risk if a parent is affected or has a CAG size of 40 or greater.
        2. An estimated risk as high as 5% (50 × 10%) of inheriting a mutant allele (≥36 CAG repeats) if the father has an intermediated allele (Chong et al. 1997).
        3. A sib who inherits an *HD* allele with reduced penetrance may or may not develop symptoms of HD.
    2. Patient's offspring
        1. A 50% risk of inheriting the disease-causing mutation from a parent with heterozygosity for the *HD* allele
        2. A 100% risk of inheriting the disease-causing allele from a parent with homozygosity for CAG repeat expansion in the *HD* gene
    3. A new mutation for Huntington disease following maternal transmission of an intermediate allele: While the likelihood remains exceedingly low, the possibility that intermediate alleles may unexpectedly undergo large expansions and produce a

new mutation following maternal transmission is important information to share when providing genetic counseling to families (Semaka et al. 2015)

2. Prenatal diagnosis (Warby et al. 2014)
    1. Prenatal diagnosis is possible for pregnancies at 50% risk by analyzing DNA extracted from fetal cells obtained by amniocentesis or CVS, provided the disease-causing allele in the affected parent or in an affected relative has been confirmed.
    2. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member.
3. Management (Harris et al. 2009)
    1. No definitive cure
    2. Limited therapeutic options currently
    3. Multidisciplinary team approach
        1. Medical
        2. Social work
        3. Physical therapy
    4. Selective serotonin reuptake inhibitors – effective in treating depression symptoms:
        1. Depression
        2. Mania
        3. Delusions
        4. Paranoia
        5. Chorea
        6. Other symptoms related to depression
            1. Rumination
            2. Perseveration
            3. Obsessive-compulsive disorder
            4. Suicide
        7. Mood stabilizers (valproate, carbamazepine, lamotrigine, or lithium) for bipolar disorders
    5. Neuroleptic for delusions and paranoia symptoms as well as chorea
    6. Atypical antipsychotics (risperidone, clozapine, olanzapine, and quetiapine) provide sufficient control of psychotic symptoms with a lower risk for extrapyramidal adverse effects and tardive dyskinesia.
    7. Nutritional management (Żukiewicz-Sobczak et al. 2014)
        1. In the early stages of HD, small amounts of blenderized foods given orally are recommended.
        2. In more advanced stages, enteral nutrition is essential using gastric, or jejunal tubes for short term.
        3. Most severe cases require gastrostomy or gastrojejunostomy.
    8. Palliative care in managing the latter stage of the disease
        1. Bedridden
        2. Mute
        3. Rigid
        4. Dysphagia
        5. Aspiration
4. Frequently used interventions, both pharmacologic and nonpharmacologic, in the management of the commonest HD symptoms and complications (Dayalu and Albin 2015)
    1. Chorea
        1. Dopamine depletion (tetrabenazine)
        2. Dopamine-receptor blockers
        3. Amantadine
    2. Parkinsonism and rigidity: Levodopa (juvenile HD)
    3. Dysarthria: speech therapy
    4. Dysphagia
        1. Speech and swallow therapy
        2. Dietary modification
    5. Gait impairment and falls
        1. Physical therapy
        2. Assistive devices
        3. Home modification
    6. Depression
        1. Selective serotonin reuptake inhibitors (SSRIs)
        2. Other antidepressants
    7. Anxiety
        1. SSRIs
        2. Buspirone
    8. Obsessive-compulsive behaviors: SSRIs
    9. Outbursts and impulsivity
        1. Antipsychotics
        2. Mood-stabilizing anticonvulsants
    10. Delusions and hallucinations: antipsychotics
    11. Apathy: structured routine and cues

12. Cognitive dysfunction and dementia: structured routine and cues
13. Weight loss
    1. High-calorie supplements
    2. Dietary consultation
14. Caregiver burden and family stress
    1. Social work services
    2. Individual and family therapy
    3. Respite care

5. Treatment advances in HD: A number of promising agents are in various phases of clinical investigation (Shannon and Fraint 2015)
    1. Deuterated tetrabenazine, pridopidine, cysteamine, resveratrol, the PDE10A inhibitor PF-02545920, laquinimod, green tea polyphenol, and an experimental lipid peroxidation inhibitor are currently ongoing, and others are planned.
    2. These represent a great hope for the HD community that real treatments are on the horizon for this devastating disease.

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Fig. 1 The patient, a 42-year-old lady, was evaluated for increasing weakness of her legs over the past 1 year, dropping things out of her hands and increased balance difficulties. She was ambulatory but had difficulty going upstairs and on uneven surfaces. She later developed typical movement disorders, chorea, dystonia, cognitive decline, and behavioral changes. The family history was significant for affected family members (mother and two brothers). The diagnosis of Huntington disease was confirmed by the presence of over 40 CAG repeats

Hydranencephaly

Contents

Hydranencephaly is a severe central nervous system disorder, characterized by complete or almost complete absence of cerebral cortex with preservation of meninges, basal ganglia, pons, medulla, cerebellum, and falx. Cerebral hemispheres are completely or partially destroyed and transformed into membranous sacs containing cerebrospinal fluid (Greco et al. 2001). Hemihydranencephaly is an extremely rare brain condition in which the vascular occlusion is presumed to be unilateral. Hydranencephaly occurs in less than 1 in 10,000 births (To and Tang 1999).

Synonyms and Related Disorders

Fowler syndrome; Hemihydranencephaly

Genetics/Basic Defects

1. Maternal risk factors
    1. Intercurrent infections
        (i) Toxoplasmosis
        (ii) Rubella
        (iii) Cytomegalovirus
        (iv) Herpes simplex
    2. Exposure to irradiation
    3. Exposure to teratogenic agents
        (i) Warfarin
        (ii) Estrogens
        (iii) Valproic acid
        (iv) Drug abuse: cocaine
    4. Twin-twin transfusion
    5. Intrauterine death of a monozygotic co-twin leading to vascular disruption of cerebral tissue
    6. Alloimmune and idiopathic thrombocytopenia
    7. Von Willebrand disease
    8. Congenital factor X and factor V deficiencies leading to hemorrhage into various congenital tumors
2. Presumably resulting from intrauterine bilateral internal carotid artery occlusion
    1. The structural defects occurring during the 4th and 6th months of gestation, after neuronal migration (Greco et al. 2001)
    2. Occurring between the 8th and 12th weeks, based on fetal ultrasound data, histopathologic findings, embryogenic vascular development, and postnatal CT and MRI findings (Cecchetto et al. 2013)
3. May be associated with porencephaly and congenital hydrocephalus

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Fowler (proliferative vasculopathy and hydranencephaly-hydrocephaly) syndrome (Fowler et al. 1972; Meyer et al. 2010):
    1. An autosomal recessively inherited prenatal lethal disorder characterized by hydranencephaly
    2. Brain stem, basal ganglia, and spinal cord diffuse clastic ischemic lesions with calcifications
    3. Glomeruloid vasculopathy of the central nervous system and retinal vessel
    4. A fetal akinesia deformation sequence with muscular neurogenic atrophy
    5. Associated with mutations in *FLVCR2* (feline leukemia virus subgroup C receptor 2)

Clinical Features

1. Markedly reduced life expectancy
    1. Stillborn
    2. Dying within a few weeks or months after birth
    3. Rare reports of prolonged survival (McAbee et al. 2000; Bae et al. 2008)
2. First year of life
    1. Typically marked by medical emergencies (Merker 2008)
        1. Uncontrolled epileptic seizures
        2. Pulmonary sequels to reflux and aspiration
        3. Unregulated intracranial pressure (hydrocephalus)
        4. Problems with temperature regulation
    2. Other features
        1. Macrocephaly
        2. Hyperirritability
        3. Retardation
        4. Transillumination
3. Survivors after first year of life
    1. The previously mentioned problems brought under control by medication, shunting, and other interventions
    2. Cases reported with diagnosis of developmental or persistent vegetative state (The Multi-society Task Force on the Persistent Vegetative State 1994)
    3. Cases reported exhibiting a responsiveness to surroundings incompatible with the classification vegetative state (Shewmon et al. 1999)
    4. Merker (2007) provided a detailed examination of functional reasons for expecting individuals with early and drastic (even complete) loss of cortical tissue to display forms of coherent responsiveness to their surroundings incompatible with a diagnosis of vegetative state.

Diagnostic Investigations

1. Transillumination of the skull (Alexander et al. 1956; Levin 1957; Barozzino and Sgro 2002)
    1. Used as a screening procedure for infants with macrocephaly and those suspected of having the following:
        1. Hydranencephaly
        2. Subdural effusion
        3. Subdural hematoma
        4. Hydrocephalus
        5. Porencephaly
        6. Increased intracranial pressure
        7. Skull fracture
        8. Nutritional deficiencies
    2. Has become a somewhat forgotten tool with advancements in and increased availability of neuroimaging techniques, but sometimes even a simple otoscope placed in the appropriate position can provide clinical "enlightenment."
2. CAT angiography (Jordan et al. 2004): A fast and safe way to assess the vascular anatomy of newborn babies with significant cerebral anomalies
3. MRI of the brain: better delineation of detail anatomy of the brain
    1. Absence of cerebral mantle (temporal and occipital lobe remnants commonly present)
    2. Falx cerebri partially or completely intact
    3. Thalamus and hypothalamic mesencephalic structures usually preserved
    4. Brainstem usually atrophic
    5. Cerebellum always intact

4. EEG for seizures
5. Comprehensive molecular test for Fowler syndrome (Sanger sequencing and HDT array deletion duplication) for FL/VCR2 mutation is available clinically

Genetic Counseling

1. Recurrence risk
   1. Sporadic occurrence
      1. Patient's sib: not increased
      2. Patient's offspring: not reported due to reduced life expectancy
   2. Autosomal recessive inheritance (Fowler syndrome)
      1. Patient's sib: 25%
      2. Patient's offspring: low unless the spouse is affected
2. Prenatal diagnosis (Lam and Tang 2000)
   1. Ultrasonography
      1. Hydranencephaly is suspected when there is a large fluid collection in the head with no recognizable cerebral cortex.
      2. During the early stages of disease, hydranencephaly is characterized by the presence of a large intracranial saclike structure containing homogeneous echogenic material, representing blood and necrotic debris secondary to massive liquefaction of the developing cerebral hemispheres (Sepulveda et al. 2012).
      3. Differentiated sonographically from holoprosencephaly by identifying the presence of dural attachments and distinctly separate thalami (McGahan et al. 1988)
      4. In severe hydrocephalus, a rim of cerebral cortex around the cystic cavity and enlargement of the 3rd ventricle may be visualized.
   2. Fetal MR imaging (Ghosh et al. 2013) shows normal-appearing brain stem, cerebellum, portions of the occipital and temporal lobes, and unfused thalami with the remainder of the supratentorium all representing fluid
   3. Molecular genetic analysis for Fowler syndrome
3. Management: symptomatic

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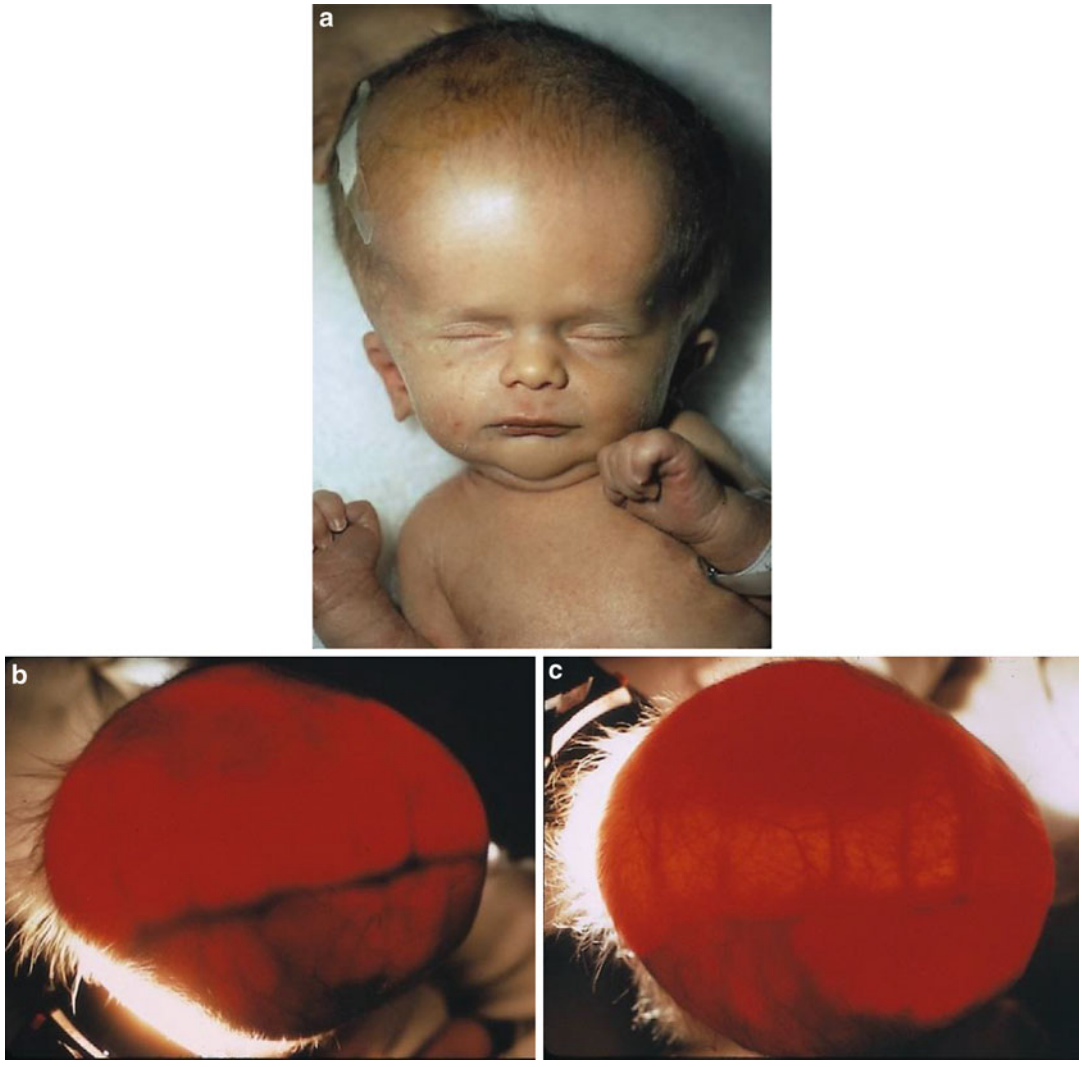

Fig. 1 (**a**, **b**, **c**) Transillumination of the skull in a neonate with hydranencephaly in a dark room shows the light illuminates the entire brain from the forehead through the back of the head. The transillumination is most drastic

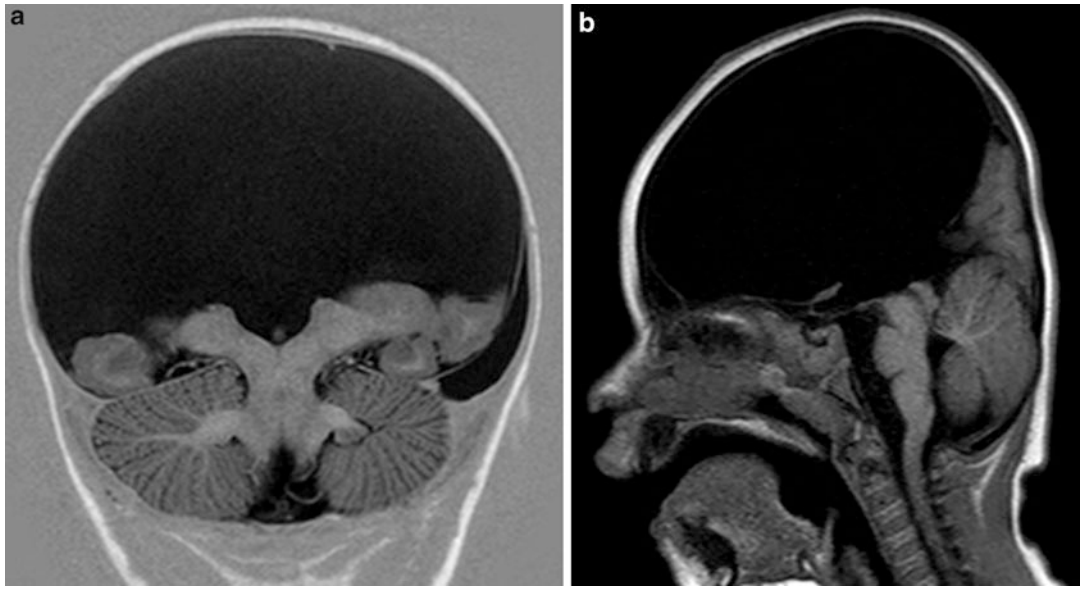

Fig. 2 (**a**, **b**) These two MRI images of the brain was from 1-year-old girl with seizures. Coronal image shows complete absence of the cerebral hemispheres with the exception of some portions of the inferior temporal lobes. The cerebellum is normal (**a**). The sagittal image shows absence of most of the cerebrum with a portion of occipital lobe present. Brainstem appears diffusely atrophic (**b**). The separated bilateral thalami are present (Courtesy of Dr. Grace Guo)

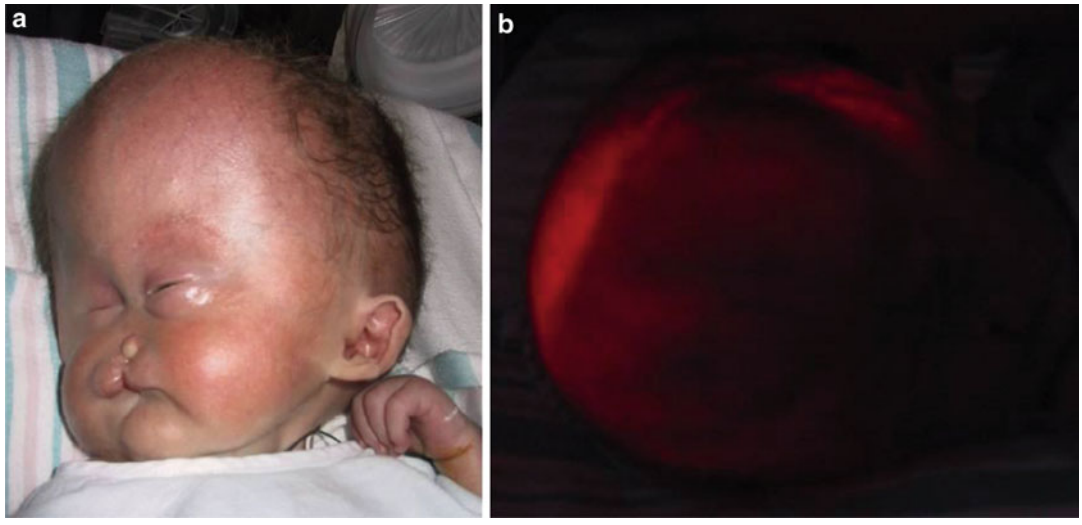

Fig. 3 (**a**, **b**) Transillumination of the skull in a neonate with alobar holoprosencephaly, difficult to differentiate from hydranencephaly

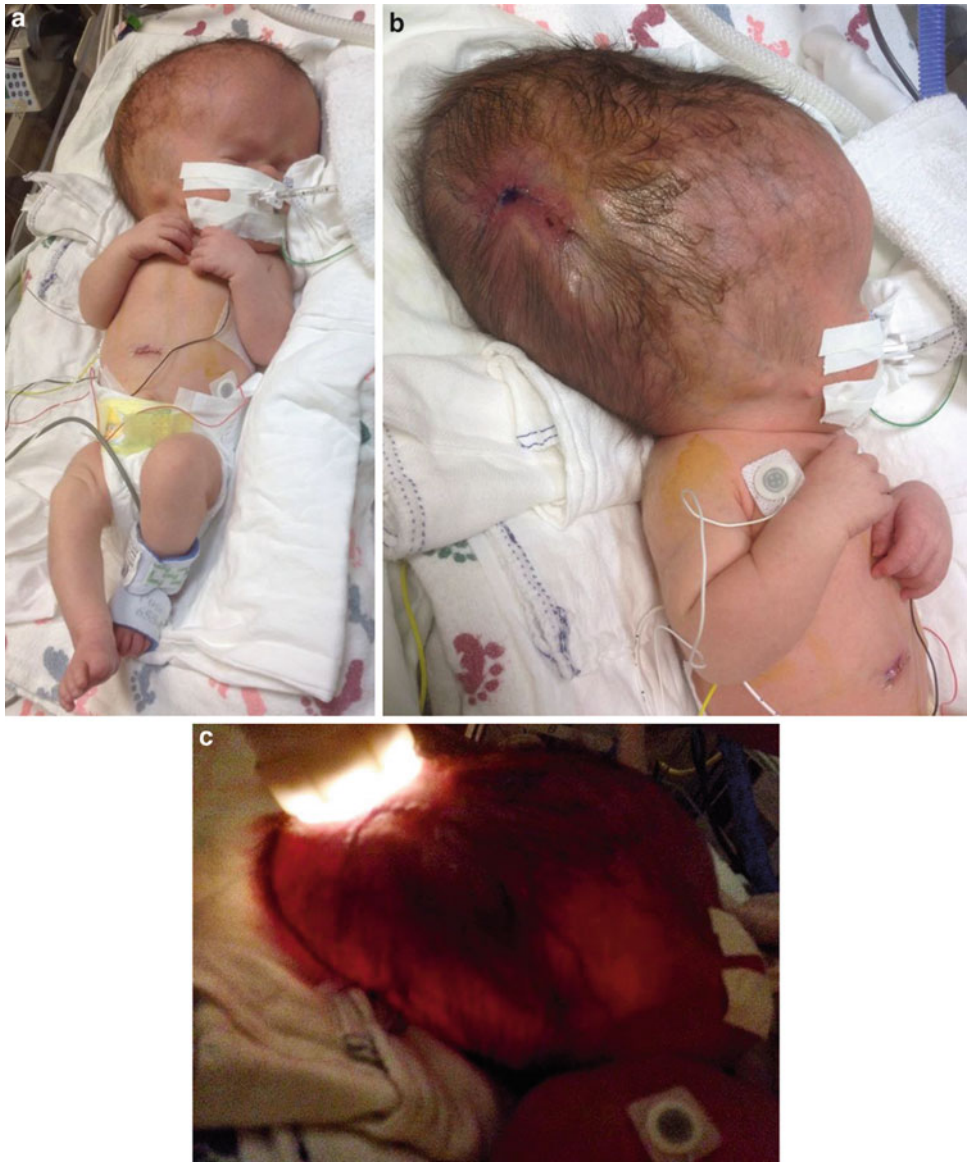

Fig. 4 (**a**, **b**, **c**) Transillumination of the skull in a neonate with massive hydrocephaly, difficult to differentiate from hydranencephaly

Hydrolethalus Syndrome

Contents

Hydrolethalus syndrome was coined by Salonen et al. in 1981 in patients with severe CNS malformations, hydrocephalus, micrognathia, cleft lip/palate, lung hypoplasia club foot, and polydactyly, distinguishable from the Meckel syndrome by the absence of polycystic kidneys (Salonen et al. 1981). The majority of cases were reported from Finland, rarely from other races (Adetoro et al. 1984; Shotelersuk et al. 2001).

Synonyms and Related Disorders

Salonen-Herva-Norio Syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Anyane-Yeboa et al. 1987; Salonen and Herva 1990)
2. Hydrolethalus syndrome locus: assigned to 11q23–11q25 in Finnish families (Visapaa et al. 1999)
3. *HYLS1* gene mutation (Mee et al. 2005; Paetau et al. 2008)
    1. Responsible for hydrolethalus syndrome in the Finnish population
    2. *HYLS1* c.632A > G (D211G) mutation: the common mutation carried in the Finnish population

Clinical Features

1. A lethal condition: stillborn or died within a few hours of birth in majority of cases.
2. Rarely, a mild case may survive over 5 months (Aughton and Cassidy 1987).
3. Hydramnios.
4. Severe midline CNS malformations:
    1. A midline cerebral cleft: more common
    2. The absence of the corpus callosum
    3. The absence of the septum pellucidum
    4. Holoprosencephaly (Bachman et al. 1990)
    5. Hydrocephalus secondary to aqueductal stenosis
    6. Dorsal midline defect of the foramen magnum, forming a keyhole-shaped opening (occipitoschisis)
    7. Cerebellar heterotopias

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_122

8. Brain stem malformations
9. Cerebral gyral abnormalities
10. Absent olfactory lobes
11. Hypothalamic hamartomas
12. Dandy-Walker malformation (Morava et al. 1996)
13. Optic nerve coloboma and hypoplasia (Kivela et al. 1996)

5. Craniofacial features:
   1. Microphthalmia
   2. Nasal anomalies
   3. Small mandible
   4. Cleft lip/palate
   5. Small tongue
   6. Low-set, malformed ears
6. Pulmonary anomalies:
   1. Abnormal larynx, trachea, and bronchi
   2. Pulmonary hypoplasia/agenesis (Toriello and Bauserman 1985)
   3. Defective lung lobulation
7. Congenital heart defects:
   1. Ventricular septal defect
   2. Open foramen ovale
   3. Common atrioventricular canal
8. Renal anomalies.
9. Duplex/bicornis uterus.
10. A typical "keyhole" occipital bone defect.
11. Polydactyly (Bachman et al. 1990):
    1. Hands: always postaxial
    2. Feet: almost always preaxial
12. Differential diagnosis (Muenke et al. 1991):
    1. Acrocallosal syndrome (Christensen et al. 2000):
       1. Macrocephaly.
       2. Craniofacial anomalies.
       3. Hallux duplication.
       4. Postaxial polydactyly.
       5. Absence of corpus callosum.
       6. Mental retardation.
       7. Reported to display a *GLI3* mutation.
       8. Mutations in the KIF7 gene, encoding a molecule within the Sonic hedgehog (SHH) pathway, have been identified as causative for acrocallosal syndrome but also for the fatal hydrolethalus syndrome and some cases of Joubert syndrome (Ibisler et al. 2015).
    2. Smith-Lemli-Opitz syndrome (severe form) (Rakheja et al. 2004):
       1. Hydrocephalus
       2. Cerebellar hypoplasia
       3. Cardiac anomalies
       4. Genital anomalies
       5. Polydactyly
    3. Orofacialdigital syndrome, type VI:
       1. Cerebellar anomalies
       2. Hypertelorism
       3. Micrognathia
       4. Midline cleft lip
       5. Cleft palate
       6. A small tongue with lingual nodules and multiple frenula
       7. Laryngeal anomalies
       8. Cardiac anomalies
       9. Preaxial polysyndactyly of the hands and feet
       10. Postaxial polysyndactyly of the feet
    4. Pallister-Hall syndrome (Paetau et al. 2008).
       1. Caused by nonsense and splicing mutations of *GLI3* gene at chromosome 7p13
       2. Hypertelorism
       3. Micrognathia
       4. Midline cleft lip
       5. Cleft palate
       6. A small tongue with lingual nodules and multiple frenula
       7. Hamartoma/hamartoblastoma
       8. Laryngeal anomalies
       9. Lung segmental anomalies
       10. Cardiac anomalies
       11. Postaxial polysyndactyly of the feet
    5. Overlap between short-rib polydactyly syndromes and hydrolethalus syndrome (Sharma et al. 1992).
    6. Walker-Warburg syndrome:
       1. Overlapping features
          1. Encephalocele
          2. Agenesis of midline brain structures
          3. Hydrocephalus
       2. Features usually not seen
          1. Eye abnormalities
          2. Polydactyly

7. Pseudotrisomy 13 syndrome (Verloes et al. 1991; Dincsoy et al. 1995).
8. Endocrine-cerebro-osteodysplasia (ECO) syndrome (Oud et al. 2016):
    1. Caused by a recessive mutation (p. R272Q) in intestinal cell kinase (ICK).
    2. Showing significant clinical overlap with ciliary disorders.
    3. Similarities are strongest between ECO syndrome, the Majewski and Mohr-Majewski short-rib thoracic dysplasia (SRTD) with polydactyly syndromes, and hydrolethalus syndrome.
9. Mutations in *KIAA0586* cause lethal ciliopathies ranging from a hydrolethalus phenotype to short-rib polydactyly syndrome (Alby et al. 2015).

Diagnostic Investigations

1. Radiologic studies (Herva and Seppanen 1984)
    1. Skull
        1. Microcephaly
        2. Occipital bone defect continuous with the foramen magnum
        3. A keyhole-shaped defect at the base of the skull
    2. Digital anomalies
        1. Postaxial polydactyly of the hands
        2. Preaxial polydactyly or hallux duplication of the feet
2. Ultrasound or MRI of the brain for delineation of brain anomalies
3. Echocardiogram for delineation of congenital heart defects
4. Molecular genetic study: target mutation analysis of *HYLS1* gene (c.632A > G)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Recurrence risk: 25%
        2. Unaffected sibs of a proband: two thirds chance of being heterozygotes
    2. Patient's offspring: a lethal entity not surviving to reproduction
2. Prenatal diagnosis
    1. Prenatal ultrasonography (Hartikainen-Sorri et al. 1983; Siffring et al. 1991; Pryde et al. 1993; Aughton 1994; Ammala and Salonen 1995; Norgard et al. 1996; de Ravel et al. 1999; Chan et al. 2004)
        1. Polysyndactyly
        2. CNS abnormality
        3. Congenital heart defects (atrioventricular septal defect or common atrioventricular canal)
    2. Possible for pregnancies at risk when the disease-causing mutation in the family is known
3. Management
    1. Supporting care
    2. No treatment available for the underlying lethal disorder

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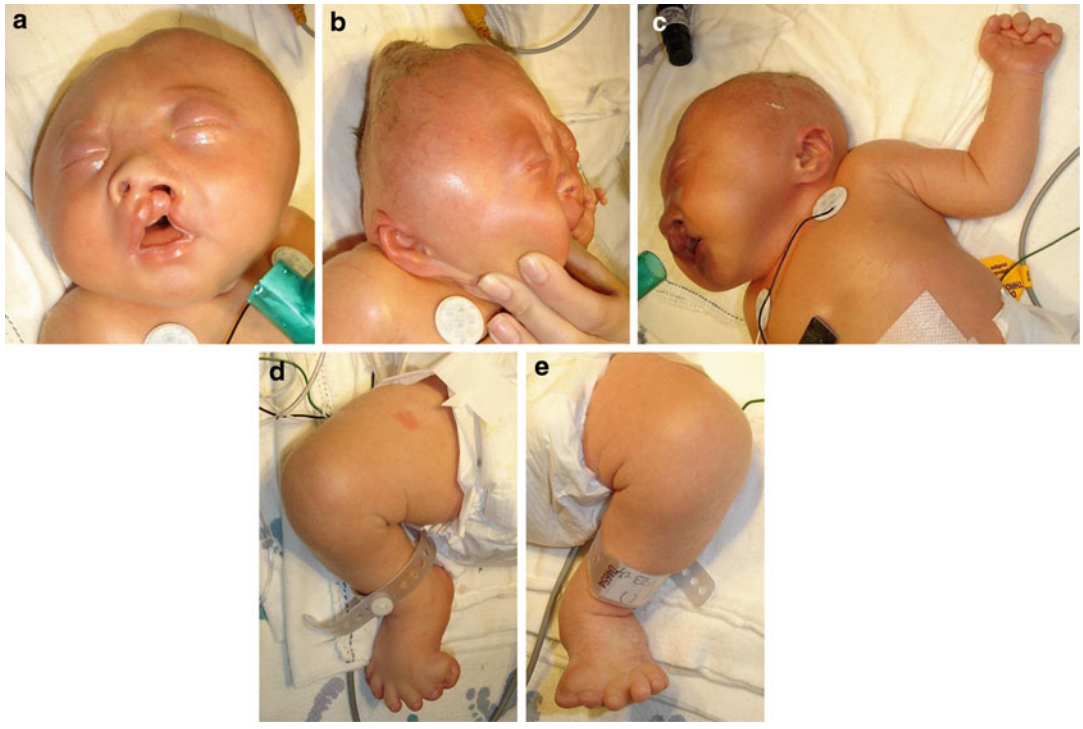

Fig. 1 (**a**–**e**) A neonate with hydrolethalus syndrome showing malformed skull, microcephaly, ocular hypertelorism, anomalous nose, micrognathia, left cleft lip and palate, a small tongue, low-set and malformed ears, short neck, postaxial polydactyly of the hands, and preaxial polydactyly of the feet

Hydrops Fetalis

Contents

Hydrops fetalis is a condition in which fluid accumulates in the serous cavities and/or in the soft tissues of the fetus. It is classified as immune if there is an indication of a fetomaternal blood group incompatibility, otherwise it is classified as nonimmune. The incidence of nonimmune hydrops fetalis is estimated to be approximately 1 in 2,500 to 1 in 3,500 neonates.

Synonyms and Related Disorders

Hydrops fetalis syndrome; Immune hydrops; Nonimmune hydrops

Genetics/Basic Defects

1. Causes of immune hydrops (IH)
    1. Rh-D disease (approximately 90% of immune hydrops)
        1. Prior to the 1960s, this is the most common cause (up to 80%) of all cases with hydrops fetalis. The incidence of rhesus isoimmunization has declined steadily because of the widespread use of anti-D gamma globulin. The majority of hydrops is now of the nonimmune type (Holzgreve et al. 1985).
        2. Mother (Rh−), father (Rh+), and fetus (Rh+).
        3. After sensitization, maternal Rh antibody (IgG anti-D) crosses the placenta and destroys the Rh-positive fetal red blood cells. It results in fetal anemia.
        4. Previous pregnancy, including maternal-fetal blood mixing.
        5. Previous abortion (spontaneous, missed, therapeutic).
        6. First trimester bleeding.
        7. Trauma.
        8. Blood transfusion.
    2. ABO incompatibility (rare, overall incidence about 1%)
        1. ABO incompatible pregnancies (about 20%) in which only 5% of these cases lead to hydrops
        2. Mother (nearly always O+ with antibodies to A, B, or both)
        3. Fetus (A, B, or AB)
    3. Other autoimmune causes (targeting other RBC antigens)
        1. Anti-Lewis antibodies: benign ("Lewis lives")

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_123

2. Anti-Kell antibodies (the second most common type accounting for about 10% of antibody-mediated severe fetal anemia): mild to severe hydrops ("Kell kills")
3. Anti-Duffy antibodies: mild to severe hydrops ("Duffy dies")

2. Pathophysiology of immune hydrops
   1. Sensitization of the mother to an antigen (usually Rh-D)
      1. Presence of antigen on fetal RBC but not on mother's RBC
      2. Primary response generally a maternal IgM anti-RBC response
   2. Production of IgG antibodies by the mother on the secondary exposure. The IgG antibodies can cross the placenta
   3. Destruction of fetal RBC by maternal anti-fetal RBC antibodies
      1. A Coombs' positive process
      2. Destruction most likely mediated by complement and macrophages
      3. Jaundice frequently observed secondary to increased bilirubin production
   4. Compensatory increase in fetal cardiac output due to decreased fetal hematocrit
   5. Heart failure resulting from high cardiac output by the fetal heart
      1. Edema
      2. Ascites
      3. Circulatory failure with fetal death *in utero*
3. Conditions associated with nonimmune hydrops fetalis (NIHF). Nonimmune type now represents majority of hydrops fetalis after the practice of anti-D gammaglobulin prophylaxis since the 1960s (Holzgreve et al. 1985; Watson and Campbell 1986; Poeschmann et al. 1991; Anandakumar et al. 1996; Heinonen et al. 2000; Ismail et al. 2001).
   1. Cardiovascular disorders (5.3–26%, the most frequent underlying cause of NIHF) (Knilans 1995; Bukowski and Saade 2000)
      1. Tachyarrhythmia (supraventricular tachycardia, atrial flutter)
      2. Bradyarrhythmias (complete heart block)
      3. Congenital heart block
      4. Hypoplastic left heart syndrome (31%)
      5. Endocardial cushion defects (13%)
      6. Agenesis of the ductus venosus
      7. Other anatomic defects of the heart
      8. Premature closure of the ductus arteriosus
      9. Generalized arterial calcification
      10. Cardiomyopathy
      11. Myocarditis (Coxsackie virus or CMV)
      12. Cardiac rhabdomyoma
      13. Intracardiac teratoma
   2. Chromosome abnormalities (7.5–77.8%, the second most frequent underlying causes of NIH)
      1. Trisomies
         1. Trisomy 21
         2. Trisomy 18
         3. Trisomy 13
      2. Turner syndrome (most common chromosome anomaly)
      3. Triploidies
      4. Deletions
      5. Others
   3. Recognizable syndromes (2.2–27.6%)
      1. Skeletal dysplasias (van Maldergem et al. 1992)
         1. Thanatophoric dysplasia
         2. Arthrogryposis multiplex congenita
         3. Asphyxiating thoracic dystrophy
         4. Hypophosphatasia
         5. Osteogenesis imperfecta
         6. Achondrogenesis
         7. Saldino-Noonan syndrome
         8. McKusick-Kaufman syndrome
         9. Klippel-Trenaunay-Weber syndrome
         10. Conradi syndrome
         11. Other types of skeletal dysplasias
      2. Metabolic diseases (Stone and Sidransky 1999)
         1. Mucopolysaccharidosis type IV Morquio disease (β-galactosidase deficiency)
         2. Mucopolysaccharidosis Type VII (β-glucuronidase deficiency)
         3. I-cell disease
         4. Niemann-Pick disease
         5. Gaucher disease

6. Sialidosis
7. Galactosialidosis
8. Salla disease (Finnish type sialuria)
9. Wolman disease
10. Farber disease
11. Carnitine deficiency
12. Disorder of glycosylation (Léticée et al. 2010)

3. Other genetic syndromes
   1. Pena-Shokeir syndrome
   2. Neu-Laxova syndrome
   3. Recessive cystic hygroma
   4. Multiple pterygium syndrome
   5. Meckel syndrome
   6. Caudal regression syndrome
   7. Noonan syndrome
   8. Tuberous sclerosis
   9. Myotonic dystrophy
   10. X-linked dominant disorders with male lethality (e.g., hypomelanosis of Ito)
   11. Other single-gene disorders

4. Twin pregnancy (twin-twin transfusion syndrome) (3–8%)
5. Hematologic disorders (10–27%) (Arcasoy and Gallagher 1995)
   1. Intrinsic hemolysis
      1. α-thalassemia syndromes (Homozygous α-thalassemia-1 is the most common cause of hydrops fetalis in Southeast Asia) (Lam et al. 1999)
      2. G6PD deficiency
      3. Pyruvate kinase deficiency
      4. Glucosephosphate isomerase deficiency
      5. Spectin abnormalities
   2. Extrinsic hemolysis (Kasabach-Merritt syndrome)
   3. Hemorrhage
      1. Fetomaternal hemorrhage
      2. Twin-twin transfusion syndrome
      3. Fetal hemorrhage
   4. Fetal liver and bone marrow replacement syndromes
      1. Transient myeloproliferative disorder
      2. Congenital leukemia
   5. Red cell aplasia and dyserythropoiesis
      1. Parvovirus B19 infection
      2. Blackfan-Diamond syndrome
      3. Congenital dyserythropoiesis
6. Thoracic abnormalities (2.5–13%)
   1. Diaphragmatic hernia
   2. Congenital cystic adenomatous malformation of the lung
   3. Extralobar pulmonary sequestration
   4. Congenital hydrothorax or chylothorax
   5. Mediastinal teratoma
   6. Laryngeal atresia
   7. Pulmonary hypoplasia
7. Genitourinary malformations (2.5–3.5%)
   1. Urethral obstruction
   2. Posterior urethral valves
   3. Neurogenic bladder with reflux
   4. Ureterocele
   5. Prune belly syndrome
   6. Upper urinary tract obstruction
   7. Renal dysplasia
   8. Cloacal malformations
8. Gastrointestinal anomalies
   1. Jejunal atresia
   2. Midgut volvulus
   3. Malrotation of the intestine
   4. Duplication of the intestinal tract
   5. Meconium peritonitis
   6. Gastroschisis
   7. Tracheoesophageal fistula
9. Hepatic diseases
   1. Polycystic disease of the liver
   2. Hepatic fibrosis
   3. Cholestasis
   4. Biliary atresia
   5. Hepatic vascular malformations
   6. Familial cirrhosis
10. Neurological abnormalities
    1. Encephalocele
    2. Intracranial hemorrhage
    3. Cerebral aneurysm
    4. Intracranial arteriovenous malformation
11. Maternal diseases/complications
    1. Medications (indomethacin taken to stop premature labor causing fetal ductus closure and secondary non-immune hydrops fetalis)
    2. Mirror syndrome
       1. Maternal edema

2. Preeclampsia
3. Systemic diseases
    1. Severe diabetes mellitus
    2. Severe anemia
    3. Hypoproteinemia
4. Antepartum/postpartum hemorrhage
5. Theca lutein cyst development

12. Placenta-umbilical cord abnormalities
    1. Chorioangioma
    2. Chorionic vein thrombosis
    3. Fetomaternal transfusion
    4. Placental and umbilical vein thrombosis
    5. Umbilical cord torsion
    6. True cord knots
    7. Angiomyxoma of the umbilical cord
    8. Aneurysm of umbilical artery
13. Intrauterine infections (2–17.5%)
    1. Viruses
        1. Parvovirus B19
        2. CMV
        3. Rubella
        4. Adenovirus
        5. Enteroviruses
        6. Coxsackie virus
        7. Polio
        8. Influenza B
        9. Respiratory syncytial virus
        10. Congenital hepatitis
        11. Herpes simplex, type I
    2. Bacteria/spirochetes
        1. *Treponema pallidum*
        2. *Listeria monocytogenes*
        3. *Leptospira interogans*
    3. Parasites
        1. *Toxoplasma gondii*
        2. *Trypanosoma cruzii*
    4. Other
        1. Chlamydia
        2. *Ureaplasma urealyticum*
14. Miscellaneous conditions
    1. Congenital lymphedema
    2. Congenital hydrothorax or chylothorax
    3. Polysplenia syndrome
    4. Amniotic band syndrome
    5. Congenital neuroblastoma
    6. Tuberous sclerosis
    7. Ovarian cyst torsion
    8. Fetal trauma
    9. Large fetal angioma
    10. Sacrococcygeal teratoma
    11. Cloacal malformation
15. Idiopathic (without an identifiable cause)

4. Pathophysiology of nonimmune fetal hydrops
    1. Cardiac failure directly involving the heart
        1. Arrhythmias
        2. Malformations
        3. Myocarditis
        4. Infarction
        5. Cardiomyopathy
    2. Abnormal vascularization causing high-output cardiac failure
        1. Twin-twin transfusion syndrome
        2. Acardiac twinning
        3. Tumors
        4. AV fistulas
        5. Placental vascular anomalies
    3. Profound anemia
        1. Hemolytic anemias
        2. Parvovirus B19 (fifth disease)
        3. Fetal-maternal hemorrhage
        4. Alpha-thalassemia, hemoglobin Bart's
        5. G6PD deficiency
        6. Glucose-6-phosphate isomerase deficiency
        7. Pyruvate kinase deficiency
        8. Defects of red cell membrane
    4. Decreased plasma oncotic pressure
        1. Congenital nephrosis
        2. Hepatic necrosis
    5. Fetal infections
        1. Increased capillary permeability (anoxia due to congenital infection)
        2. Infection of erythroid progenitor cells (e.g., parvovirus B19)
        3. Myocarditis (e.g., adenovirus, Coxsackie virus)
        4. Hepatic destruction (e.g., syphilis)
    6. Obstruction of venous return
        1. Congenital cystic adenomatoid malformation
        2. Fetal closure or restriction in the size of the ductus arteriosus, foramen ovale or ductus venosus

3. Diaphragmatic hernia
4. Pulmonary sequestration
5. Tumors of the heart, lungs, abdomen, or pelvis
6. Umbilical cord lesions
7. Obstruction of lymphatic flow (e.g., Turner syndrome)

5. Etiologies and mechanisms of nonimmune hydrops fetalis (Norton et al. 2015)
   1. Cardiovascular (17–35%): increased central venous pressure
   2. Chromosomal (7–16%): cardiac anomalies, lymphatic dysplasia, abnormal myelopoiesis
   3. Hematologic (4–12%): anemia, high-output cardiac failure; hypoxia (alpha thalassemia)
   4. Infectious (5–7%): anemia, anoxia, endothelial cell damage, and increased capillary permeability
   5. Thoracic (6%): vena caval obstruction or increased intrathoracic pressure with impaired venous return
   6. Twin-twin transfusion (3–10%): hypervolemia and increased central venous pressure
   7. Urinary tract abnormalities (2–3%): urinary ascites; nephrotic syndrome with hypoproteinemia
   8. Gastrointestinal (0.5–4%): obstruction of venous return; gastrointestinal obstruction and infarction with protein loss and decreased colloid osmotic pressure
   9. Lymphatic dysplasia (5–6%): impaired venous return
   10. Tumors, including chorioangiomas (2–3%): anemia, high-output cardiac failure, hypoproteinemia
   11. Skeletal dysplasias (3–4%): hepatomegaly, hypoproteinemia, impaired venous return
   12. Syndromic (3–4%): various mechanisms
   13. Inborn errors of metabolism (1–2%): visceromegaly and obstruction of venous return, decreased erythropoiesis and anemia, and/or hypoproteinemia
   14. Miscellaneous (3–15%)
   15. Unknown (15–25%)

Clinical Features

1. Maternal history associated with hydropic infants
   1. Previous history of hydrops
   2. Severe maternal anemia
   3. Associated polyhydramnios in at least 50% of hydropic fetuses
   4. Size-date discrepancy
   5. Twin gestation
   6. Maternal diabetes mellitus
   7. Maternal pregnancy-induced hypertension/preeclampsia
   8. Fetal arrhythmia
   9. Placentomegaly
   10. Positive antibody screen
   11. Syphilis or other TORCH infections
2. Edema due to right-sided heart failure
   1. Circulatory failure
   2. Ascites
      1. First sign of fetal hydrops caused by anemia
      2. Hypertension
      3. Hypoalbuminemia
      4. Prune belly secondary to marked fetal ascites
   3. Pleural effusions
   4. Pericardial effusions
   5. Jaundice (hyperbilirubinemia)
3. Hemolysis with extramedullary hematopoiesis
4. Hepatosplenomegaly
   1. A hallmark for immune hydrops
   2. Absent in nonimmune hydrops fetalis
5. Fetal prognosis: presence of fetal hydrops often indicating fetal compromise with a significant risk of mobility and death
   1. Cardiovascular disorders
      1. Best prognosis among abnormalities underlying nonimmune hydrops.
      2. Cumulative survival rate: 29%.
      3. Treatment of tachycardia improves prognosis.
   2. Chromosome abnormalities: 2% survival rate
   3. Syndromes: 5% survival rate
   4. Fetal infections: 19% cumulative survival rate
   5. Thoracic lesions: one of the best cumulative prognosis, 26%

6. Fetofetal transfusion syndrome: 20% survival rate
7. Extremely poor prognosis
    1. Anemia secondary to parvovirus infection.
    2. Anemia resulting from fetomaternal hemorrhage.
    3. α-thalassemia: All fetuses with the Hb Bart's hydrops fetalis syndrome succumb to severe fetal hypoxia in utero during the third trimester of gestation or within hours after birth (Chui and Waye 1998).
8. Good prognosis for psychomotor development in survivors with nonimmune hydrops fetalis (Haverkamp et al. 2000)

6. Morbidity (Bukowski and Saade 2000)
    1. Morbidity depending on the underlying disorder
    2. Short-term morbidity high (neonate requires difficult resuscitation, long and intensive hospitalization, and multiple invasive procedures)
    3. Relatively low long-term morbidity in NIHF in children diagnosed prenatally
7. Mortality (Hutchinson et al. 1982)
    1. Mortality rate: 50–98%
    2. Contribute to 3% of perinatal mortality
    3. Mortality depending on the underlying disorder

Diagnostic Investigations

1. Diagnostic evaluation of immune hydrops
    1. ABO and Rh typing and a serum antibody screen (positive indirect Coombs test) for every pregnant woman as early as possible during each pregnancy
    2. Spectrophotometric estimation of bilirubin pigments in the amniotic fluid, obtained by amniocentesis in selected patients, to estimate the risk of severe hemolytic disease while the fetus is still in utero
    3. Direct Coombs test on cord blood
        1. Nearly always positive in Rh-induced hemolytic disease of newborns (HDN)
        2. Frequently but not always positive in ABO-induced HDN
    4. Usually increased cord blood bilirubin and decreased cord blood hemoglobin in severe HDN
2. Diagnostic evaluation of newborn babies with nonimmune hydrops (Carlton et al. 1989; Steiner 1995)
    1. Cardiovascular disorders
        1. Echocardiogram
        2. Electrocardiogram
    2. Thoracic abnormalities
        1. Chest radiographs
        2. Pleural fluid examination
    3. Hematologic disorders
        1. Complete blood cell count
        2. Differential
        3. Platelet count
        4. Blood type
        5. Coombs test
        6. Blood smear for morphology
        7. Hemoglobin electrophoresis
    4. Gastrointestinal abnormalities
        1. Abdominal radiographs
        2. Abdominal ultrasound
        3. Liver function tests
        4. Peritoneal fluid examination
        5. Total protein
        6. Albumin
    5. Renal malformations
        1. Urinalysis
        2. BUN
        3. Creatinine
    6. Genetics
        1. Chromosome analysis (Santolaya et al. 1992)
        2. Skeletal radiographs
    7. Congenital infections: viral cultures or serology (Barron and Pass 1995)
        1. Parvovirus B19
            1. Maternal infection: specific IgM and IgG
            2. Fetal/neonatal infection: specific IgM, virus detection by PCR
        2. Syphilis
            1. Maternal infection: RPR or VDRL
            2. Fetal/neonatal infection: RPR or VDRL, dark-field examination of material from lesions

3. CMV
   1. Maternal infection: CMV-IgM or IgG seroconversion
   2. Fetal/neonatal infection: isolation of virus from amniotic fluid, fetal, or neonatal body fluid
4. HSV
   1. Maternal infection: HSV culture of lesion
   2. Fetal/neonatal infection: HSV culture of amniotic fluid, fetal tissue, or neonate
5. Toxoplasmosis
   1. Maternal infection: capture IgM, specific IgG
   2. Fetal/neonatal infection: capture IgM ELISA
6. Rubella
   1. Maternal infection: specific IgM and IgG or proven exposure plus compatible illness
   2. Fetal/neonatal infection: isolation of virus from fetal or neonatal body fluid, rubella IgM

8. Autopsy indicated for stillbirth or perinatal death including examination of the placenta and babygram (Norton 1994; Rodriguez et al. 2002)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Immune hydrops fetalis: will be affected unless sensitization is prevented
      2. Nonimmune hydrops fetalis
         1. Sporadic: no increased risk
         2. Autosomal recessive disorder: 25%
         3. Autosomal dominant disorder: not increased unless a parent is affected
         4. Chromosome disorder: increased especially when a parent is a translocation carrier
   2. Patient's offspring
      1. Immune hydrops fetalis: recurrence risk not increased
      2. Nonimmune hydrops fetalis
         1. Sporadic: no increased risk
         2. Autosomal recessive disorder: not increased unless the spouse is a carrier
         3. Autosomal dominant disorder: 50%
         4. Chromosome disorder: increased if the patient survives to reproductive age
2. Prenatal evaluation of immune hydrops fetalis
   1. Rh testing and ABO typing indicated for all pregnancies
   2. Positive maternal antibody screen (indirect Coombs test)
   3. Suspicious for immune hydrops
      1. Cord blood for testing of hemolysis and hematocrit
      2. Amniocentesis for bilirubin
   4. Specific testing for antibodies in women with previous pregnancy losses
   5. Doppler ultrasonography (Mari et al. 2000)
      1. Used to measure peak velocity of systolic blood flow in fetus
      2. Increased peak systolic blood flow velocity in fetuses with anemia
      3. Increased systolic velocity: 100% sensitive to fetal anemia
   6. Prenatal diagnosis of fetal Rh-D status by molecular analysis (Lo et al. 1998)
3. Maternal evaluation of nonimmune hydrops fetalis (Holzgreve et al. 1984, 1985)
   1. Complete blood count and indices for hematologic disorders
   2. Hemoglobin electrophoresis (α-thalassemia)
   3. Kleihauer-Betke stain for evidence of fetomaternal hemorrhage
   4. Maternal blood chemistry for fetal red cell enzyme deficiency
      1. Glucose-6-phosphate deficiency screen
      2. Pyruvate kinase carrier status
   5. Infection screening
      1. Syphilis by VDRL
      2. TORCH titers
      3. Parvovirus titers
      4. Group B streptococcus
      5. Listeria monocytogenes
   6. Autoantibody screen
      1. Systemic lupus erythematosus

2. Anti-Ro (anti-SS-A) and Anti-La (anti-SS-B) antibody titers for Sjogren's syndrome
7. Fetal echocardiography for presence of congenital heart defects

4. Prenatal ultrasonography (Forouzan 1997)
   1. Immune hydrops secondary to α-thalassemia (Tongsong et al. 1996)
      1. Hepatosplenomegaly (>95%)
      2. Cardiomegaly (>95%)
      3. Edematous placenta (>95%)
      4. Ascites (>95%)
      5. Oligohydramnios (82%)
      6. Subcutaneous edema (75%)
      7. Decreased fetal movement (74%)
      8. Cord edema (63%)
      9. Enlarged umbilical vessel (62%)
      10. Pericardial/pleural effusion (15%)
   2. Nonimmune hydrops (McGillivray and Hall 1987; Jauniaux 1997)
      1. Fetal ascites
      2. Fetal pleural effusion
      3. Fetal pericardial effusion (the earliest finding)
      4. Fetal skin thickening
      5. Maternal polyhydramnios
      6. Placentomegaly, especially Rh disease or chorioangioma
      7. Cystic hygroma as early as 13 weeks of gestation
5. Fetal evaluation of nonimmune hydrops fetalis
   1. Fetal echocardiography, M-mode, pulsed, and color flow Doppler
      1. Congenital heart defects
      2. Fetal rhythmic abnormalities
      3. Cardiac biometry
   2. Doppler flow velocity studies
      1. Umbilical artery
      2. Middle cerebral artery
      3. Tricuspid ejection velocity
   3. Amniocentesis
      1. Amniotic fluid index
      2. Fetal karyotype (chromosome abnormality) (Jauniaux et al. 1990; Iskaros et al. 1997)
      3. Amniotic fluid viral cultures
      4. Alpha-fetoprotein (congenital nephrosis, sacrococcygeal teratomas)
      5. Isolation of CMV virus for identification of CMV DNA by PCR
      6. Specific metabolic tests
         1. Tay-Sachs disease
         2. Gaucher disease
         3. GM_1 gangliosidosis
      7. Metabolic disease screening panel
         1. Acid sphingomyelinase deficiency
         2. Deficient cholesterol esterification
         3. Acid β-glucosidase deficiency
         4. Acid β-galactosidase deficiency
         5. Acid sialidase deficiency
         6. Sialidase deficiency
         7. β-galactosidase deficiency
         8. Ceramidase deficiency
         9. Glucose phosphate isomerase deficiency
         10. *N*-acetylglucosamine phosphotransferase deficiency
      8. Restriction endonucleases tests (e.g., thalassemias)
   4. Fetal blood sampling
      1. Rapid karyotype (chromosome abnormality)
      2. Fetal complete blood count (fetal anemia)
      3. Blood group and Coombs test
      4. Hemoglobin electrophoresis (α-thalassemia)
      5. Fetal plasma analysis for specific IgM (e.g., CMV-specific IgM antibody, PCR)
      6. G6PD in male fetuses
      7. Fetal plasma albumin (fetal hypoalbuminemia)
      8. Metabolic testing
         1. Tay-Sachs disease
         2. Gaucher disease
         3. GM_1 gangliosidosis
   5. Fluid aspirated for biochemistry and viral screen
      1. Pleural effusion
      2. Ascites
      3. Amniotic fluid
   6. Placenta
      1. Morphology
      2. Thickness
6. Management (Machin 1989; Jones 1995)
   1. Immune hydrops fetalis

1. Prevent sensitization by Rhogam or Rh immune globulin
2. Prevent fetal heart failure when mother has sensitization reaction
3. Fetal transfusion for fetal anemia via cordocentesis (Socol et al. 1987; Saltzman et al. 1989; Sosa et al. 1998)
4. Induction of labor
5. Postpartum exchange blood transfusion to prevent kernicterus, the most feared complication of Rh-induced HDN

2. Nonimmune hydrops fetalis (Swain et al. 1999)
   1. Screen tests to detect couples at risk for having a fetus with the Hb Barts hydrops fetalis by simple blood counts and hemoglobin electrophoresis
   2. Neonatal resuscitation (McMahan and Donovan 1995)
   3. Intrauterine or immediate postdelivery transfusions to babies (e.g., homozygous α-thalassemia, Parvovirus B19 infection)
   4. Fetal cardiac arrhythmias treated by transplacental antiarrhythmic therapy
   5. Flecainide acetate for fetal supraventricular tachycardia with hydrops fetalis
   6. Continuous arteriovenous hemodilution for fluid overload in newborns with hydrops fetalis
   7. Pleurocentesis in utero to drain pleural effusion to minimize pulmonary hypoplasia
   8. Treatment of maternal infection (Barron and Pass 1995)
      1. Parvovirus B19: intrauterine transfusion
      2. Syphilis: IV penicillin
      3. CMV: No pharmaceutical regimens available for treatment of maternal and fetal CMV infections. Treatment with antiviral agents (ganciclovir, foscarnet) is limited to severe infections (CMV retinitis) in immunocompromised patients and not currently used in pregnancy
      4. HSV: acyclovir warranted in disseminated disease; fetal effect unknown
      5. Toxoplasmosis: spiramycin and/or pyrimethamine, sulfadiazine, and folinic acid
   9. Fetal surgery (Bullard and Harrison 1995) attempted for congenital cystic adenomatoid malformation, pulmonary sequestration, fetal pleural effusions, and sacrococcygeal teratoma
   10. In utero therapy (Anandakumar et al. 1996)
       1. Fetal intravascular blood transfusion
       2. Direct fetal drug therapy
       3. Fetal pleuro-amniotic shunting
   11. Fetal therapy options for selected etiologies of nonimmune hydrops (Norton et al. 2015)
       1. Cardiac tachyarrhythmia, supraventricular tachycardia, atrial flutter, or atrial fibrillation
          1. Maternal transplacental administration of antiarrhythmic medication(s)
          2. Treatment with antiarrhythmic medication unless gestational age is close to term or there is maternal or obstetrical contraindication to therapy
       2. Fetal anemia secondary to parvovirus infection or fetomaternal hemorrhage
          1. Fetal blood sampling followed by intrauterine transfusion
          2. Fetal intrauterine transfusion if anemia is confirmed, unless pregnancy is at an advanced gestational age and risks associated with delivery are considered to be less than those associated with procedure
       3. Fetal hydrothorax, chylothorax, or large pleural effusion associated with bronchopulmonary sequestration
          1. Fetal needle drainage of effusion or placement of thoracoamniotic shunt; if gestational age is advanced, needle drainage prior to delivery in selected cases

2. Consider drainage of large unilateral pleural effusion(s) resulting in NIHF or, if gestational age is advanced, consideration of needle drainage prior to delivery
4. Fetal CPAM (congenital pulmonary airway malformation)
    1. Macrocystic type: fetal needle drainage of effusion or placement of thoracoamniotic shunt; microcystic type: maternal administration of corticosteroids, betamethasone 12.5 mg IM q24h Â 2 doses, or dexamethasone 6.25 mg IM q12 h Â 4 doses
    2. Consider drainage of large macrocystic CPAM that has resulted in NIHF; if large microcystic CPAM has resulted in NIHF, management options include maternal corticosteroid administration
5. TTTS (twin-twin transfusion sequence) or TAPS (twin-anemia polycythemia sequence)
    1. Laser ablation of placental anastomoses or selective termination
    2. Consideration of fetoscopic laser photocoagulation of placental anastomoses for TTTS or TAPS that has resulted in NIHF <26 weeks
6. Twin-reversed arterial perfusion sequence
    1. Percutaneous radiofrequency ablation
    2. Referral for consideration of percutaneous radiofrequency ablation that has resulted in NIHF

12. Survival (Derderian et al. 2015)
    1. Fetal intervention in well-selected patients improves survival.
    2. Those who received medical therapy (percutaneous or fetoscopic intervention) were more likely to survive than those who received no treatment.
    3. There is still a high rate of mortality in hydropic fetuses undergoing open fetal surgery (possibly secondary to a significant inflammatory response from the surgery coupled with the underlying disease state, which often leads to preterm delivery).

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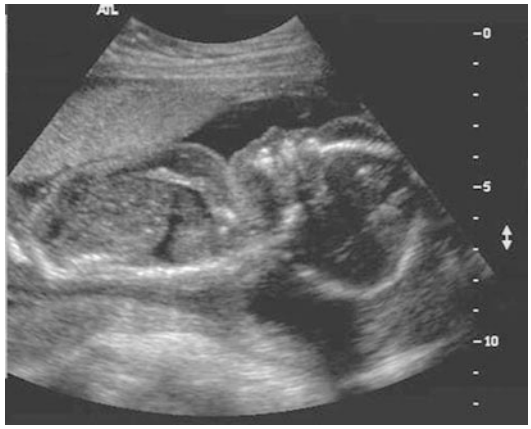

Fig. 1 An 18-week gestation fetus with hydropic change of the scalp and chest

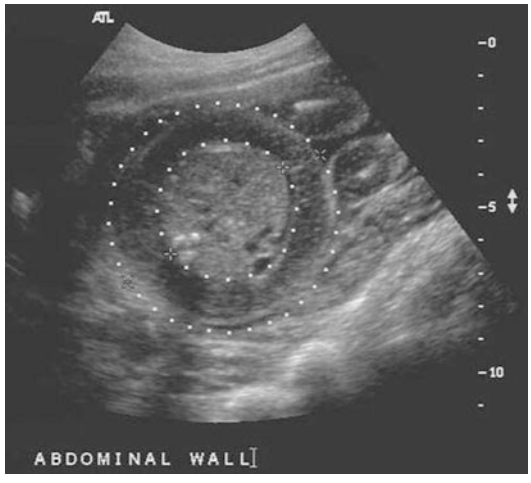

Fig. 2 A fetus showing hydropic change of the abdominal wall

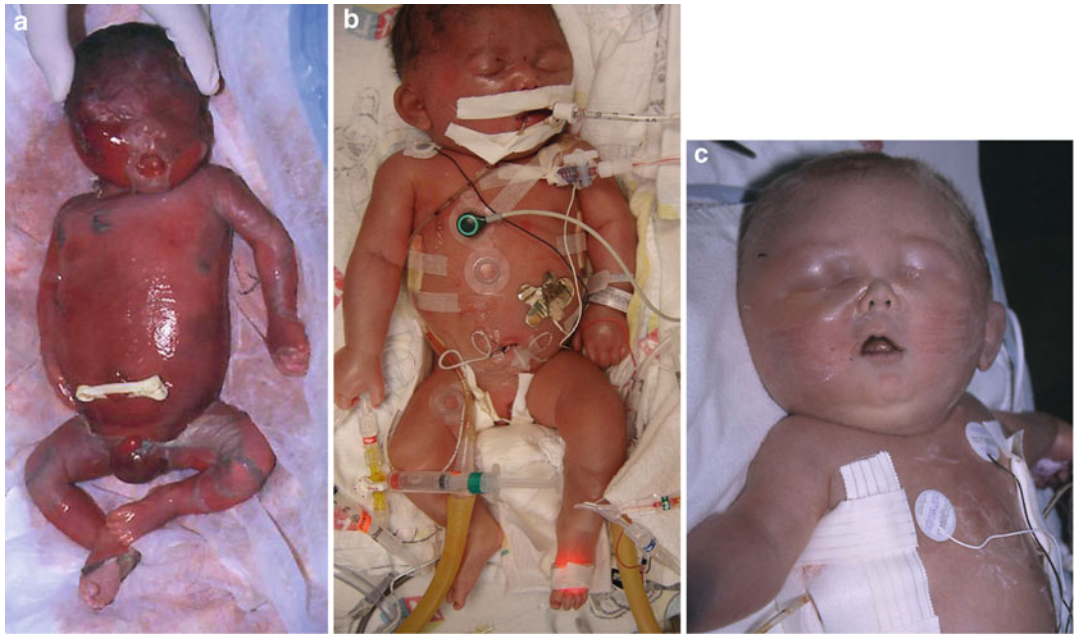

Fig. 3 (**a**–**c**) A macerated fetus, a newborn, and an infant with nonimmune hydrops fetalis

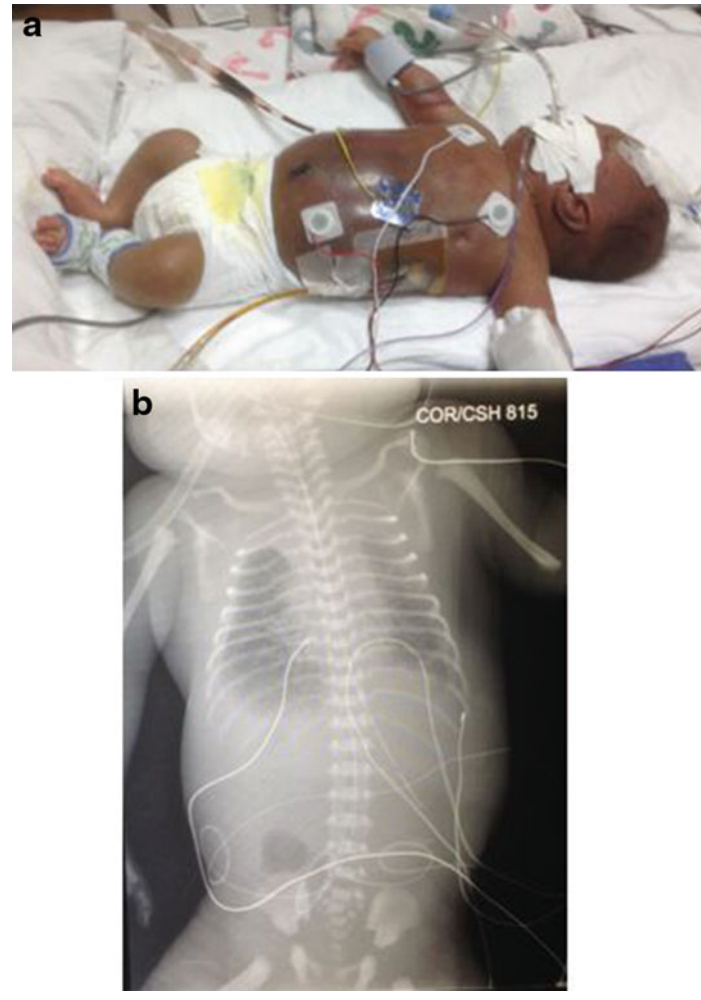

Fig. 4 (**a**, **b**) This premature baby boy was delivered at 29 and 5/7 weeks via cesarean section. Prenatal ultrasound examinations showed maternal polyhydramnios, intrauterine growth retardation, and hydrops with large pleural effusion and ascites. After birth, he was noted to have generalized edema in severe respiratory distress (**a**). There was a short neck with extra skin folds at the back of the neck. He was hypotonic and had acrocyanosis noted with mottled skin and micropenis with cryptorchidism. The AP view of the babygram (**b**) showed generalized edema, pleural effusion, ascites, and hemivertebra of the sacrum (Courtesy of Dr. Lea Bonifacio)

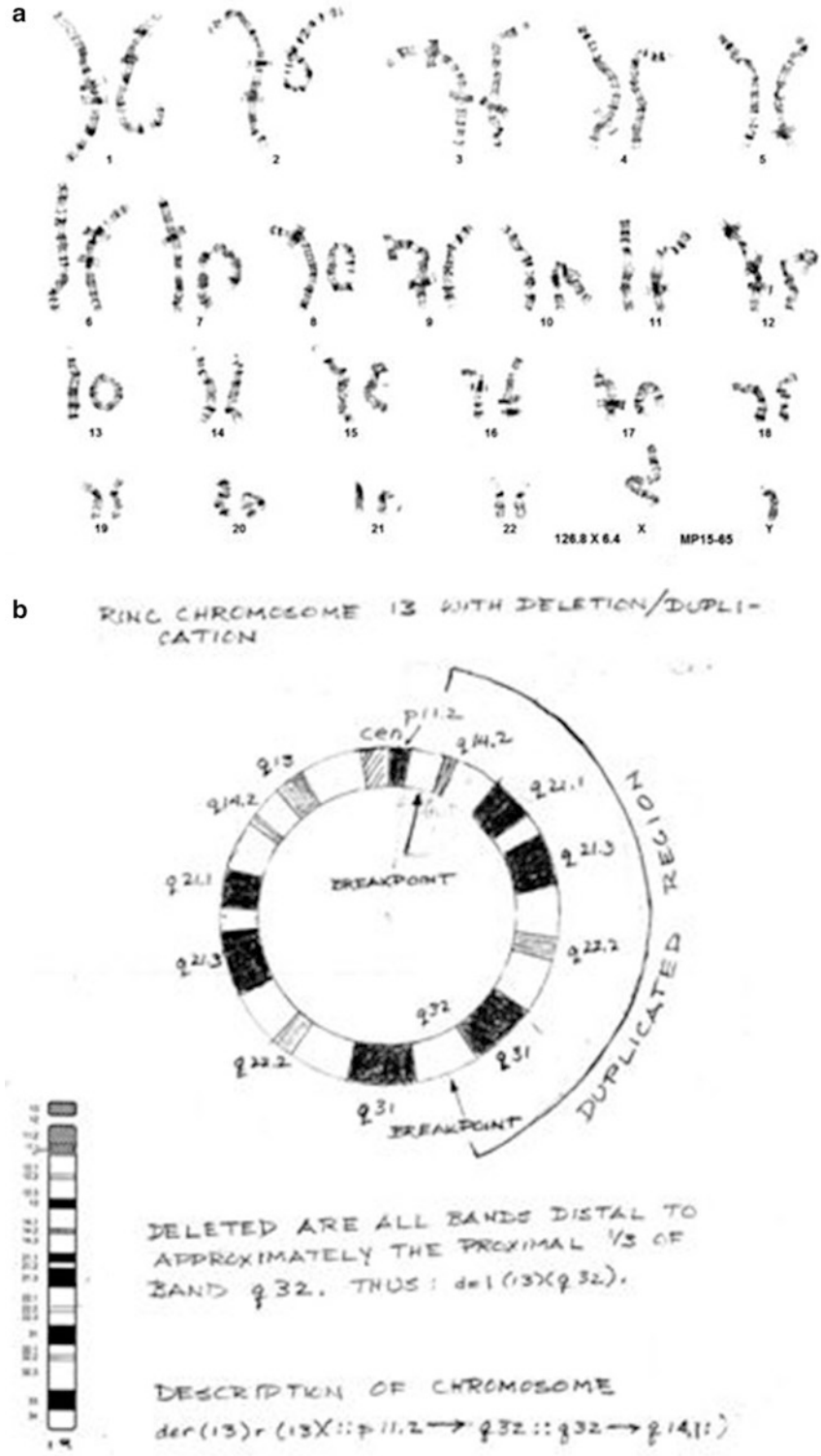

Fig. 5 (**a**, **b**) Chromosome analysis showed the presence of a normal chromosome 13 and a ring chromosome 13 with duplication of the region involving q14.1 through q32 and deletion involving all bands distal to approximately the proximal one-third of the band q32 (**a**). Idiogram (**b**) shows ring chromosome with deletion/

Fig. 5 (continued) duplication regions (Courtesy of Dr. Leonard Prouty).The cytogenetic finding was confirmed by chromosome microarray analysis (Mayo Clinic Laboratories), which indicated the presence of a complex ring chromosome 13 with a duplication of 42.7 megabases of material from 13q14.3[dup(13q14.3q32.1)] and an 18.6 megabase terminal deletion from 13q32.1 to 13q34[del (13q32.1q34)]

Hyper-IgE Syndrome

Contents

Hyper-IgE syndrome (HIES) is a rare, hereditary multisystem disorder characterized clinically by hyperimmunoglobulinemia E, recurrent infections, and eczematoid dermatitis. In 1966, Davis et al. reported two patients with Job's syndrome with recurrent, "cold," staphylococcal abscesses (Davis et al. 1966). In 1972, Buckley et al. expanded the clinical picture by adding elevated immunoglobulin E (IgE) (Buckley et al. 1972).

Synonyms and Related Disorders

Buckley syndrome; Job syndrome

Genetics/Basic Defects

1. Inheritance (Erlewyn-Lajeunesse 2000)
    1. Autosomal dominant with variable penetrance and expressivity
    2. Linkage to a region on chromosome 4q21demonstrated in several affected families (Grimbacher et al. 1999b)
    3. An upregulating mutation in the interleukin-4 receptor gene on chromosome 16, demonstrated in some patients with hyper-IgE syndrome
    4. Autosomal recessive hyper-IgE syndrome: a similar but distinct syndrome reported by Renner et al. (2004)
2. Autosomal dominant hyper-IgE syndrome (AD-HIES): caused by dominant-negative mutations in signal transducer and activator of transcription 3 (*STAT3*) in most cases of autosomal dominant HIES (Holland et al. 2007; Minegishi et al. 2007; Jiao et al. 2008; Renner et al. 2008)
    1. Most cases are sporadic.
    2. When familial, all individuals carrying the mutation have the HIES phenotype.
    3. Somatic mosaicism may be present in both STAT3- deficient and DOCK8-deficient HIES. Yet, while it may lead to an intermediate phenotype in STAT3-deficient HIES, mosaicism is usually insufficient to rescue DOCK8-deficient patients from severe affection (Farmand and Sundin 2015).
3. Autosomal recessive hyper-IgE syndrome (AR-HIES) (Freeman and Holland 2009; Engelhardt et al. 2009)
    1. Homozygous mutation of *Tyk2* with a four nucleotide deletion resulting in a premature stop codon reported in one patient

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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(Minegishi et al. 2006). This patient had the following common features of AR-HIES:
   1. Eczema
   2. Viral infections
   3. Recurrent sinopulmonary infections
   4. Bacille Calmette-Guerin and *Salmonella* infections, classic for IL-12/IFN-gamma defects
2. Mutations of Tyk2 have been absent in the other reported cases of AR-HIES (Woellner et al. 2007).
3. Recently, mutations in phosphoglucomutase 3 (encoding PGM3, which is involved in the protein glycosylation pathway) have been identified in autosomal recessive forms of hyper-IgE syndromes (Yang et al. 2014). Elevation of IgE in patients with *PGM3* mutations and atopic conditions might be caused by defective glycosylation of IgE or its receptors.
4. Homozygous mutations (large deletions and point mutations) in the dedicator of cytokinesis 8 (*DOCK8*) identified recently in most patients with AR-HIES (Engelhardt et al. 2009). Mutations in DOCK8 result in autosomal recessive hyper-IgE syndrome with combined immunodeficiency (Aydin et al. 2015)

Clinical Features

1. Classic triad (77%) (Grimbacher et al. 1999a; Erlewyn-Lajeunesse 2000)
   1. Abscesses
   2. Pneumonia
   3. An elevated IgE
2. Skin manifestations (Buckley 2001; Minegishi and Saito 2012)
   1. Onset with distinctive neonatal rash
      1. Newborn rash
      2. Typically pruritic, secondary to intradermal mast cell histamine release triggered by the elevation of available IgE
      3. Often lichenified
      4. A distribution atypical for true atopic dermatitis
   2. Chronic eczema and dermatitis
   3. Skin infections
      1. Frequent presentation in infancy
         1. Furuncles
         2. Occasional "cold" abscesses
         3. Cellulitis
      2. Multiple staphylococcal abscesses on the skin (furunculosis)
         1. Most common around the face
         2. Tender and warm to touch
      3. Cold abscesses (Davis et al. 1966; Donabedian and Gallin 1983)
         1. A large fluctuant mass that feels like a tumor or cyst
         2. Neither hot or tender
         3. Not associated with systemic symptoms, fever, or other signs of local or generalized inflammation
         4. Filled with pus that always grows *Staphylococcus aureus*
         5. Pathognomic to hyper-IgE syndrome
         6. Not essential to the diagnosis
   4. Skin abscesses
   5. Candidiasis
3. Infections
   1. Pulmonary infections
      1. Recurrent and severe
      2. Most common infecting organism: *Staphylococcus aureus* (Donabedian and Gallin 1983)
      3. Chronic infections
         1. Sinusitis
         2. Discharging otitis media
         3. Otitis externa
         4. Mastoiditis
      4. Long-term complications
         1. Bronchiectasis
         2. Bronchopleural fistulae
         3. Pneumatocele secondary to staphylococcal pneumonia
   2. Mucocutaneous candidiasis and fungal infection
      1. Chronic candidiasis (83%)
         1. Mucosa sites (oral moniliasis)
         2. Nail fungal infection and dystrophy secondary to *Candida albicans*
      2. *Aspergillus* infection
      3. Cryptococcal infection

3. Other serious infections
    1. Skin, sinopulmonary, and bone infections: most common
    2. Staphylococcus: the most frequently infecting organisms
    3. Encapsulated organisms
        1. Haemophilus
        2. *Streptococcus pneumoniae*
    4. Opportunistic infections: *Pneumocystis carinii*
4. Facial and dental abnormalities
    1. Characteristic coarse facies
        1. Frontal bossing
        2. Wide alar base of the nose
        3. Wide outer canthal distance
        4. Rare craniosynostosis
        5. Midline facial defects
        6. High-arched palate
    2. Red hair: uncommon finding
    3. Retained primary teeth (72%): failure or delay of shedding of the primary teeth secondary to lack of root resorption (Buckley 2001)
5. Skeletal abnormalities (Buckley 2001)
    1. Scoliosis (76%)
    2. Pathological fractures
        1. Secondary to minor trauma
        2. Associated with osteopenia
        3. Frequent recurrent fractures (57%) (Buckley 2001)
        4. Systemic infections at fracture sites
            1. Recurrent bacterial arthritis
            2. Staphylococcal osteomyelitis
    3. Generalized joint hyperextensibility (68%)
        1. Fingers
        2. Wrists
        3. Shoulders
        4. Hips
        5. Knees
        6. Genu valgum
6. Vascular features (Yavuz and Chee 2009): constitute one of the major clinical characteristics in HIES
    1. Types of vascular abnormalities
        1. Aneurysms (coronary, aortic, carotid, and cerebral)
        2. Pseudoaneurysms
        3. Congenital patent ductus venosus
        4. Superior vena cava syndrome
        5. Vasculitides
        6. Vascular ectasia
        7. Thrombosis
        8. Others
    2. May be congenital or acquired, in the veins and arteries, affecting both sexes.
    3. Can be seen in all subtypes of HIES.
    4. Can be fatal in children and adults.
    5. Limited pathological investigations revealed the presence of vasculitis.
    6. Presence of hypereosinophilia, vasculitis, and defective angiogenesis in HIES may contribute to the formation of vascular abnormalities in HIES.
7. Association with isolated reports of autoimmune disease
    1. Systemic lupus erythematosus
    2. Dermatomyositis
    3. Membranoproliferative glomerulonephritis
8. Malignant changes
    1. Hodgkin disease
    2. Lymphoma
    3. Leukemia
    4. Cancers of the vulva, liver, and lung
9. Autosomal recessive hyper-IgE syndrome (AR-HIES) (Renner et al. 2004)
    1. Similar features
        1. Extremely elevated serum IgE
        2. Severe eczema
        3. Recurrent skin bacterial and viral infections as well as sinopulmonary infection
    2. Distinctive features
        1. Lacks the somatic features, such as the characteristic facies, scoliosis, and the failure of baby teeth to exfoliate.
        2. Although pneumonias occur in AR-HIES, pneumatoceles do not form.
        3. Has a much higher rate of cutaneous viral infections such as *Molluscum contagiosum*, Herpes simplex, and varicella infections.
        4. Has frequent neurologic disease, ranging from facial paralysis to hemiplegia, in some cases due to CNS vasculitis.
        5. Mortality: high at a young age in AR-HIES with sepsis more frequent than in AD-HIES.

6. Eosinophilia and elevated serum IgE: the most consistent laboratory findings and may be more dramatic than in AD-HIES.
7. Autoimmune cytopenias may occur.

Diagnostic Investigations

1. Routine laboratory workup
   1. Grossly elevated serum polyclonal IgE: at least ten times normal (peak serum IgE >2,000 IU/mL)
   2. Accompanying eosinophilia
2. Radiographs, CT scan, and MRI imaging
   1. Pulmonary abnormalities (Jhaveri et al. 2000)
      1. Recurrent alveolar lung infections
      2. Pneumatoceles
      3. Occasional pneumothorax
   2. Skeletal abnormalities
      1. Full evaluations and monitor vigilantly for fractures after even minor trauma
      2. Scoliosis
   3. CNS abnormalities on brain MRI (Freeman et al. 2007)
      1. Remarkably common and previously unrecognized aspect of HIES.
      2. Several patients with lacunar infarcts in addition to focal hyperintensities suggest possible small vessel disease.
3. Skin biopsy (Chamlin et al. 2002)
   1. An eosinophilic infiltrate similar to that seen in eosinophilic pustular folliculitis
   2. Spongiosis
   3. Perivascular dermatitis
4. Molecular genetic diagnosis
   1. AD-HIES: investigate *STAT3* mutations
   2. AR-HIES: investigate *DOCK8* mutations in patients with a phenotype of elevated IgE, eosinophilia, and recurrent skin boils, pneumonia, and viral infections (especially molluscum contagiosum and herpes) (Engelhardt et al. 2009)

Genetic Counseling

1. Recurrence risk
   1. Autosomal recessive inheritance
      1. Patient's sib: 25%
      2. Patient's offspring: not increased unless the spouse is a carrier
   2. Autosomal dominant inheritance
      1. Patient's sib: not increased unless one of the parents is affected, in which case, there will be 50% risk of sibling affected
      2. Patient's offspring: 50%
      3. Challenges of genetic counseling in patients with autosomal dominant diseases such as the hyper-IgE syndrome (STAT3-HIES) because of possible presence of parental gonadal mosaicism (Spielberger et al. 2012)
2. Prenatal diagnosis for AD-HIES (Freeman et al. 2010)
   1. Possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling (CVS): The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
   2. Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified previously.
3. Management (Erlewyn-Lajeunesse 2000; Freeman and Holland 2009)
   1. Largely supportive.
   2. Prompt treatment of infection with prolonged intravenous antibiotics.
   3. Treatment of eczema and prevention of *S. aureus* abscesses are most successfully accomplished with antiseptics such as bathing in bleach (120 mL of bleach in tub of water for 15 min three times weekly) or swimming in chlorinated pools.
   4. Active suspicion of pneumonia is necessary because systemic symptoms of illness are often lacking.
   5. Antimicrobial prophylaxis

1. Prevents recurrent sinopulmonary infections with trimethoprim-sulfamethoxazole, a frequent choice.
2. Pneumonias should be treated aggressively to try to prevent parenchymal damage.
3. If pneumatoceles and bronchiectasis are present, antimicrobial prophylaxis often needs to be broadened to cover Gram-negative bacteria and fungi.
4. Management of pneumatoceles is complex, as these cysts when secondarily infected carry significant risk for morbidity and mortality; however, surgery is not without risk, as HIES patients may have trouble re-expanding their lungs and silage of the pleural space can occur.

6. Cimetidine, the histamine receptor-2 (H2) antagonist (Mawhinney et al. 1980)
   1. Shown to reverse the hyper-IgE syndrome neutrophil chemotactic defect in vitro.
   2. A single patient showed a clinical improvement on treatment with improved neutrophil chemotaxis in spite of a clinical relapse.
   3. Another seven patients treated with H2 antagonist with benefit.
7. Cyclosporine may be helpful.
8. Bronchoscopy may help isolate causative pathogens and clear pus.
9. Dental extraction of primary teeth to avoid further complex orthodontic treatment (Esposito et al. 2012).
10. Surgical intervention by incision and drainage of abscesses.
11. Chest tube drainage and lobectomy for complications of pneumonias.
12. Orthopedic cares for fractures and scoliosis.
13. Dermatitis.
    1. Topical steroid
    2. Topical antifungals
    3. Emollient creams
14. Isotretinoin used to improve dermatitis.
15. High-dose intravenous γ-globulin for patients with aberrant humoral immunity (Kimata 1995): Intravenous immunoglobulin (IVIG) may decrease the number of infections for some individuals and is the most frequent immunomodulator used.
16. Invasive approach with plasmapheresis with temporary improvement of skin condition and free of infections (Dau 1988).
17. Bone marrow transplantation: only hope of cure at present, likely not fully corrective (Gennery et al. 2000).
18. A single report of a peripheral stem cell transplantation (Nester et al. 1998).
    1. Serum IgE returned to normal.
    2. Disappearance of symptoms.
    3. Unfortunately, patient died of interstitial pneumonia.
19. Hematopoietic cell transplantation (Gatz et al. 2010).
    1. Curative in patients with AR-HIES
    2. Should be considered early before life-threatening complications develop, which include malignancies
20. Antimicrobial treatment and IgG replacement are essential in the care for patients with STAT3-deficient HIES, whereas hematopoietic stem cell transplantation seems justified in DOCK8-deficient HIES (Farmand and Sundin 2015).

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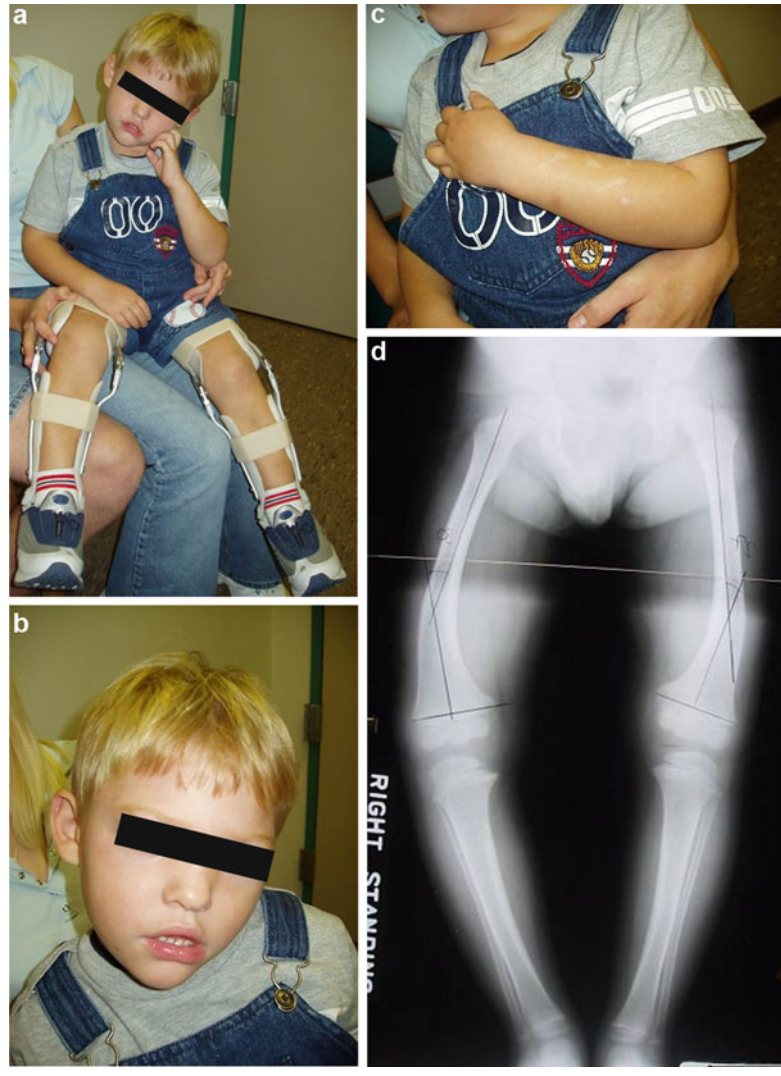

Fig. 1 (**a**–**d**) A 3-year-9-month-old patient with hyperimmunoglobulin E syndrome showing skin scars on his arm and bowing of the legs. Facial features included frontal bossing, wide alar basis of the nose, and wide outer canthal distance. He had history of recurrent pneumonias, otitis media, asthma, and fractures of the leg bones. At 2 years and 10 months of age, IgE was 15,610 (≤93 KU/L). He is currently on intravenous immunoglobulin therapy with antibiotic prophylaxis

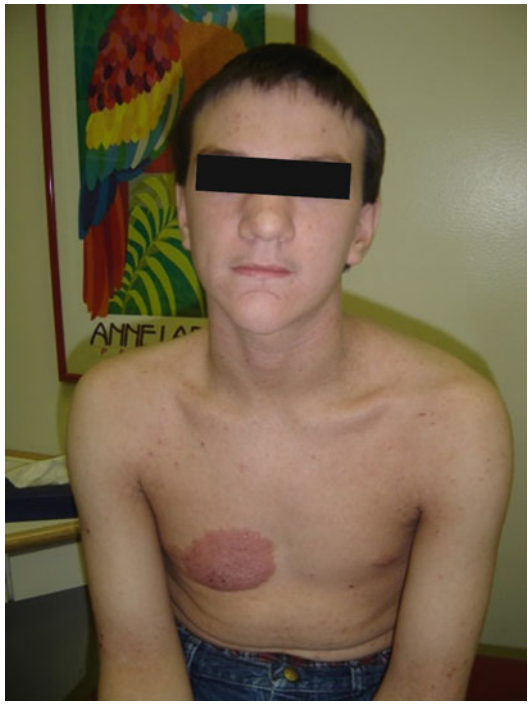

Fig. 2 A 13-year-old boy had a history of recurrent pneumonias, a right hip infection, and significant atopic dermatitis. Facial features included frontal bossing, wide alar basis of the nose, and wide outer canthal distance. Laboratory tests showed hyperimmunoglobulin E

Fig. 3 A 3-year-old boy and a 9-year-old maternal half brother were evaluated for frequent infections. The young brother had a history of multiple abscesses. Immunoglobulin studies showed normal IgG of 540 (231–1,411 mg per deciliter) and a highly elevated IgE of 1,553 (0–15 IU/mL). He also had developmental delay. CT of the brain showed Dandy-Walker variant and corpus callosum agenesis. The older half brother had a history of chronic dermatitis, asthma, eczema, and food allergy. His recent IgE level was elevated at 8,670 IU/ml (0–90). The half brothers both have hyper-IgE syndrome

Hypertrophic Cardiomyopathy

Contents

Hypertrophic cardiomyopathy (HCM) is a disorder characterized by unexplained left ventricular hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient with the caveat that patients who are genotype positive may be phenotypically negative without overt hypertrophy (Gersh et al. 2011). The prevalence is estimated to be approximately 1 in 500 in the general population (Wallis and Fricker 2012). This is the most common monogenic cardiac disorder and the most frequent cause of sudden cardiac death in young people and trained competitive athletes (Maron et al. 1995; Maron 2003; Charron 2012; Figs. 1 and 2).

Synonyms and Related Disorders

Hypertrophic obstructive cardiomyopathy; Idiopathic subaortic stenosis

Genetics/Basic Defects

1. Inheritance: autosomal dominant (Jacoby and McKenna 2012) in most cases
    1. Marked phenotypic heterogeneity
    2. Age-dependent penetrance
    3. Variable expression
2. Caused by mutations in sarcomeric protein encoding genes and its constituent myofilament elements
    1. Intergenetic diversity is compounded by considerable intragene heterogeneity, with >1,400 mutations identified among at least 8 genes (Gersh et al. 2011).
    2. The distribution of pathogenic sarcomeric mutations is uneven (Richard 2003).
        1. Myosin heavy chain 7 (MYH7) and myosin-binding protein C3 (MYPBC3) making up about 25% each
        2. Cardiac troponin T (TNNT2), cardiac troponin I (TNNI), myosin ventricular regulatory light chain (MYL2), and myosin ventricular essential light chain (MYL3) accounting for most of the remainder
    3. 30–40% of the patients with clinical HCM do not have sarcomere mutations (Jacoby and McKenna 2012).
    4. Individuals with β-MHC mutations typically present in the first two decades of life.
    5. Individuals with cMyBP-C mutations may be asymptomatic until the fifth or sixth decades (Niimura et al. 1998).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Pathophysiology (Gersh et al. 2011)
    1. Complex, consisting of multiple interrelated abnormalities
        1. Left ventricular outflow tract (LVOT) obstruction
        2. Mitral regurgitation
        3. Myocardial ischemia
        4. Arrhythmias
    2. Clinically important to distinguish between the obstructive and nonobstructive forms of HCM because management strategies are largely dependent on the presence or absence of symptoms caused by obstruction

Clinical Features

1. Significant variability in clinical presentation
    1. Asymptomatic
    2. Symptomatic
        1. Shortness of breath (particularly with exertion)
        2. Chest pain
        3. Palpitations
        4. Dizziness
        5. Orthostasis
        6. Presyncope
        7. Syncope
        8. Sudden cardiac death: ventricular fibrillation which is the most common cause (O'Mahony and Elliott 2014)
2. Left ventricular hypertrophy of HCM: most often becomes apparent during adolescence or young adulthood, although it may also develop late in life, in infancy, or in childhood
3. Potential dangers in HCM patients during labor (Turner et al. 1968; Krul et al. 2011)
    1. Reduced venous return because of the expulsive effort.
    2. Acute blood loss.
    3. Increased or new obstruction of the left ventricular outflow tract through increase in the contractile forces of the heart and tachycardia caused by physical stress.
    4. The chance of maternal cardiac complications increases in the presence of prior cardiac events, poor functional class, severe left ventricular systolic dysfunction, and left outflow tract obstruction.
4. Differential diagnosis of HCM with other cardiac conditions with left ventricular hypertrophy (Gersh et al. 2011)
    1. Hypertensive heart disease
    2. Physiologic remodeling associated with athletic training ("athlete's heart")
5. Syndromes associated with hypertrophic cardiomyopathy (Moak and Kaski 2012; Wallis and Fricker 2012)
    1. Malformation syndromes associated with HCM
        1. Noonan syndrome: see the chapter.
        2. Multiple lentigines (LEOPARD syndrome): please see the chapter.
        3. Beckwith-Wiedemann syndrome: please see the chapter.
        4. Trisomy 21 syndrome: please see the chapter.
        5. Costello (faciocutaneoskeletal) syndrome.
        6. Prune belly syndrome: please see the chapter.
    2. Neuromuscular disorders
        1. Friedreich ataxia: please see the chapter.
        2. Myotonic dystrophy: please see the chapter.
        3. Refsum disease.
    3. Metabolic disorders
        1. Glycogen storage disease type II (Pompe disease): please see the chapter.
        2. Fabry disease
            1. Caused by deficient activity of the enzyme alpha-galactosidase and progressive lysosomal deposition in cells throughout the body.
            2. Acroparesthesias (periodic crises of severe pain in the extremities) usually begins in childhood or adolescence.
            3. Angiokeratomas (vascular cutaneous lesions).
            4. Hypohidrosis.
            5. Characteristic corneal and lenticular opacities.
            6. Proteinuria.

7. Gradual deterioration of renal function to end-stage renal disease usually by 3rd to 5th decade.
8. In affected males, cardiovascular and/or cerebrovascular disease and cardiac variant phenotype (left ventricular hypertrophy, mitral insufficiency, and/or cardiomyopathy) may develop.

3. Danon disease
   1. An X-linked lysosomal storage disorder caused by mutations in the gene encoding lysosome-associated membrane protein-2 (*LAMP2*)
   2. Cardiomyopathy
   3. Skeletal myopathy
   4. Developmental delay
4. Mucopolysaccharidosis I, II, III, IV, and VII: HCM caused by accumulation of glycosaminoglycans within myocardial cells.
5. Severe hypertrophic cardiomyopathy caused by γ_2 subunit of the adenosine monophosphate-activated protein kinase (*PRKAG2*) gene mutation
   1. Hypertrophic cardiomyopathy
   2. Conduction abnormalities
   3. Ventricular preexcitation
   4. Skeletal myopathy associated with ragged red fibers on skeletal muscle biopsy
   5. Mortality related to thromboembolic stroke resulting from atrial fibrillation and sudden death

4. Fatty acid oxidation disorders
   1. Carnitine deficiency
   2. Carnitine palmitoyltransferase deficiency
   3. Medium-chain acyl-coenzyme A (CoA) dehydrogenase deficiency
   4. Very-long-chain acyl-CoA dehydrogenase deficiency
   5. Long-chain3-hydroxyacyl-CoA dehydrogenase deficiency
5. Mitochondrial cardiomyopathies
   1. Complex I, III, and IV defects
   2. MERRF (myoclonic epilepsy with ragged red fibers) syndrome
   3. MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome
   4. Adenine nucleotide translocator abnormalities

Diagnostic Investigations

1. Radiology: enlarged cardiac silhouette with central vascular congestion
2. Electrocardiogram: often shows left atrial enlargement and high voltages representing biventricular hypertrophy
3. Echocardiography
   1. HCM is usually recognized by maximal LV wall thickness $\geq$15 mm, particularly in the presence of other compelling information (e.g., family history of HCM) (Gersh et al. 2011).
   2. In children, increased LV wall thickness is defined as wall thickness $\geq$2 standard deviations above the mean (Z score $\geq$2) for age, sex, or body size.
   3. Characteristically shows biventricular hypertrophy which can be concentric or asymmetric.
   4. Hypercontractile ventricle with diastolic dysfunction.
4. Cardiovascular magnetic resonance (CMR): an emerging role in the contemporary evaluation of patients with hypertrophic cardiomyopathy (Maron et al. 2009)
5. Pathognomonic histopathologic findings in cardiac tissue: myocyte disarray and fibrosis
6. Family history: a key clinical predictor of a positive genetic diagnosis and has direct clinical relevance, particularly in the pretest genetic counseling setting (Ingles et al. 2013)
7. Molecular genetic analysis (Charron 2012)
   1. Identify first a disease-causing mutation in the proband: sequencing and deletion/duplication panel is available commercially.
   2. Predictive testing in asymptomatic apparently healthy relatives or in relatives with mild cardiac abnormalities of unknown significance.

1. Identified mutation carriers will benefit from regular cardiac screening and allow early cardiac expression to be diagnosed, and this may reduce mortality by the early discussion of prophylactic implantable cardioverter defibrillations (ICD).
2. Identified relatives without the causal mutation can be released from all future cardiac surveillance, and their children are likewise no longer at risk.

Genetic Counseling

1. Recurrence risk: according to autosomal dominant inheritance (Cirino and Ho 2014)
   1. Patient's sib
      1. 50% if a parent has the disease-causing mutation.
      2. The clinical severity and age of onset cannot be predicted from the mutation.
   2. Patient's offspring
      1. 50% risk of inheriting the mutation and therefore being at risk for developing HCM.
      2. Penetrance may be incomplete.
      3. Disease severity and age of onset cannot be predicted.
2. Prenatal diagnosis at increased risk is possible if the disease-causing mutation has been identified in an affected family member.
3. Preimplantation genetic diagnosis may be an option for families in which a definitive disease-causing mutation has been identified.
4. Management
   1. Beta-blockers (propranolol, metoprolol, bisoprolol, or atenolol): initial drug for medical therapy of symptomatic LV outflow tract obstruction (Moak and Kaski 2012).
   2. Beta-blockers and calcium channel blockers used to slow heart rate and increase diastolic filling time.
   3. Avoidance of competitive or highly strenuous exercise: usually recommended (Corrado et al. 2005).
   4. Implantable cardioverter defibrillators (ICDs) for secondary or primary prevention of sudden death in patients with risk factors (Maron et al. 2000; Maron et al. 2007; Maron and Spirito 2008; O'Mahony and Elliott 2014).
   5. Drugs appropriate to control heart failure symptoms (principally those of exertional dyspnea and chest discomfort) (Maron 2002; Maron et al. 2003).
   6. Surgical septal myotomy (myectomy) (Ommen et al. 2005) or alcohol septal ablation (Sorajja et al. 2008) for progressive and drug-refractory heart failure caused by left ventricular outflow tract (LVOT) obstruction.
   7. Heart transplantation for systolic (or less frequently intractable diastolic) dysfunction associated with severe unrelenting symptoms (Harris et al. 2006).
   8. Drug therapy or possibly radiofrequency ablation or surgical maze procedure for atrial fibrillation (AF) (Bunch et al. 2008; Gaita et al. 2007; Kilicaslan et al. 2006).
   9. Currently recommended follow-up strategy involves periodic evaluation of first-degree relatives every 1–5 years with echocardiography and ECG (Hershberger et al. 2009; Charron et al. 2010).

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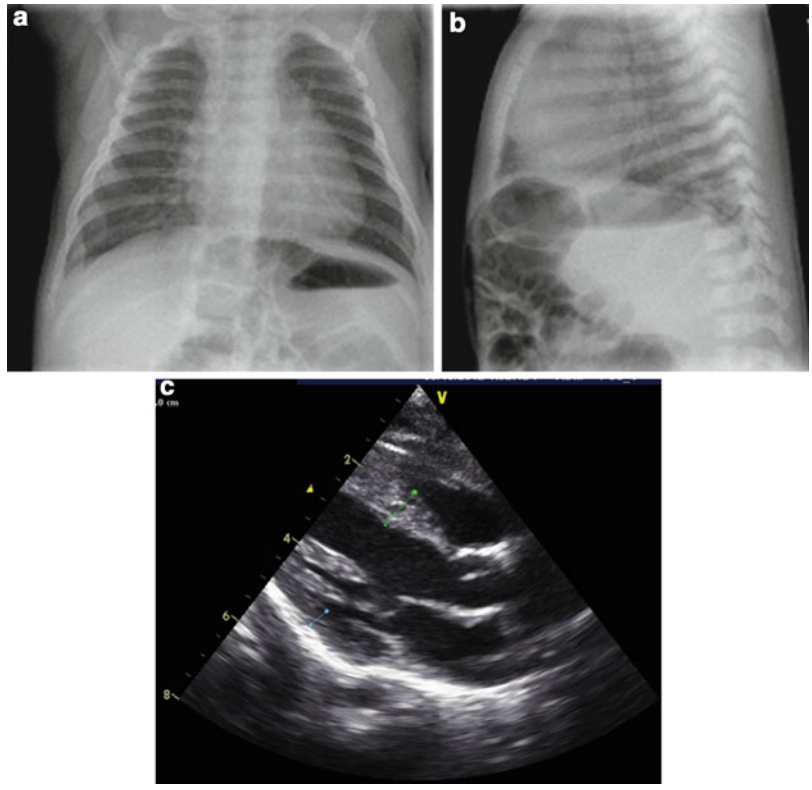

Fig. 1 (**a**–**c**) This 6-week-old male infant was evaluated for hypertrophic cardiomyopathy (HCM). Respiratory infections at 2 weeks of age which necessitated chest X-ray which showed left ventricular hypertrophy and thickened septum which was confirmed by CT scan of the chest. Echocardiogram showed left ventricular hypertrophy and moderate septal wall hypertrophy, suggestive of hypertrophic cardiomyopathy. No hypotonia was noted. Family history revealed that the mother has mitral valve prolapse and the maternal great grandfather has a brother and a sister died of sudden cardiac death early in life. Chest X-rays showed enlarged cardiac silhouette with mild central vascular congestion (**a**, **b**). Echocardiograms showed left ventricular hypertrophy with septal hypertrophy (**c**). Blood acid alpha-glucosidase (GAA) activity was noted to be low – 5.2 (10.0–49.0 pmol/punch/h). GAA sequencing for Pompe disease revealed no GAA mutations. However, the patient is heterozygous for a published missense mutation in the *MYBPC3* gene (p.Arg502Trp(R502W), c.1504C>T), consistent with a genetic form of HCM. He is also heterozygous for a novel missense variant of unknown significance in the *PRKAG2* gene. Mutations in the *MYBPC3* gene have been reported in 20–30% of patients with autosomal dominant familial hypertrophic cardiomyopathy and have been reported less frequently in patients with autosomal dominant familial dilated cardiomyopathy (Cirino & Ho 2011; Hershberger et al. 2009). Mutations in the *PRKAG2* gene are a rare cause of autosomal dominant familial hypertrophic cardiomyopathy and associated with ventricular preexcitation, Wolff-Parkinson-White (WPW) syndrome (Cirino & Ho 2011) (Courtesy of Dr. Ernest Kiel)

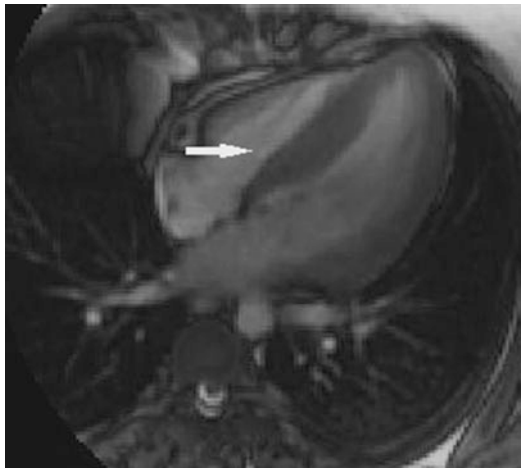

Fig. 2 A 15-year-old boy with hypertrophic cardiomyopathy presented with tachycardia. Cardiac MRI showed hypertrophy of the left ventricle with increased thickness of the septum (*arrow*). There is systolic anterior motion of the anterior mitral leaflet with associated mitral regurgitation and left ventricular outflow tract obstruction (Courtesy of Dr. Grace Guo)

Hypochondroplasia

Contents

Hypochondroplasia (HCH) is a disproportionate short stature disorder resembling achondroplasia but with less severe phenotype.

Synonyms and Related Disorders

FGFR3 mutation; Homozygous hypochondroplasia; Hypochondroplasia/achondroplasia compound heterozygote

Genetics/Basic Defects

1. Inheritance (Le Merrer et al. 1994).
    1. Autosomal dominant with full penetrance
    2. Sporadic in 90% of cases
    3. Observation of an increased paternal age effect at the time of conception, suggesting involvement of de novo mutations of paternal origin
    4. Presence of clinical and genetic heterogeneity (Rousseau et al. 1996)
2. Evidence supporting the view that hypochondroplasia and achondroplasia are allelic disorders (McKusick et al. 1973; Le Merrer et al. 1994).
    1. A remarkable inter- and intrafamilial variation in expression of hypochondroplasia with some cases resembling minor forms of achondroplasia
    2. Offspring of an achondroplastic parent and hypochondroplastic parent with severe neonatal achondroplasia resembling homozygous achondroplasia
    3. Similar histopathological aspects of the growth cartilage for the two disorders
3. Molecular defect (Bellus et al. 1996).
    1. About 70% of affected individuals who are heterozygous for a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which is mapped on chromosome 4p16.3 (Francomano 2005)
    2. *FGFR3* mutations reported in hypochondroplasia (Prinos et al. 1995)
        1. 1620C-A (Asn540Lys): two thirds of cases
        2. 1620C-G (Asn540Lys): one third of cases
        3. 1658A-C (Asn540Thr) and other *FGFR3* mutations: rare
    3. *FGFR3* mutation reported in hypochondroplasia association with acanthosis nigricans (Castro-Feijóo et al. 2008;

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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Cossiez Cacard et al. 2016) and acanthosis nigricans and hyperinsulinemia (Blomberg et al. 2010): p.Lys650Thr mutation
   4. Homozygous *N540K* hypochondroplasia (Garcia De Rosa et al. 2014)
   5. Common mutations in FGFR3 gene also account for achondroplasia and thanatophoric dysplasia (Bonaventure et al. 1996; Cohen 1998)
4. Hypochondroplasia/achondroplasia compound heterozygote (Sommer et al. 1987; Chitayat et al. 1999; Huggins et al. 1999b).
   1. Born to a hypochondroplastic parent and an achondroplastic parent
   2. The severity of the child: clinical and radiographic findings more severe than achondroplasia (ACH) or hypochondroplasia alone but less severe than homozygous achondroplasia (Huggins et al. 1999b)
   3. Demonstration of both the hypochondroplasia (Asn540Lys) and achondroplasia (Gly380Arg) mutations at the *FGFR3* locus in a patient with the genetic compound

Clinical Features

1. Short stature (Francomano 2005)
   1. Evident by school age
   2. Adult height: 128–165 cm
2. Stocky build
3. Facial appearance
   1. Usually normal
   2. Mild macrocephaly may be present
4. Skeletal features
   1. General features: usually similar but milder to achondroplasia
   2. Limbs
      1. Disproportionately short compared with the length of the trunk
      2. Shortening of the proximal (rhizomelia) or middle (mesomelia) segments of the extremities
      3. Mild limitation of elbow extension
      4. Broad and short hands and feet (brachydactyly)
      5. Absence of trident hand deformity
      6. Bow legs (genu varum): usually mild
      7. Adult onset osteoarthritis: less common
   3. Spine
      1. Scoliosis
      2. Slight lumbar lordosis with a sacral tilt
5. Rare association with acanthosis nigricans
6. Medical complication
   1. Following complications: less frequent compared to achondroplasia
      1. Spinal stenosis with neurologic complications
      2. Tibial bowing
      3. Obstructive apnea
   2. Deficits in mental capacity and/or function: may be more prevalent than achondroplasia
7. Clinical criteria in hypochondroplasia (Song et al. 2012)
   1. Major criteria
      1. Short stature (3 SD below the mean height)
      2. Mesomelic dwarfism
      3. Limitation of elbow extension
      4. Generalized laxity
      5. Brachydactyly
      6. Genu varum
      7. Macrocephaly with relatively normal faces
   2. Minor criteria
      1. Scoliosis
      2. Lumbar lordosis with protruding abdomen
      3. Intelligence disability
8. Homozygous N540K hypochondroplasia (Garcia De Rosa et al. 2014)
   1. More severe clinical and radiological features than those described for heterozygous HCH, as expected.
   2. Height: between -4SD and -6SD.
   3. Facial appearance, hypotonia, and the narrowing of the inferior lumbar interpedicular distances: less severe than those of ACH/HCH complex patients.
   4. In contrast, clinical features seems to be more pronounced than those of the usual heterozygous ACH, especially in regard to cognitive development.

5. Gross motor and cognitive severe delay and also have temporal lobe abnormalities. This neurological severity could be attributed to having *N540K* mutation in double dose.

Diagnostic Investigations

1. Skin biopsy of the hyperpigmented skin and of a verrucous keratosis: hyperkeratosis and papillomatosis with moderate irregular acanthosis compatible with acanthosis nigricans (Cossiez Cacard et al. 2016)
2. Radiography (Hall and Spranger 1979; Kozlowski 1973; Mortier et al. 2000; Francomano 2005; Song et al. 2012)
    1. The most common features
        1. Short proximal (rhizomelic) and/or middle (mesomelic) segments of the long bones with mild metaphyseal flare, especially femora and tibiae
        2. Caudal narrowing or unchanged lumbar interpedicular distance
        3. Shortening (anterior-posterior) of the lumbar pedicles
        4. Posterior scalloping of the lumbar vertebral bodies
        5. Squared and shortened ilia
        6. Coxa breva
        7. Short and broad femoral neck
        8. Mild to moderate brachydactyly
    2. The less common but significant features
        1. Shortening of the distal ulna
        2. Low articulation of sacrum on pelvis with a horizontal orientation
        3. Flattened acetabular roof
        4. Elongation of the distal fibula
        5. Anterior-posterior shortening of the lumbar vertebrae
        6. Dorsal concavity of the lumbar vertebral bodies
        7. Long ulnar styloid in adults
        8. Prominence of muscle insertions on the long bones
        9. Shallow "chevron" deformity of distal femur metaphysis
    3. Criteria for radiologic diagnosis of hypochondroplasia in neonates (Saito et al. 2016)
        1. Short greater sciatic notches
        2. Broad femora
        3. Short ilia
        4. Horizontal acetabulum
        5. Femoral shortening
        6. Ovoid radiolucency of the femoral neck
3. Brain MRI (Philpott et al. 2013)
    1. Temporal lobe enlargement (9/9)
    2. Abnormal triangular-shape temporal horn (9/9)
    3. Deep transverse temporal sulci (9/9)
    4. Overly sulcated mesial temporal lobes (9/9)
    5. Megalencephaly (8/9)
    6. Mild ventriculomegaly (7/9)
    7. Globular amygdala (7/7)
    8. Hippocampal dysplasia (7/7)
    9. Deficient dentate gyrus (7/7)
    10. Extension of oversulcation to calcar avis (7/7)
    11. Abnormal G/W matter differentiation (2/3)
    12. Subependymal neuronal heterotopia (1/7)
    13. Aberrant sulcation of the inferior surface and deep transverse clefts in the mesial temporal lobe (Garcia De Rosa et al. 2014)
4. Molecular genetic testing
    1. Mutation analysis
        1. 1620C-A (Asn540Lys)
        2. 1620C-G (Asn540Lys)
        3. Other *FGFR3* mutations
    2. Sequence analysis of mutations in *FGFR3* exons 10, 13, and 15
    3. *FGFR3* mutation identified by next-generation sequencing (Wang et al. 2013)

Genetic Counseling

1. Recurrence risk (Francomano 2005; Bober et al. 2013)
    1. Patient's sib: an extremely low risk (<0.01%) of having an affected sib if

parents are not affected (germline mosaicism has not been reported for hypochondroplasia)
2. Patient's offspring
    1. 50% risk of having an affected offspring if the spouse is normal
    2. If the spouse is an achondroplastic:
        1. 25% chance of having an affected offspring with hypochondroplasia
        2. 25% chance of having an affected offspring with achondroplasia
        3. 25% chance of having an affected offspring with achondroplasia-hypochondroplasia genetic compound
        4. 25% chance of having a normal offspring
    3. If the spouse also has hypochondroplasia or other dominant form of skeletal dysplasia: genetic counseling becoming more complicated due to the high incidence of genetic heterogeneity and the lack of medical literature addressing these circumstances
2. Prenatal diagnosis (Bober et al. 2013)
    1. Prenatal diagnosis by amniocentesis or CVS for family with high-risk pregnancy with a parent who has hypochondroplasia
        1. When the spouse is normal: testing for disease-causing FGFR3 mutation in the fetus
        2. When the spouse is affected with another dominantly inherited skeletal dysplasia caused by a known gene mutation: testing for the known mutation for that skeletal dysplasia and the mutation for the hypochondroplasia in the fetus
    2. Prenatal diagnosis by ultrasonography, amniocentesis, or CVS in low-risk pregnancy without family history of affected individual
        1. Ultrasonography: short limbs detected by routine ultrasound examination late in pregnancy (Huggins et al. 1999a)
        2. DNA-based diagnosis of *FGFR3* mutations to confirm the diagnosis of hypochondroplasia
        3. Prenatal genetic diagnosis of highly suspected HCH fetuses with gene sequencing technologies (Zhao et al. 2015)
    3. Prenatal MRI detection of temporal lobes and hippocampal anomalies in a case of hypochondroplasia, molecularly confirmed through postnatal *FGFR3* analysis (Cesaretti et al. 2014)
    4. Preimplantation genetic diagnosis (PGD)
        1. May be an option for some families in which the disease-causing mutation has been identified
        2. Successful birth with preimplantation genetic diagnosis using single-cell allele-specific PCR and sequencing in a woman with hypochondroplasia due to *FGFR3* mutation (c.1620C > A, p. N540K) (Park et al. 2013)
3. Management
    1. Follow closely developmental milestones and signs of learning disability or mental retardation.
    2. Treatment of short stature
        1. Trials of growth hormone therapy with mixed results (Appan et al. 1990; Ramaswami et al. 1999)
        2. Surgical limb lengthening for severe case of hypochondroplasia
            1. An invasive procedure
            2. Entails considerable disability and discomfort over a long period of time
            3. Prefer postponement of the procedure until adolescence when the patient can make an informed decision

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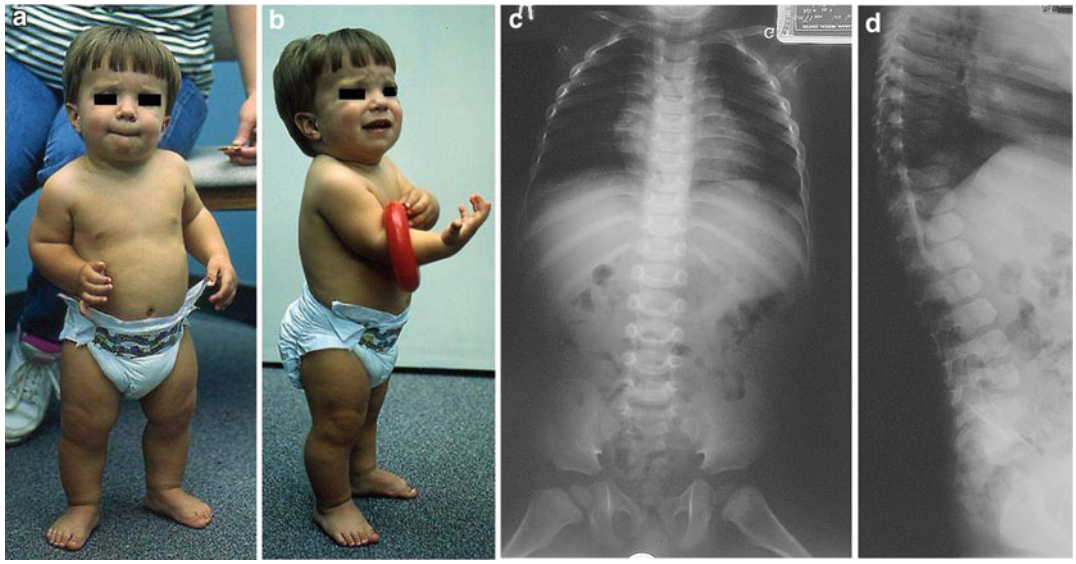

Fig. 1 (**a**–**d**) A young child affected with hypochondroplasia showing mild short stature and mild rhizomelic shortening of the extremities. Radiographs showed unchanged lumbar interpedicular distance

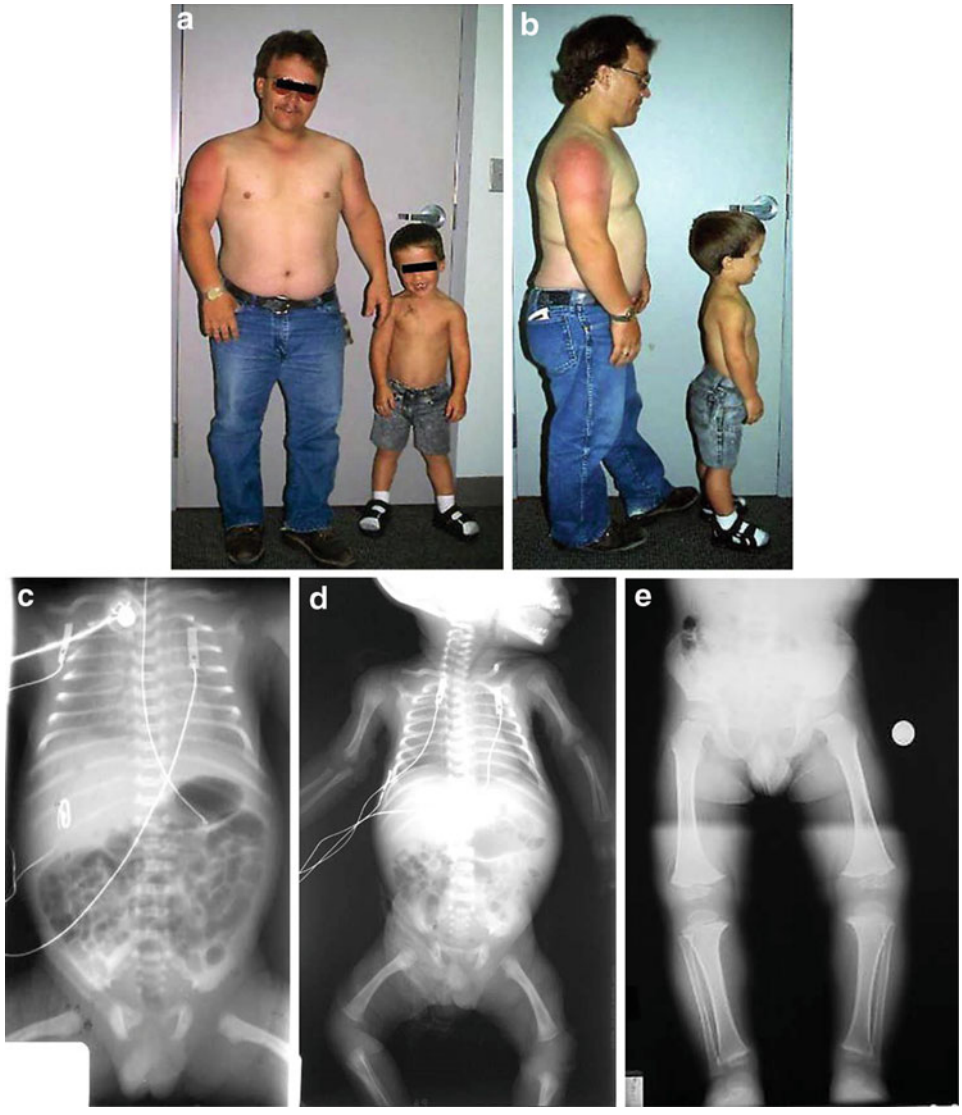

Fig. 2 (**a**–**e**) Father and son showing typical features of hypochondroplasia. The son's radiographs at birth, 17 days, and 2 years, and 6 months showing unchanged lumbar interpedicular distance, mild shortening of long bones, and short, squared ilia

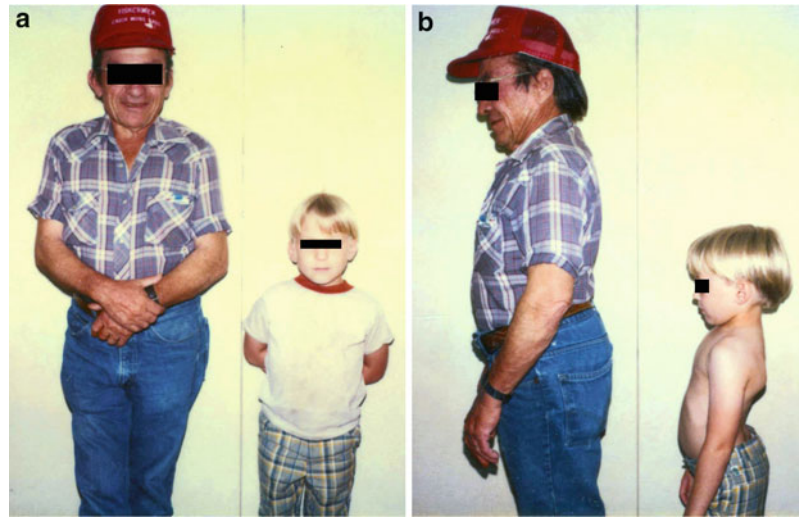

Fig. 3 (**a**, **b**) Father and son with clinical features of hypochondroplasia

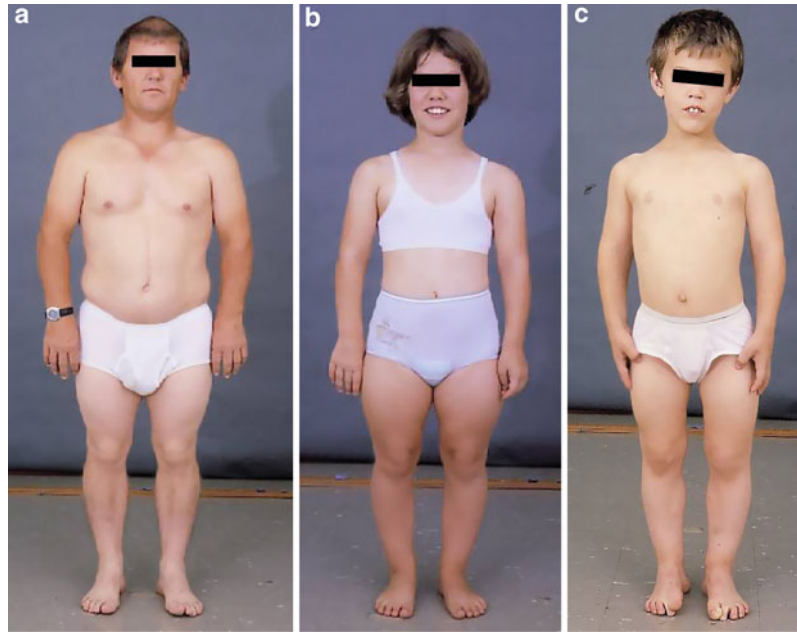

Fig. 4 (**a**–**c**) Father, daughter, and son affected with hypochondroplasia showing stocky build, mild short stature, normal facial appearance, rhizomelic shortening of the extremities, and absence of trident hands

Fig. 5 A 2-year-old boy with disproportional short stature with relatively short upper arms and thighs and mild lumbar gibbus. Molecular testing identified the presence of a C > A transversion at nucleotide 1620 (c.1620 C > A) of the fibroblast growth factor receptor 3 (*FGFR3*) gene. The presence of this mutation is consistent with a clinical diagnosis of hypochondroplasia

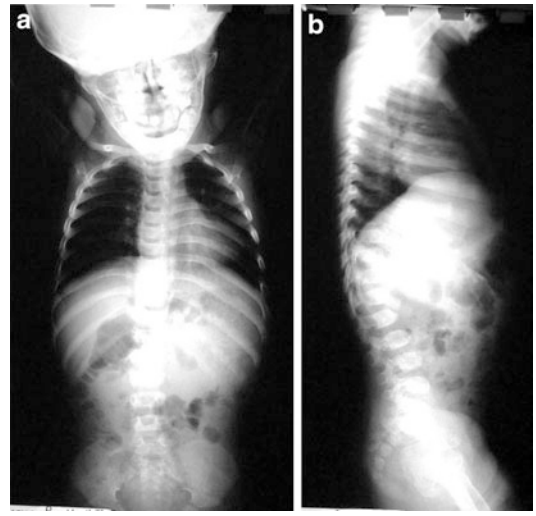

Fig. 6 (**a**, **b**) Radiographs of the spine (AP and lateral views) show caudal narrowing of lumbar interpedicular distance and the dorsal convexity of the lumbar vertebral bodies

Hypoglossia-Hypodactylia Syndrome

Contents

Hypoglossia-hypodactylia syndrome is an extremely rare condition characterized by a small tongue associated with distal limb deficiency. The syndrome is also called aglossia-adactylia syndrome, which is a misnomer since the tongue is never completely absent, and the term "adactylia" does not convey the variation in limb defects of affected individuals. The syndrome is also known as oromandibular-limb hypogenesis syndrome, a spectrum of congenital anomalies that affect the tongue, the oromandibular region, and the limbs.

Synonyms and Related Disorders

Aglossia-adactylia syndrome; Hanhart syndrome; Oromandibular-limb hypogenesis syndrome; Peromelia with micrognathia

Genetics/Basic Defects

1. Inheritance
    1. Sporadic in all reported cases (Nevin et al. 1975).
    2. Autosomal dominant inheritance cannot be ruled out.
2. Pathogenesis (Yasuda et al. 2003)
    1. Impairments or insults to fetus during the early fetal life (fourth to seventh week) may be responsible for the findings of tongue and limb abnormalities seen in hypoglossia-hypodactylia syndrome because of the close chronological relationship between the development of the tongue and the limbs.
    2. A hypoplastic mandible with concurrent hypoglossia could be explained by the fact that the mandible originates from the same visceral arch as the tongue.
    3. Vascular mechanism (either hemorrhage or vaso-oclusion) may be responsible for defects that are asymmetric and always distal.
3. Disruptive first-trimester factors associated with oromandibular-limb hypogenesis syndrome (OLHS)
    1. Disruptive first-trimester factors previously associated with OLHS include maternal teratogen exposures, hyperthermia, infec-

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tion, and uteroplacental vascular insufficiency causing a transient hypoxic/ischemic insult to the fetus.
2. First-trimester disruption: severe illness with dehydration and hypovolemia in a mother with a bicornuate uterus and early gestational diabetes caused fetal ischemia and necrosis during the sixth week postconception (Milam et al. 2014).

Clinical Features

1. Mouth
   1. Mandible
      1. Micro-/retrognathia
         1. Minor feeding problems in infancy
         2. Minor speech impairment
      2. Oligodontia
      3. Absent mandibular incisors with concomitant hypoplasia of the associated alveolar ridge
      4. Other features
         1. Midline lower lip defect (a sulcus-like deformity with continuity of the orbicularis oris muscle disturbed at this location) (Coşkunfirat et al. 1999)
         2. Microstomia (markedly reduced mouth opening)
         3. Intraoral bands (Grippaudo and Kennedy 1998)
         4. Oral frenula
         5. Oral syngnathia
   2. Tongue
      1. Varying degrees of hypoglossia/aglossia: a reduction in tongue size (Harwin and Lorinsky 1970; Lustmann et al. 1981)
      2. Ankyloglossia
      3. Marked enlargement of the sublingual muscular ridges
      4. Hypertrophy of the sublingual and submandibular glands
2. Variable limb anomalies
   1. May involve any limb
   2. Distal reduction anomalies
      1. Oligodactyly (absence of some fingers and toes)
      2. Adactylia (congenital absence of the fingers and toes)
      3. Peromelia (severe congenital malformation of the extremity, including the absence of hand and foot)
   3. Syndactyly
3. Other associated anomalies
   1. Moebius syndrome
   2. Complex cardiopathy in severe form of hypoglossia-hypodactylia syndrome (Elalaoui et al. 2010)
   3. Fused labia majora
   4. Unilateral renal agenesis
   5. Imperforate anus
   6. Short stature caused by growth hormone deficiency (Goyal et al. 2014)
4. Normal intelligence
5. Hall's classification of syndromes of oromandibular and limb hypogenesis (Hall 1971)
   1. Type I
      1. IA: hypoglossia
      2. IB: aglossia
   2. Type II (Alexander et al. 1992)
      1. IIA: hypoglossia-hypodactylia
      2. IIB: hypoglossia-hypomelia (peromelia) (Meundi et al. 2013)
      3. IIC: hypoglossia-hypodactylomelia (Castelino et al. 2010)
   3. Type III
      1. IIIA: glossopalatine ankylosis
      2. IIIB: with hypoglossia
      3. IIIC: with hypoglossia-hypodactylia
      4. IIID: with hypoglossia-hypomelia
      5. IIIE: with hypoglossia-hypodactylomelia
   4. Type IV
      1. IVA: intraoral bands and fusion
      2. IVB: with hypoglossia
      3. IVC: with hypoglossia-hypodactylia
      4. IVD: with hypoglossia-hypomelia
      5. IVE: with hypoglossia-hypodactylomelia
   5. Type V (Herrmann et al. 1976; Robertson and Bankier 1999)
      1. VA: Hanhart syndrome
      2. VB: Charlie M syndrome (Jung et al. 2016)

3. VC: Pierre Robin syndrome
4. VD: Moebius syndrome
5. VE: amniotic band syndrome

6. Embryologic and clinical classification (Chicarilli and Polayes 1985)
   1. Type I: micrognathia (mandibular)
      1. Pierre Robin syndrome
      2. Hanhart syndrome
   2. Type II: microglossia
      1. Hypoglossia
      2. Hypoglossia-hypodactyly
   3. Type III: dysgnathia (maxillomandibular)
      1. Glossopalatine ankylosis
      2. Glossopalatine ankylosis-hypodactyly
   4. Type IV: others
      1. Moebius syndrome
      2. Charlie M syndrome
7. Differential diagnosis with other oromandibular-limb hypogenesis syndromes (Cohen et al. 1971; Bonneau et al. 1999)
   1. Hanhart syndrome (Bersu et al. 1976)
      1. Micrognathia
         1. Microglossia
         2. Hypodontia
      2. Limb anomalies
         1. Terminal deficiency of all limbs: ranging from stunted digits, oligodactyly, to more severe peromelia
         2. May affect any limb
      3. Imperforate anus
   2. Glossopalatine and ankylosis syndrome
      1. Tongue.
         1. Usually attached to the hard palate
         2. May adhere to the maxillary alveolar ridge
         3. Mildly cleft tongue tip
      2. High-arched or cleft palate.
      3. Hypoplastic mandible.
      4. Hypodontia principally affects the incisor teeth.
      5. Ankylosis of the temporomandibular joint.
      6. Facial paralysis.
      7. Extremely variable limb anomalies.
         1. Oligodactyly
         2. Syndactyly
         3. Polydactyly
         4. Peromelia
   3. Limb deficiency-splenogonadal fusion syndrome (Pauli and Greenlaw 1982; Bonneau et al. 1999; McPherson et al. 2003)
      1. Splenogonadal fusion
         1. A rare malformation in which the spleen is abnormally connected to the gonad or, more rarely, to a derivative of the mesonephros
         2. May occur as a rare malformation
      2. Association with other malformations, especially with terminal limb defects
   4. Moebius syndrome (please refer to the chapter of "Moebius Syndrome")

Diagnostic Investigations

1. Radiography (Johnson and Robinow 1978)
   1. Fusion of the temporomandibular joints
   2. Micro-/retrognathia
   3. Hypodontia
   4. Limb defects
      1. Variable distal limb deficiency
      2. Asymmetric reduction deformities of the distal extremities
      3. Severity ranging from hypoplastic digits to peromelia
   5. Other rare anomalies
      1. Dextrocardia
      2. Transposition of abdominal organs
      3. Jejunal atresia (David et al. 1992)
      4. Short bowel
      5. "Apple-peel" bowel
2. Reconstructed 3-D CT imaging of the craniofacial skeletal structures (Yasuda et al. 2003)
   1. Retruded and reduced mandible
   2. Steep inclination of the anterior surface of the mandible in relation to the lower mandibular plane
   3. Bone defect of the alveolar ridge at the midline area of the mandible
3. MRI of the tongue and the floor of the mouth (Yasuda et al. 2003)
   1. Degree of the hypoglossia

2. Space between the tongue and the inferior surface of the palate
3. Hypertrophy of the floor of the mouth

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased
   2. Patient's offspring: not increased unless the condition represents an autosomal dominant inheritance, in which case there will be 50% risk to have an affected offspring
2. Prenatal ultrasonography at 19 weeks' gestation (Allanson et al. 2011)
   1. Severe micrognathia with almost complete absence of the mandible.
   2. Absent fluid-filled fetal stomach was identified.
   3. Absent bilateral radius, ulna, or hand.
3. Management (Yasuda et al. 2003; Cappellette et al. 2013)
   1. Early surgical intervention for the presence of severe anomalies that are life-threatening and interfere swallowing, breathing, and eating (Coşkunfirat et al. 1999)
   2. Extraction of the supernumerary tooth
   3. Dental alignment
   4. Orthopedic maxillary expansion
   5. Orthodontic expansion appliance for widening the mandibular dental arch
   6. Distraction osteogenesis to improve the size and shape of the hypoplastic mandible
   7. Mandibular advancement (Uğurlu et al. 2013)

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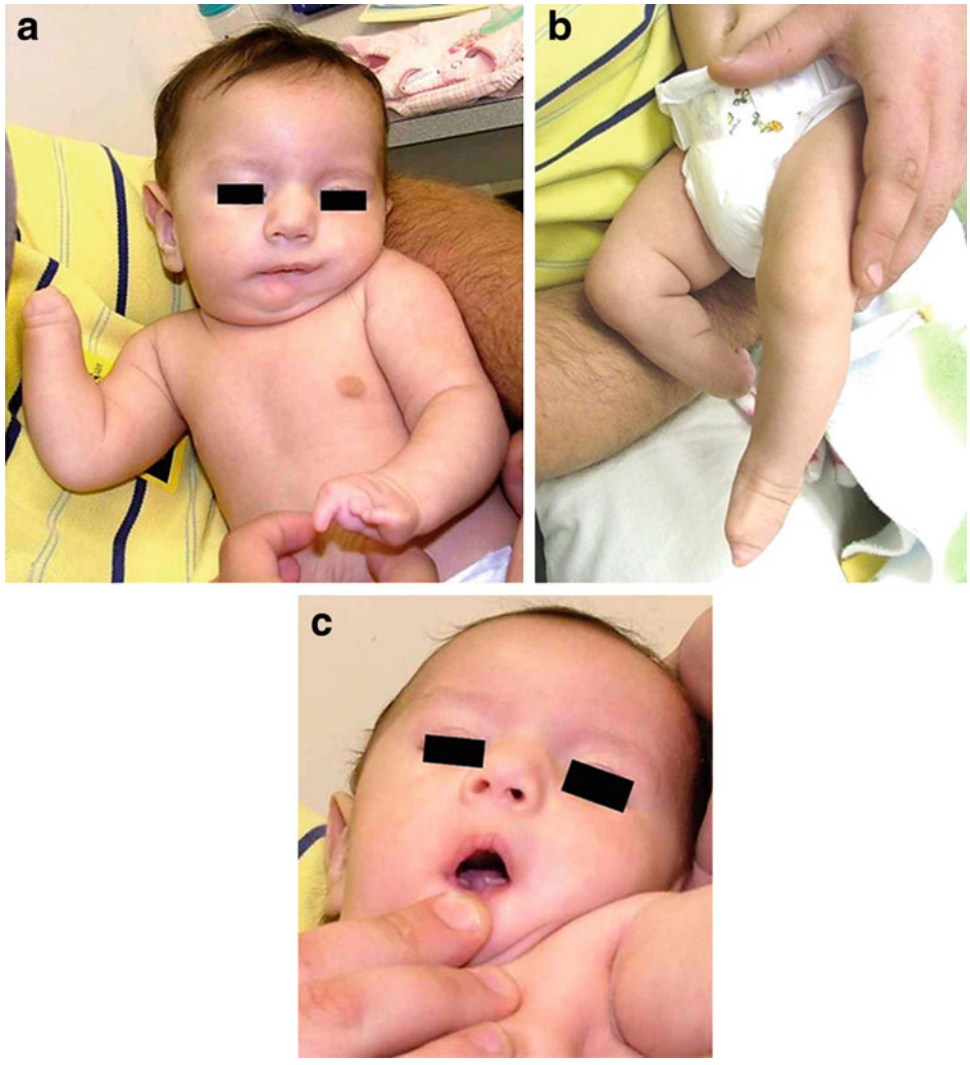

Fig. 1 (**a**–**c**) A 2-month-old female infant with hypoglossia-hypodactylia syndrome showing antimongoloid slant of the palpebral fissures, facial palsy, micro-/retrognathia, microstomia, hypoglossia, and limb anomalies with adactylia of the right hand and both feet and oligodactyly of the left hand

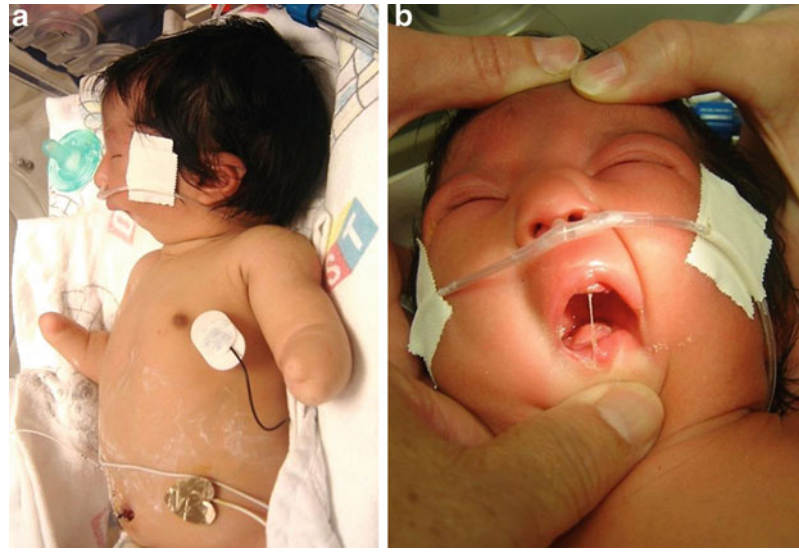

Fig. 2 (**a**, **b**) Another infant with hypoglossia-hypodactylia syndrome showing extreme micro-/retrognathia, hypoglossia, microstomia, and adactylia of both hands

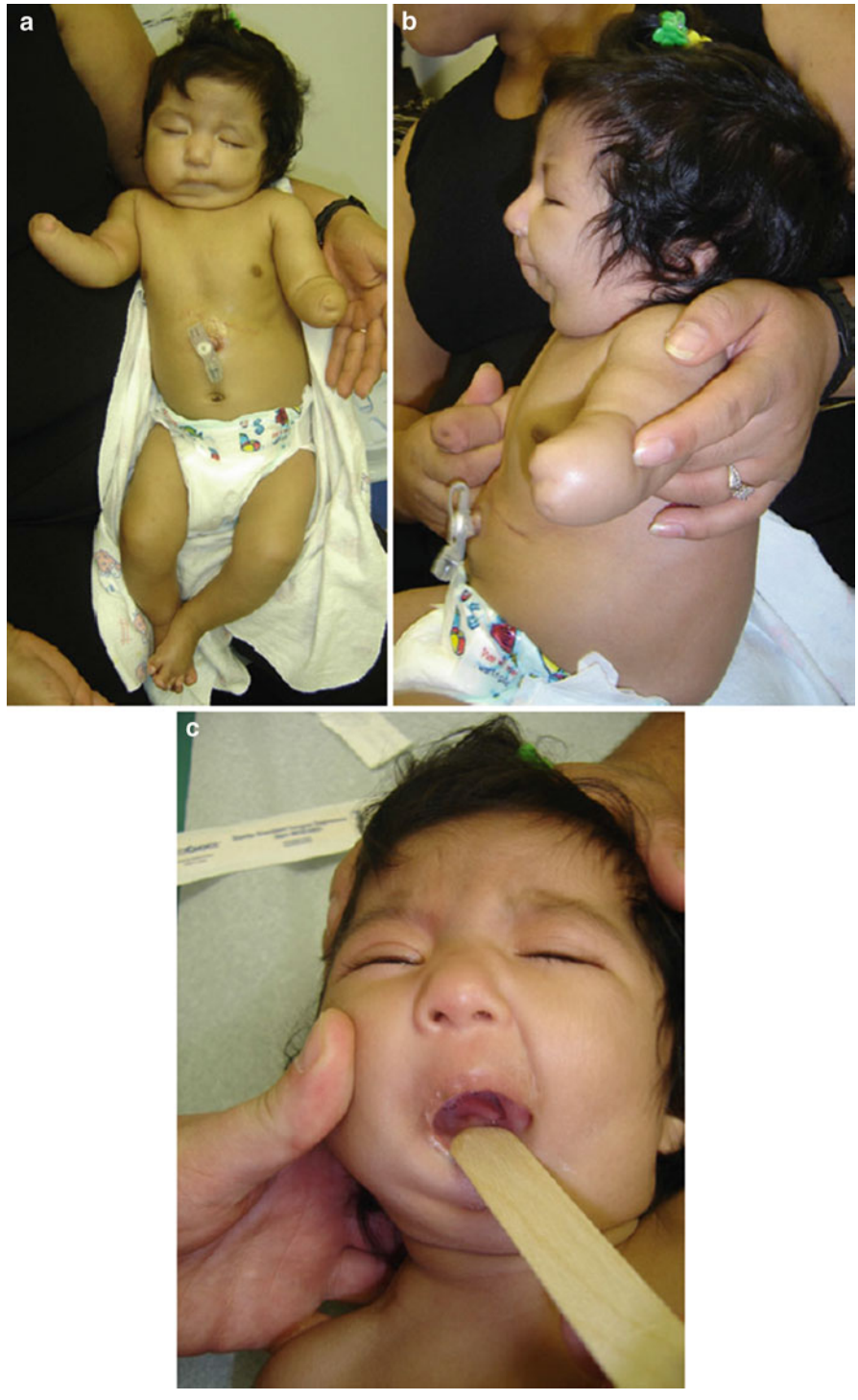

Fig. 3 (**a**–**c**) A 3-month-old girl with hypoglossia-hypodactylia syndrome showing extreme micro-/retrognathia, hypoglossia, microstomia, and adactylia of both hands (*right upper* extremity showed a transverse growth arrest beyond the wrist, and *left upper* extremity showed a transverse arrest beyond the proximal one third of the forearm)

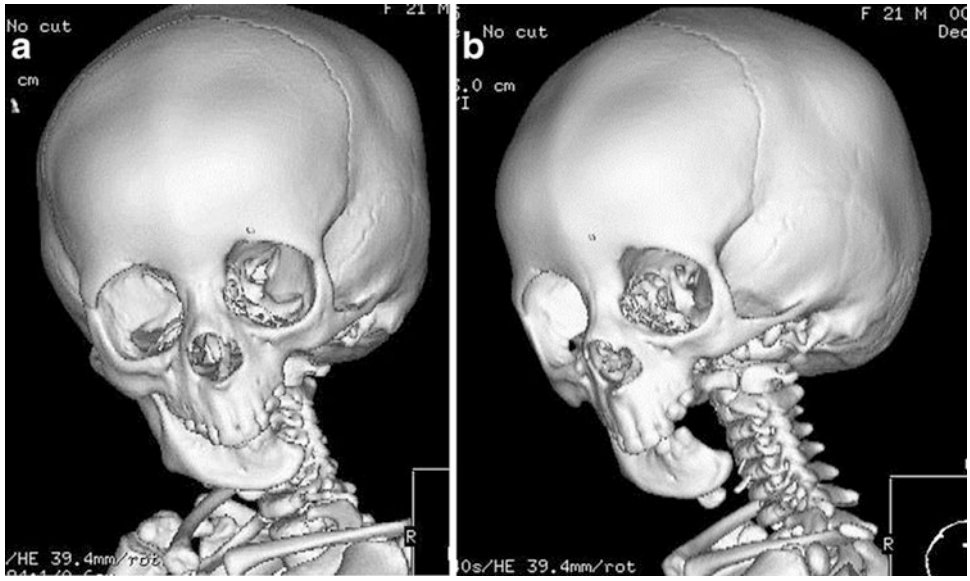

Fig. 4 (**a**, **b**) CT of the face (AP and lateral views) show left hemimandibular agenesis (complete absence of the body, angle, ramus, and condyle) and a significant aplasia of posterior maxilla on the *left*

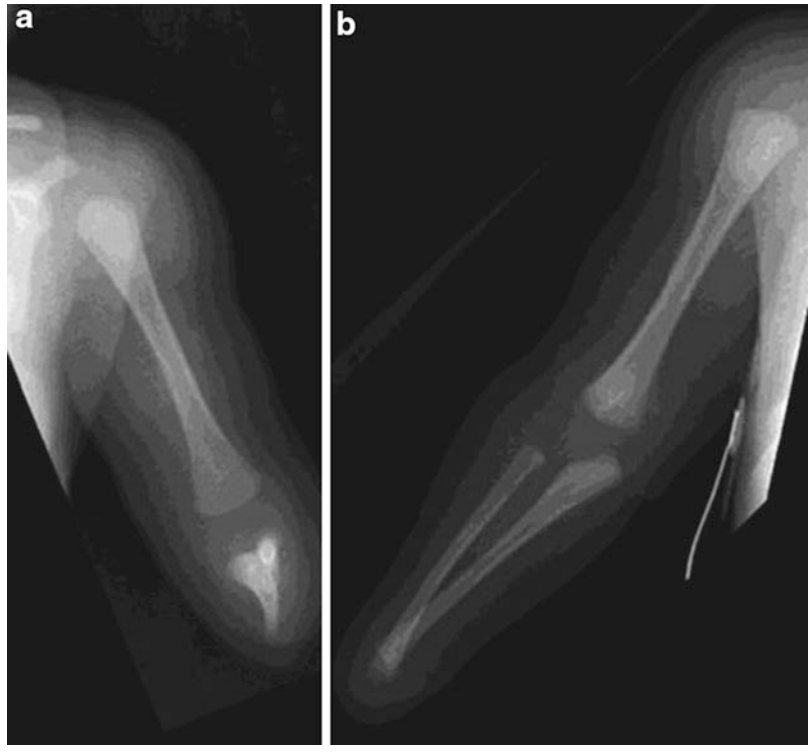

Fig. 5 (**a**, **b**) Plain radiographs show transverse growth arrest past the proximal one third of the left forearm and V-shaped formation of the radius and ulna with growth arrest past the right wrist

Fig. 6 The previous girl was seen at 3 years of age

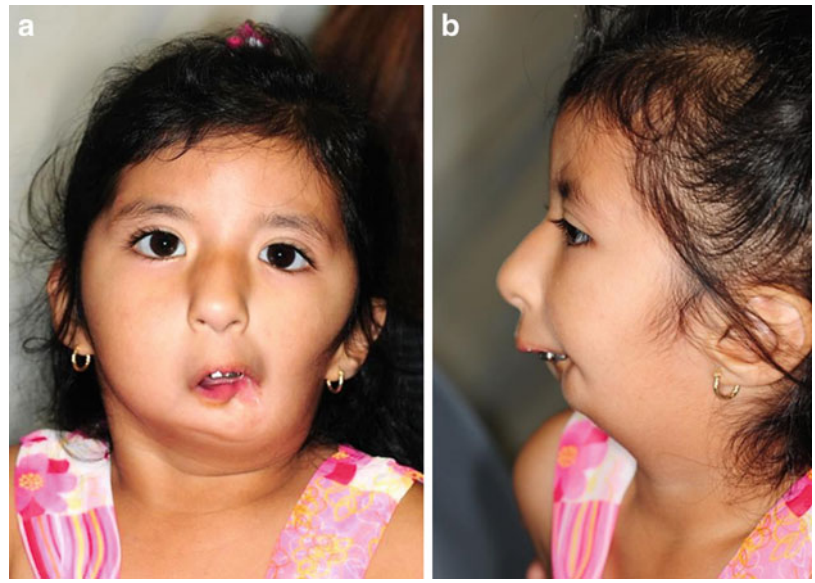

Fig. 7 (**a**, **b**) Preoperative photos at 5 years of age

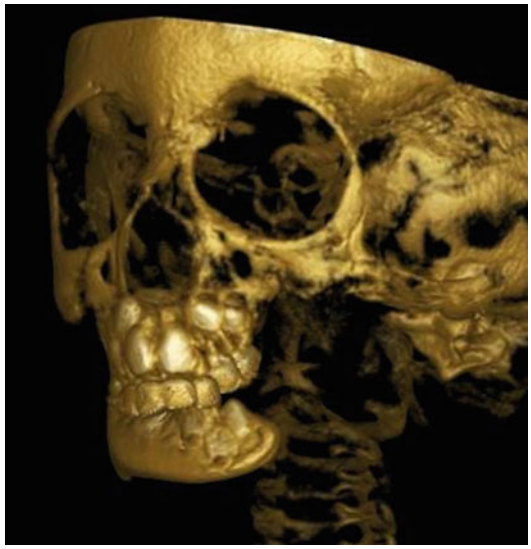

Fig. 8 Preoperative CT at the age of 5

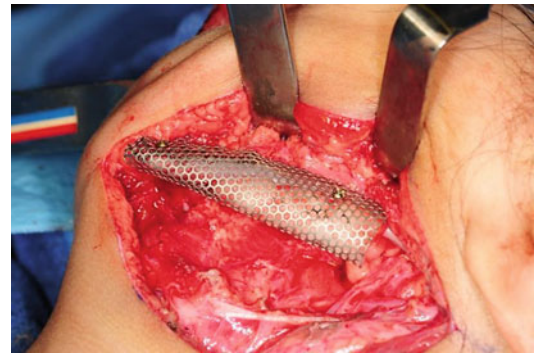

Fig. 10 Titanium mesh used as a crib for BMP at the inferior border of the rib graft

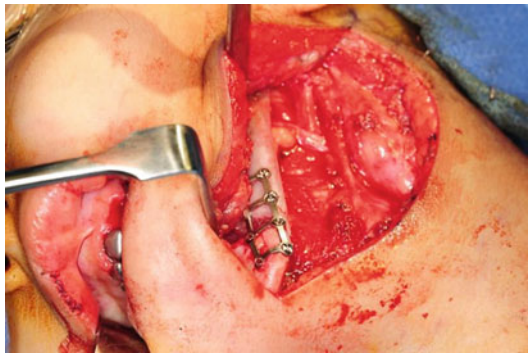

Fig. 9 Intraoperative photo. Costochondral graft fixated to the adjacent mandible. Cartilaginous cap seated in the glenoid fossa

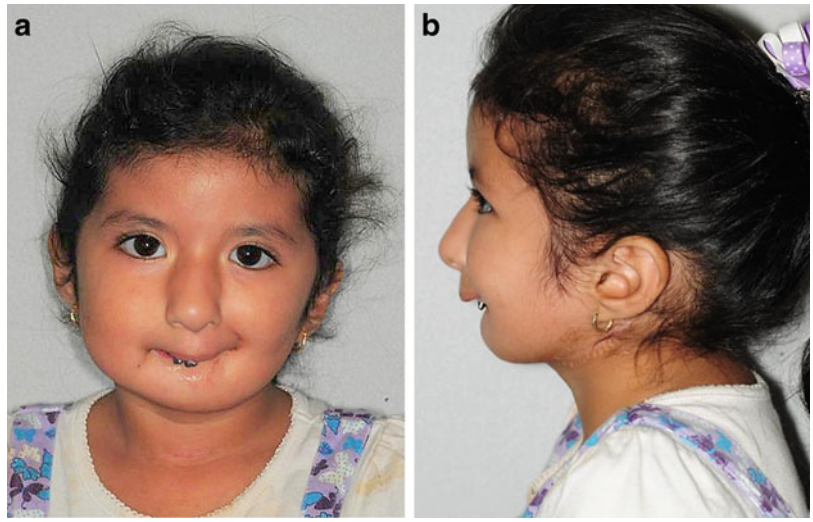

Fig. 11 (**a**, **b**) Postoperative photos at age 5. She was reconstructed with a right costochondral rib graft to replace the condyle and ramus region and established continuity of her mandible. This was combined with the use of a titanium mesh crib and some bone morphogenetic proteins (BMP) at the junction of the native mandible and the costochondral graft. Note the improved facial profile on the *left*. Despite improved result, the patient will require further surgery as she grows to correct her facial profile

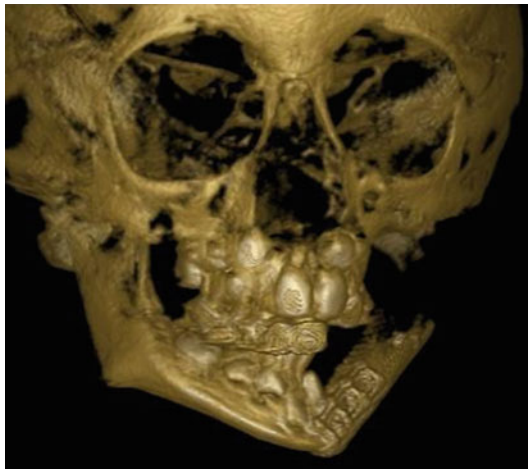

Fig. 12 Three-month postoperative cone-beam CT. Cartilaginous cap not apparent on this view

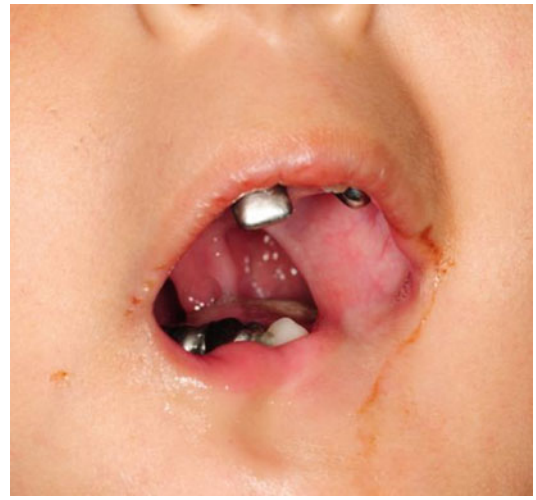

Fig. 13 Note the broad intraoral band extending from the left subglossal region to the soft palate. This band also attaches to the left lower lip causing retraction of the lip

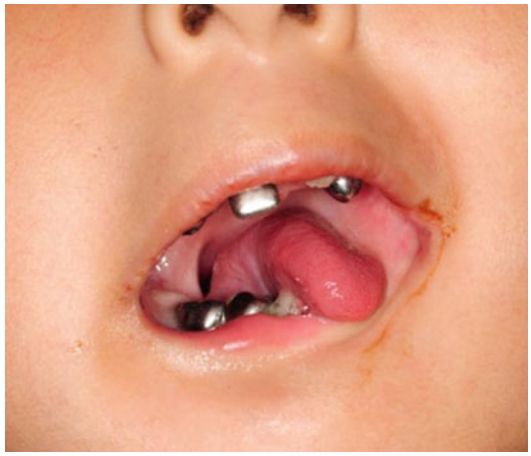

Fig. 14 The patient protruding her tongue past the intraoral band. Maximum protrusion. Based on the hypoglossia, the oral band extending from the floor of mouth and left cheek to the soft palate, and the limb abnormalities (hypodactylomelia), the patient would fit best as Hall's type IVD (intraoral bands and fusion with hypoglossia-hypodactylomelia). Thus, the patient is classified as a type IVD with hemimandibular agenesis (Qaisi et al., 2010, Oromandibular limb hypogenesis syndrome with a unique presentation of hemimandibular agenesis, personal communication)

Hypohidrotic Ectodermal Dysplasia

Contents

Hypohidrotic ectodermal dysplasia (HED) is a common form of ectodermal dysplasia characterized by a defect in the hair, in the teeth, and in mucosal and sweat glands. It is also known as anhidrotic ectodermal dysplasia. The incidence is estimated to be 1 in 10,000 to 1 in 100,000 male live births (Crawford et al. 1991).

Synonyms and Related Disorders

Anhidrotic ectodermal dysplasia; Christ-Siemens-Touraine syndrome

Genetics/Basic Defects

1. Inheritance: genetically heterogeneous (Pinheiro and Freire-Maia 1994)
    1. X-linked recessive type: the most common form of over 170 different ectodermal dysplasias
    2. Autosomal dominant type: less common
    3. Autosomal recessive type (Passarge et al. 1966): less common
2. X-linked HED: the most common form
    1. Caused by mutations in the ectodysplasin-A gene (*EDA1*) which (Monreal et al. 1998; Doffinger et al. 2001):
        1. Codes for the tumor necrosis factor (TNF) family member ectodysplasin-A (EDA)
        2. Maps to chromosome Xq12-q13.1 by a manifesting female with X linked hypohidrotic ectodermal dysplasia and an X;autosome balanced translocation (46,X,t(X;9)(q13.1;p24)) (Zonana et al. 1988) and X-autosome translocation of a female EDA patient [t(X;1)(q13.1;p36.3)] (Srivastava et al. 1996)
        3. Affects a transmembrane protein expressed by keratinocytes, hair follicles, and sweat glands
        4. Possibly has a key role in epithelial-mesenchymal signaling
    2. Over 94% of patients with X-linked HED carry mutations in the *EDA1* gene.
    3. Tabby phenotype is caused by mutation in mouse homolog of the human *EDA* gene (Priolo et al. 2000).
    4. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kB signaling (Doffinger et al. 2001).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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5. Hemizygous males show severe forms of the disease, while heterozygous females often manifest mild to moderate symptoms because of X-chromosome inactivation.

3. Autosomal dominant form and some familial cases of autosomal recessive form of HED caused by at least two genes:
   1. *EDAR* (*EDA* receptor) gene (2q11-q13) (Ho et al. 1998; Baala et al. 1999)
      1. Cause either dominant or recessive forms
      2. Mutated in approximately 25% of non-EDA-related HED
   2. *EDARADD* (*EDAR*-associated death domain) gene (1q42-q43)
      1. Encodes a protein that interacts with the EDA receptor
      2. Known to cause either autosomal recessive or dominant HED
      3. Implicated in a very small number of HED patients (Chassaing et al. 2010)
4. Four genes (*EDA1*, *EDAR*, *EDARADD*, and *WNT10A*): account for 90% of hypohidrotic/anhidrotic ectodermal dysplasia cases (Cluzeau et al. 2011)

Clinical Features

1. General features
   1. Characterized by a triad of symptoms
      1. Atrichosis or hypotrichosis (missing or sparse hair)
      2. Anodontia, hypodontia, or misshapen teeth
      3. Absent or reduced sweating
   2. Variable clinical features
   3. Short stature
   4. Recurrent benign infectious disease seen in most patients with HED
   5. Unusually severe infections observed in:
      1. Anhidrotic ectodermal dysplasia with immunodeficiency: a distinct syndrome
      2. Ectodermal dysplasia with cleft lip/palate
      3. Ectrodactyly-ectodermal dysplasia-cleft lip/palate
   6. Otitis media
   7. Infantile fever of unknown etiology
   8. Hyperthermia
   9. Hoarse voice
2. Clinical features in X-linked recessive hypohidrotic ectodermal dysplasia
   1. Affected individuals
      1. Hemizygous males: affected
      2. Heterozygous female carriers: variable clinical symptoms (normal or mild or partially affected)
         1. Dental abnormalities, such as hypodontia
         2. Mild hypohidrosis
         3. Mild hypotrichosis
   2. Clinical evidence of the distribution of normal and abnormal skin along Blaschko lines in heterozygous and postzygotic mutation carriers of X-linked hypohidrotic ectodermal dysplasia
      1. The presence of two different cell lines in a female heterozygous for the XHED due to random inactivation of one of the two X chromosomes during embryogenesis, reflected by the presence of different skin areas, some normal and some showing the result of the genetic abnormality.
      2. These abnormal areas, disposed along Blaschko lines, reflect the lines of embryonal development of the epidermis and epidermal derivatives.
      3. This clonal inactivation ("lyonization") of the X chromosome results in variable degree of clinical expression of the disorder.
   3. Clinically differentiating X-linked HED from autosomal forms of HED
      1. Finding heterozygous females with XHED
      2. Finding parents with partial manifestations of the disorder due to a postzygotic mutation
   4. Clinical features
      1. Scalp hair
         1. Sparse
         2. Thin
         3. Light pigmented
         4. Slow growing

5. Excessive fragility of the shafts, breaking easily with the usual wear and tear of childhood
2. Body hair
1. Sparse
2. Normal sexual hair (beard, pubic hair)
3. Sweating
1. Greatly deficient sweating (hypohidrosis)
2. Leading to hyperthermia
4. Teeth
1. Congenital absence of teeth (hypodontia)
2. Teeth that are present (smaller than average and have conical crowns)
5. Facial features
1. Frontal bossing
2. A saddle nose (depressed nasal bridge)
3. Thick lips
4. Periorbital hyperpigmentation
6. Other features (Clarke et al. 1987)
1. Normal growth and psychomotor development
2. Atopic dermatitis
3. Bronchial asthma
4. Fever of unknown reason
5. Sudden death during infancy and early childhood

3. Clinical features in autosomal recessive hypohidrotic ectodermal dysplasia
1. Similar to (but indistinguishable from) the hemizygous form of X-linked hypohidrotic ectodermal dysplasia (Munoz et al. 1997)
1. Decreased sweating
2. Hypodontia
3. Conical teeth
4. Hypotrichosis of the scalp
5. Sparse or absent eyebrows and eyelashes
6. Sparse or absent body hair
7. Dry skin or eczema
8. Hypoplastic nails
9. Hypoplastic breasts
10. Atrophic rhinitis
11. Depressed nasal bridge
12. Hyperpigmented and wrinkled periorbital skin
2. Males and females equally affected

4. Clinical features in autosomal dominant hypohidrotic ectodermal dysplasia (Aswegan et al. 1997): milder in expression
1. Hypodontia, anodontia, microdontia, or other dental anomalies (100%)
2. Sparse eyelashes (100%)
3. Sparse eyebrows (96%)
4. Sparse, fine, slow-growing hair (89%)
5. Decreased sweating (85%)
6. Thin skin (78%)
7. Sparse body hair (62%)
8. Decrease heat tolerance (50%)
9. Onychodysplasia (39%)

5. Classification of ectodermal dysplasias (Deshmukh and Prashanth 2012)
1. Currently there are about 150 different types of ectodermal dysplasias. In an attempt to classify these, different subgroups are created according to the presence or absence of the four primary ectodermal dysplasia (ED) defects:
1. ED1: trichodysplasia (hair dysplasia)
2. ED2: dental dysplasia
3. ED3: onychodysplasia (nail dysplasia)
4. ED4: dyshidrosis (sweat gland dysplasia)
2. Based on clinical findings, different types of ectodermal dysplasia are more relevant and may be divided into two broad categories (Vasconcelos Carvalho et al. 2013):
1. Hypohidrotic ectodermal dysplasia (X-linked hypohidrotic ectodermal dysplasia or Christ-Siemens-Touraine syndrome).
2. Hidrotic ectodermal dysplasia (Clouston's syndrome)

Diagnostic Investigations

1. Radiography
1. Hypodontia and anodontia
1. Essential to determine the extent of hypodontia and anodontia

    2. Useful in the diagnosis of mildly affected individuals
  2. Recurrent respiratory infections
2. Normal hair morphology under electron microscopy
3. Starch-iodine test (Clarke and Burn 1991) to confirm a mosaic distribution of functional sweat glands in a heterozygous female carrier of X-linked HED (Cambiaghi et al. 2000)
4. Molecular analysis: clinically available
  1. Sequence analysis
    1. Mutation in *EDA* gene for the X-linked form
    2. Mutations in *EDAR* and *EDARADD* genes for the autosomal dominant or recessive forms
  2. Duplication/deletion testing: to detect exonic, multiexonic, or whole gene deletions in females which sequence analysis of *EDA* cannot detect

Genetic Counseling

1. Recurrence risk (Wright et al. 2014)
  1. Patient's sib.
    1. X-linked recessive: 50% of affected brothers if the mother is a carrier; otherwise the risk to sibs is low.
    2. Autosomal dominant: not increased unless a parent is affected, in which case the risk to the sibs is 50%.
    3. Autosomal recessive: 25% of the sibs affected.
  2. Patient's offspring.
    1. X-linked recessive
      1. Offspring of a male proband: none of the sons will be affected; 50% of the daughters will be carriers.
      2. Offspring of a female proband: 50% of her son will be affected, and 50% of her daughters will be carriers and may show minimal manifestations.
    2. Autosomal dominant: 50% risk to each child
    3. Autosomal recessive: not increased unless the spouse is also a carrier, in which case the risk to offspring is 50%
3. In X-linked form, carrier mothers exhibit minimal expression in the form of hypodontia and/or conical teeth and spottily reduced sweating (Deshmukh and Prashanth 2012).
4. Prenatal diagnosis.
  1. Three-dimensional ultrasonography to identify the distinct facial features during the third trimester (Sepulveda et al. 2003).
  2. Noninvasive prenatal diagnosis of hypohidrotic ectodermal dysplasia by Tooth Germ sonography (Wünsche et al. 2015).
  3. Analysis of fetal skin obtained from fetoscopy-guided skin biopsy in the second trimester.
  4. Prenatal diagnosis of X-linked hypohidrotic ectodermal dysplasia by linkage analysis (Zonana et al. 1990).
  5. Identification of the disease-causing mutation in the fetus.
  6. Preimplantation genetic diagnosis for at-risk pregnancies is possible, provided disease-causing mutations have been identified.
5. Management (Clarke 1987).
  1. Environmental modification to control temperature.
    1. Air condition for home, school, and work
    2. Adequate supply of water during the hot weather
  2. Control body temperature.
    1. Tepid sponging
    2. Showers
    3. Cold drink
    4. Antipyretics
    5. Wet clothing
  3. Use moisturizers to prevent xerosis or eczema for dry skin.
  4. Use artificial tears (eye drops) to prevent damage to the cornea in patients with defective tearing.

5. Remove nasal and aural concretions with suction devices or forceps and humidification of the ambient air to prevent their formation.
6. Treatment and prophylaxis for infections.
7. Dental evaluation and intervention.
    1. Early dental treatment
        1. Simple restoration
        2. Dentures
        3. Orthodontics
    2. Dental implants
    3. Orthodontic treatment
8. Wear wigs to improve appearance for patients with severe alopecia.
9. Avoid vigorous physical activities for patients with hypohidrosis.
10. Monitor growth.
11. Reconstruction surgery for saddle nose, sunken "dishpan face," and ear anomalies (Rossman and Johnson 1966).

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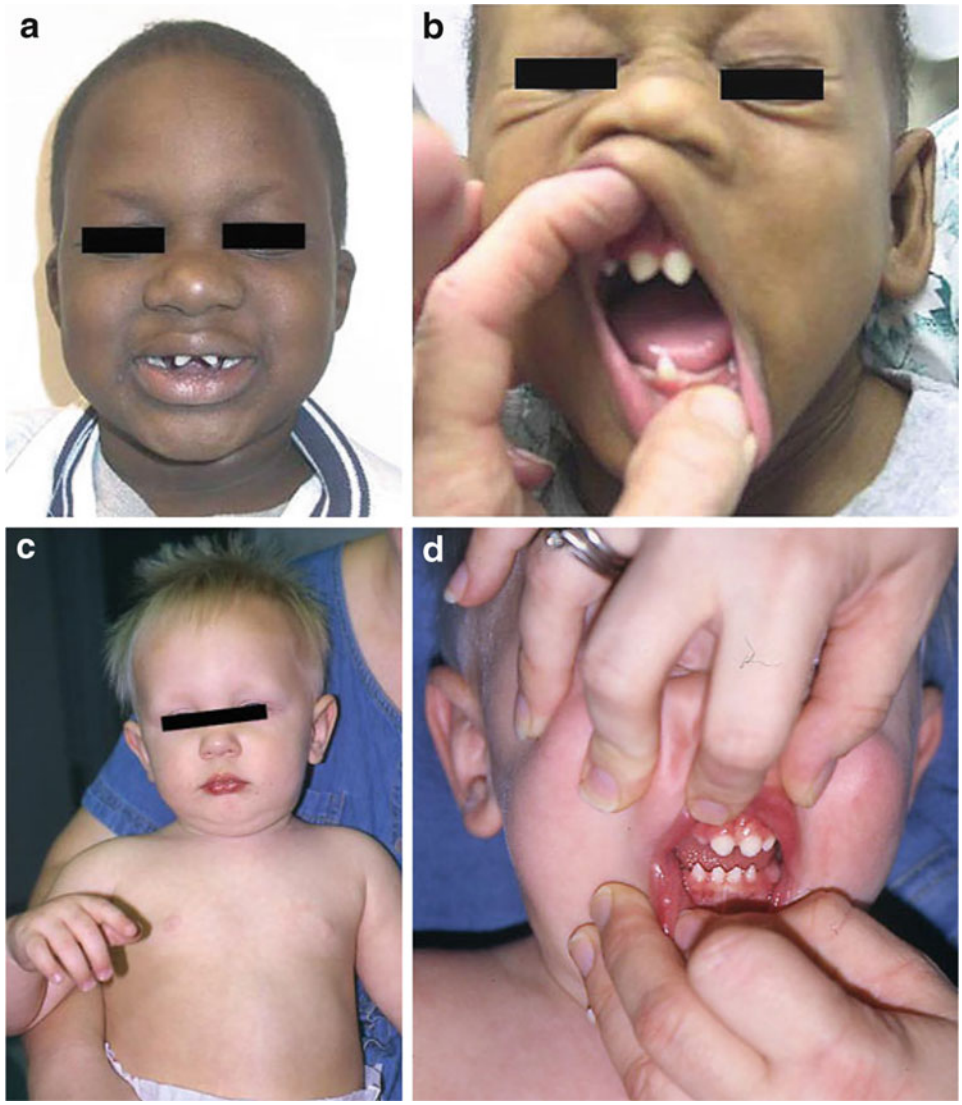

Fig. 1 (**a**–**d**) Three boys with X-linked hypohidrotic ectodermal dysplasia showing sparse scalp hair, frontal bossing, sparse eyebrows and eyelashes, saddle nose, hypodontia, and irregularly shaped conical and pointed primary incisors

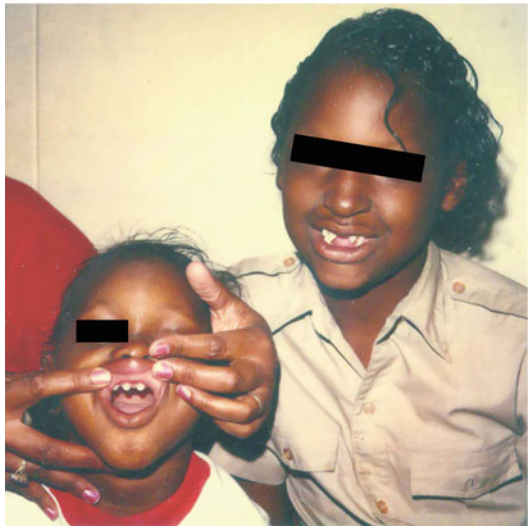

Fig. 2 Two brothers with X-linked hypohidrotic ectodermal dysplasia showing sparse eyebrows, hypodontia, and conical permanent teeth

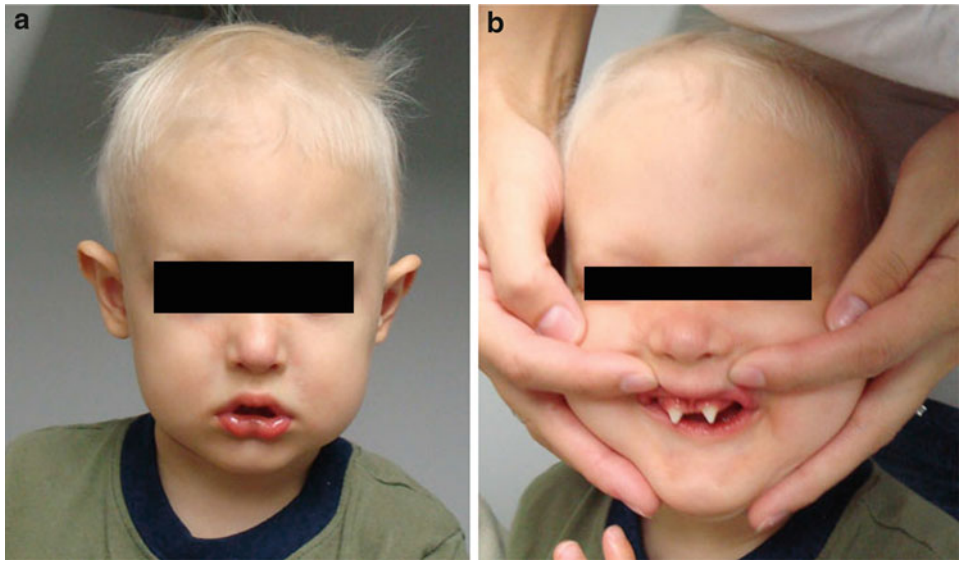

Fig. 3 (**a**, **b**) A boy with hypohidrotic ectodermal dysplasia showing sparse scalp hairs and eyebrows, hypodontia, and conical permanent teeth

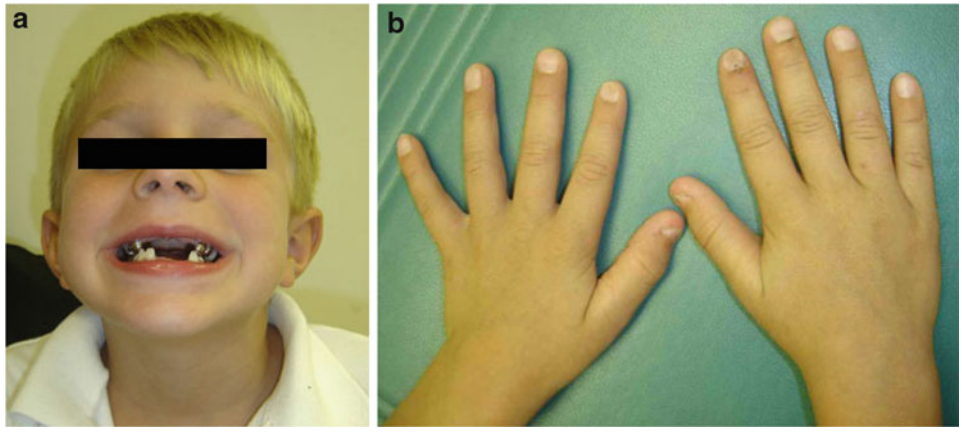

Fig. 4 (**a**, **b**) A boy with hypohidrotic ectodermal dysplasia showing sparse scalp hairs and eyebrows, hypodontia, and nail hypoplasia of the thumbs

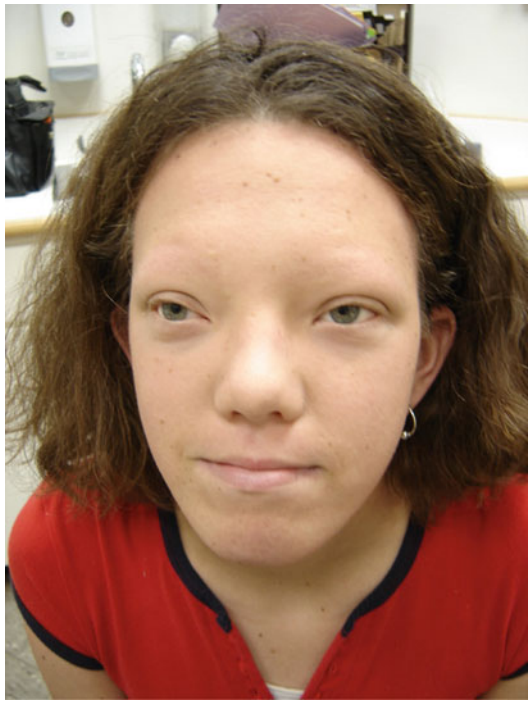

Fig. 5 A 15-year-old girl with hypohidrotic ectodermal dysplasia showing sparse eyebrows and ocular hypertelorism

Hypomelanosis of Ito

Contents

In 1952, Ito (1952) reported a female patient with a widespread, symmetric pattern of depigmented whorls and streaks, naming it incontinentia pigmenti achromians because the distribution of the depigmented lesions is the negative image of the hyperpigmented streaks of incontinentia pigment. Hypomelanosis of Ito (HI) is a relatively common disorder with a frequency of 1 in 8000–10,000 patients in a general pediatric hospital and 1 in 1000 patients in a pediatric neurology service (Küster and Konig 1999). HI is the third most common neurocutaneous syndrome, following neurofibromatosis and the tuberous sclerosis complex (Pascual-Castroviejo et al. 1998).

Synonyms and Related Disorders

Incontinentia pigmenti achromians

Genetics/Basic Defects

1. Inheritance
    1. Sporadic occurrence in nearly all cases with no affected sibs or parents (Küster and Konig 1999)
        1. Result of a de novo postzygotic mutation
        2. Mutation can only survive in a mosaic state
    2. Only a few cases with possible genetic inheritance reported
        1. X-linked dominant inheritance
        2. Autosomal dominant (Rubin 1972)
        3. Autosomal recessive
2. Pathogenesis
    1. Chromosome abnormalities (52%) (Janniger and de Menezes 2014)
        1. Mosaicism leading to generation of two cell lineages producing patterns of hypopigmented and hyperpigmented skin
        2. Balanced X/autosome translocations (Hatchwell et al. 1996)
        3. Supernumerary X chromosome/ring fragment
        4. Ring chromosomes (10, 14, 22)
        5. Mosaic triploidy
        6. Mosaic diploidy/tetraploidy
        7. Mosaic trisomies (2, 8, 13, 14, 18, 20, 22)
        8. Mosaic tetrasomy 13q
        9. Mosaic translocations

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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10. Mosaic deletions
11. Autosomal deletions and duplications involving chromosomes 7, 12, 13, 14, 15, and 18
12. Dup(Xp)

2. X chromosome abnormalities
   1. Inactivation
   2. Activation
   3. Mosaicism
3. Chromosome mosaicism
   1. Leads to variable phenotype
   2. Certain genes (9q33-qter, 15q11-q13, and Xp11 (Koiffmann et al. 1993) are implicated in hypomelanosis of Ito. However, no consensus exists about the identity of HI gene (Ratz 2014).

3. "Pigmentary mosaicism" (Flannery 1990; Ritter et al. 1990; Taibjee et al. 2004)
   1. Hypomelanosis of Ito and related disorders such as linear and whorled nevoid hypermelanosis are due to mosaicism for a variety of chromosomal abnormalities
   2. Classification of chromosome mosaicism
      1. Mosaicism with two or more different karyotypes, involving structural abnormalities of chromosomes
      2. Mosaicism involving structural abnormalities of chromosomes, where the chromosome was undetermined
      3. Chromosomal abnormality apparently affecting all cells, but where undetected mosaicism remains a possibility
      4. Balanced X/autosome translocations affecting all cells, with functional mosaicism due to ionization
      5. Polyploidy mosaicism (cells having different multiples of 23 chromosomes) can be associated with mosaic trisomy such as chromosome18
      6. Chimerism
4. A descriptive term rather than a true syndrome (Sybert 1994; Ruggieri and Pavone 2000)
   1. Suggested by the pattern of chromosomal aberrations and the polymorphic nature of the disease
   2. A term used for a phenotype
      1. Presence of linear streaks lighter than the patient's background skin color, extending around the trunk and down the long axes of the extremities, roughly following the lines of Blaschko
      2. Association with systemic findings

Clinical Features

1. Cutaneous symptoms (Küster and Konig 1999)
   1. Onset
      1. Recognizable at birth (54%)
      2. Visible during childhood (70%)
   2. No signs of inflammation or verrucous changes characteristically seen in incontinentia pigmenti
   3. Hypopigmented lesions
      1. Typical phenotype
         1. Cutaneous pattern: essentially the reverse of the third stage of incontinentia pigmenti
         2. Bilateral or unilateral whirls, patches, and streaks corresponding to the lines of Blaschko, often showing a midline cutoff
         3. Eruption not preceded by any inflammatory lesions (unlike incontinentia pigmenti)
      2. Unilateral skin lesions contralateral to the side of brain malformation in patients with HI and hemimegalencephaly
      3. Wood lamp useful in demonstrating hypopigmented lesions in persons with fair skin
      4. Atypical phenotype: checkerboard pattern zosteriform, dermatomal, or plaque-like arrangement
   4. Nonspecific skin lesions (20–40%)
      1. café-au-lait spots
      2. Persistent Mongolian blue spots
      3. Nevus of Ota
      4. Nevus marmoratus and angiomatous nevi
      5. Soft fibroma
      6. Pilomatrixoma
      7. Aplasia cutis
      8. Atopic dermatitis

2. Hair/nail/sweat gland anomalies
    1. Focal hypertrichosis
    2. Slow growth
    3. Diffuse alopecia
    4. Coarse, curly hair
    5. Trichorrhexis
    6. Widow's peak
    7. Generalized hirsutism
    8. Facial hypertrichosis
    9. Low hairline
    10. Ungual hypoplasia
    11. Hypohidrosis corresponding to hypopigmented areas
3. Associated extracutaneous anomalies (75%)
    1. CNS anomalies (Pascual-Castroviejo et al. 1988, 1998; Ruggieri and Pavone 2000)
        1. Mental retardation (50-75%)
        2. Seizures (50%)
        3. Autistic behavior (11%)
        4. Microcephaly
        5. Macrocephaly (Ross et al. 1982)
        6. Hypotonia
        7. Hyperkinesia
        8. Ataxia
        9. Deafness
        10. Hemimegalencephaly (Tagawa et al. 1997)
        11. Brain tumors: medulloblastoma, choroid plexus papilloma (Zajac et al. 1997)
        12. White matter abnormalities
        13. Cerebral, brain stem, or cerebellar atrophy
        14. Agenesis of the corpus callosum
        15. Periventricular lesions
    2. Ophthalmological abnormalities (20%) (Weaver et al. 1991)
        1. Microphthalmia
        2. Ptosis
        3. Nonclosure of the upper lid
        4. Symblepharon
        5. Dacryostenosis
        6. Strabismus
        7. Nystagmus
        8. Myopia
        9. Hyperopia
        10. Astigmatism
        11. Amblyopia
        12. Megalocornea
        13. Corneal opacification
        14. Cataracts
        15. Iridal heterochromia
        16. Scleral melanosis
        17. Heterochromia of the iris
        18. Optic atrophy
        19. Striated patchy hypopigmented fundi
        20. Retinal detachment
    3. Dental abnormalities
        1. Defective dental implantation
        2. Conical teeth
        3. Partial anodontia
        4. Dental dysplasia/hypoplasia
        5. Defective enamel
        6. Hamartomatous dental cusps
    4. Skeletal defects
        1. Short stature
        2. Facial and limb asymmetry (hemihypertrophy)
        3. Pectus carinatum or excavatum
        4. Scoliosis
        5. Syndactyly
        6. Polydactyly
        7. Brachydactyly
        8. Clinodactyly
    5. Congenital heart defect
        1. Tetralogy of Fallot
        2. Pulmonary stenosis
        3. Ventricular septal defect
        4. Atrial septal defect
        5. Incomplete right bundle branch block
        6. Cardiomegaly of unknown etiology
    6. Abdomen/gastrointestinal anomalies
        1. Diastasis recti
        2. Hepatomegaly
        3. Segmental dilation of the colon
        4. Diaphragmatic, umbilical, and inguinal hernias
    7. Genitourinary anomalies
        1. Hypospadias
        2. Micropenis
        3. Single kidney
        4. Urethral duplication
        5. Cryptorchidism
        6. Precocious puberty
        7. Gynecomastia

8. Asymmetrical breasts
9. Nephritis

4. Diagnostic criteria (Ruiz-Maldonado et al. 1992)
   1. Sine qua non criterion: congenital or early acquired nonhereditary cutaneous hypopigmentation in linear streaks or patches involving more than two body segments
   2. Major criterion
      1. One or more nervous system anomalies
      2. One or more musculoskeletal anomalies
   3. Minor criterion
      1. Two or more congenital malformations other than nervous system or musculoskeletal anomalies
      2. Chromosomal anomalies
   4. Definitive diagnosis: sine qua non criterion plus one or more major criteria or two or more minor criteria
   5. Presumptive diagnosis: sine qua non criterion alone or in association with one minor criterion
5. Classification of linear pigmentary disorders distributed along the Blaschko lines (Nehal et al. 1996; Di Lernia 2007)
   1. Linear and whorled hypermelanosis (Harre and Millikan 1994)
      1. Hyperpigmentation
      2. Diffuse distribution
      3. Presence of mosaicism
      4. Associated abnormalities ($\leq$30%)
   2. Hypomelanosis of Ito
      1. Hypopigmentation
      2. Diffuse distribution
      3. Presence of mosaicism
      4. Associated abnormalities ($\geq$30%)
   3. Progressive cribriform and zosteriform hyperpigmentation
      1. Hyperpigmentation
      2. Segmental distribution
      3. Associated abnormalities: very low incidence
   4. Segmental nevus depigmentosus
      1. Hyperpigmentation
      2. Segmental distribution
      3. Associated abnormalities: very low incidence
6. Differential diagnosis (Barbel et al. 2015)
   1. Pityriasis alba
      1. Affects approximately 5% of the pediatric population (Moreno-Cruz et al. 2012)

Diagnostic Investigations

1. Cytogenetic investigation
   1. Peripheral blood karyotyping indicated especially when systemic manifestations are present
   2. Fibroblast karyotyping by sampling the dark and light skin for demonstrating mosaicism or chromosomal abnormalities
   3. Presence of a wide variety of karyotypic abnormalities
2. Histopathology
   1. Decreased numbers of melanocytes
   2. Decreased numbers and size of pigmented melanosomes
   3. Neuropathological features
      1. Polymicrogyria
      2. Disarray of cortical lamination
      3. Heterotopic neurons in the white matter
      4. Giant cells (Glover et al. 1989; Pascual-Castroviejo et al. 1998)
3. CT and MRI of the brain
   1. White matter abnormalities somewhat predictive of a poor neurological outcome (Ruggieri et al. 1996)
   2. Neuroblast migration
      1. Heterotopia
      2. Pachygyria
      3. Polymicrogyria
   3. Localized or generalized cerebral atrophy
   4. Cerebral hemiatrophy
   5. Hemimegalencephaly
   6. Other rare anomalies
      1. Noncommunicating hydrocephalus
      2. Megacisterna magna
      3. Arteriovenous malformation (Urgelles et al. 1996)
      4. Cerebellar hypoplasia (hemispheres and vermis)
      5. Brainstem hypoplasia
      6. Brain tumors (Steiner et al. 1996)

4. Radiography for musculoskeletal anomalies
5. EEG for seizures

Genetic Counseling

1. Recurrence risk (Ruggieri 2000)
   1. Patient's sib: not increased unless a parent shows chromosomal abnormalities
   2. Patient's offspring
      1. Not increased unless the patient has chromosomal abnormalities
      2. Guarded counseling in women with a phenotype similar to HI who have nonmosaic balanced X/autosome translocations
2. Prenatal diagnosis: undetermined for affected mother who has a specific type of chromosome abnormality
3. Management
   1. Early intervention programs including physical, occupational, and speech therapies
   2. Special education
   3. Seizure control
   4. Surgical treatment of cataracts and retinal detachment
   5. Pharmacoresistant epilepsy in hypomelanosis of Ito: Palliative surgical treatment with modified anatomic posterior quadrantic resection (Manjila et al. 2014)

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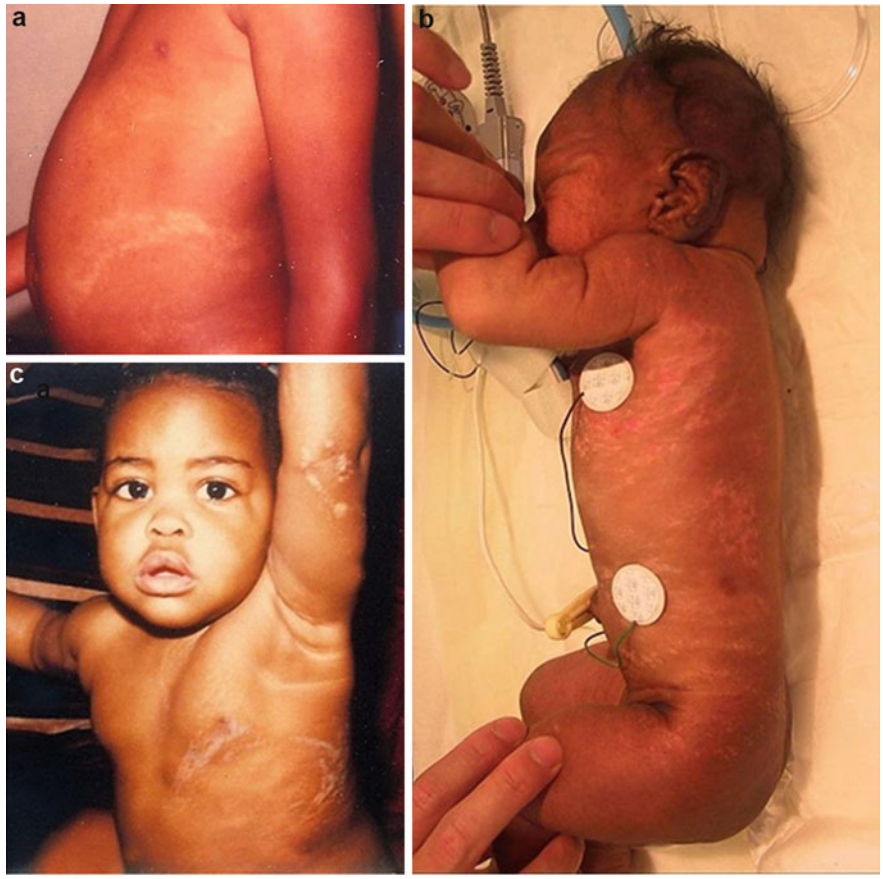

Fig. 1 (**a**–**c**) Three children (**a**–**c**) with hypomelanosis of Ito showing hypopigmented skin lesions in a characteristic distribution of whirls and streaks on the trunk and limbs. The first patient (**a**) has 49, XXXXY

Hypophosphatasia

Contents

Hypophosphatasia is a heritable metabolic disease, characterized by impaired ossification of the bones, reduction in tissue and plasma levels of alkaline phosphatase, and the presence of phosphoethanolamine in the urine. The incidence is estimated to be about 1 in 100,000 live births (Fraser 1957). The incidence of severe disease is especially high in Canadian Mennonites (1 in 2,500 newborns) (Gehring et al. 1999).

Synonyms and Related Disorders

Adult hypophosphatasia (mild hypophosphatasia, odontohypophosphatasia); Childhood hypophosphatasia; Perinatal lethal hypophosphatasia; Phosphoethanolaminuria

Genetics/Basic Defects

1. Genetic heterogeneity (Bianchi 2015)
    1. Perinatal lethal hypophosphatasia form: autosomal recessive
    2. Prenatal benign hypophosphatasia form: autosomal recessive and dominant
    3. Infantile hypophosphatasia form: autosomal recessive
    4. Childhood hypophosphatasia form: autosomal recessive (frequent) and dominant (rare)
    5. Adult hypophosphatasia form: autosomal recessive and dominant with variable penetrance
    6. Odontohypophosphatasia form: autosomal recessive and dominant
2. Cause
    1. Caused by mutations in the alkaline phosphatase gene (*ALPL*) which (Barcia et al. 1997):
        1. Codes for tissue nonspecific ("liver/bone/kidney") alkaline phosphatase (TNSALP) (Henthorn and Whyte 1992)
        2. Is mapped on chromosome 1p36.1-p34
    2. Typically, the other isoenzymes (placental and intestinal forms) are not affected (Gehring et al. 1999)
3. Pathophysiology
    1. Defects in mineralization
        1. Caused by deficiency in TNSALP
        2. Resulting in increased urinary excretion of phosphoethanolamine and inorganic pyrophosphate and an increase in serum pyridoxal 5'-phosphate

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2. Alkaline phosphatase (ALK) has a significant role in skeletal mineralization in humans. How ALP acts was clarified by the discoveries that several phosphocompound substrates for tissue-nonspecific ALP (TNSALP) accumulate endogenously in this inborn error of metabolism (Whyte 1995)
3. Osteoclasts, although morphologically normal, lack membrane-associated alkaline phosphatase activity on histochemical analysis (Barcia et al. 1997)
    1. Impede the proper incorporation of calcium into newly formed bone matrix
    2. Result in bone demineralization and hypercalcemia when the impaired matrix calcification process occurs with a rapid rate of bone resorption
4. Genotype-phenotype correlations (Hu et al. 2000)
    1. A number of different mutations account for the clinical heterogeneity
        1. Individuals with recessive hypophosphatasia with both defective TNSALP alleles
            1. In general, manifest more severe symptoms, with many of those affected being stillborn or expiring shortly after birth
            2. Exception when consanguineous marriage is a factor: the two defective alleles tend to have distinct point mutations resulting in different amino acid substitutions in the alkaline phosphatase protein
        2. Individuals with dominant hypophosphatasia with only one defective TNSALP allele: usually manifest moderate symptoms, such as the premature exfoliation of fully rooted primary teeth
        3. Division between dominant and recessive hypophosphatasia sometimes is not well defined because the heterozygous siblings with one defective TNSALP allele in kindreds with recessive hypophosphatasia may show mild or moderate symptoms of the disease
        2. Missense mutations in the TNSALP gene have been observed in some hypophosphatasia kindreds, particularly those families with the more severe perinatal and infantile forms of the disease
        3. Autosomal recessive inheritance has been observed in most cases of hypophosphatasia with affected individuals being compound heterozygotes for two different mutant hypophosphatasia alleles
        4. Autosomal dominant alleles cause a few relatively mild cases of hypophosphatasia
        5. Mild hypophosphatasia (Fauvert et al. 2009)
            1. Can result from either compound heterozygosity for severe and moderate mutations but also in a large part from heterozygous mutations with a dominant negative effect
            2. A sequence variation in linkage disequilibrium with haplotype E could in addition play the role of an aggravating factor resulting in loss of haplosufficiency

Clinical Features

1. Presence of a wide phenotypic variability (interfamilial and intrafamilial) ranging from intrauterine death and extreme hypomineralization of the skeleton to lifelong absence of clinical symptoms (Gehring et al. 1999; Hoffmann et al. 2014; Plotkin 2014)
    1. The following six different forms of hypophosphatasia have been defined (Bianchi 2015):
        1. Perinatal lethal form
        2. Perinatal benign form
        3. Infantile form
        4. Childhood form
        5. Adult form
        6. Odontohypophosphatasia
    2. In general, the earlier the age of presentation, the more severe the presenting features
2. Perinatal lethal form (Bianchi 2015)
    1. The most severe form: stillbirth or death within days/weeks after birth
    2. Skeletal deformities: presenting features

1. A profound lack of skeletal mineralization (severe hypomineralization) in utero
2. Derangements in calcium/phosphate metabolism
3. Skin-covered spurs extending from the forearms or legs (skin dimples) (Shohat et al. 1991): these spurs are often diagnostic for hypophosphatasia
4. Markedly shortening and bowing of the long bones (short-limbed dwarfism)
5. Fractures (perinatal)
6. Rickety rosary
7. Metaphyseal swelling
8. Soft, pliable cranial bones ("vault like a balloon")
9. Bulging anterior fontanelle

3. Respiratory distress due to severe hypoplastic lungs and rachitic deformities of the chest and rib fractures
4. Other features
   1. Hypotonia
   2. High-pitched cry
   3. Vomiting
   4. Constipation
   5. Unexplained fever
   6. Apnea
   7. Cyanosis
   8. Irritability
   9. Seizures
5. Prognosis
   1. Lethal in utero or within a few days of birth
   2. In the rare prenatal benign form, despite prenatal symptoms, there is a spontaneous improvement of skeletal defects (Pauli et al. 1999; Moore et al. 1999; Wenkert et al. 2007)

3. Infantile form (Fallon et al. 1984; Bianchi 2015)
   1. Appears normal at birth
   2. Onset of symptoms
      1. Before 6 months of age
      2. Poor feeding
      3. Failure to thrive (growth failure)
      4. Hypotonia
      5. Convulsions
   3. Associated with progressive bony demineralization
      1. Abnormal skull with apparent wide separation of the cranial sutures and a wide, bulging anterior fontanelle
      2. Tendency toward developing craniosynostosis
         1. Formation of a sagittal ridge
         2. A bony prominence at the position of the anterior fontanelle
      3. Rachitic skeletal deformities manifesting by age 6 months
      4. Flail chest
      5. Pulmonary insufficiency
   4. Premature craniosynostosis
      1. Chiari I malformation
      2. Hydrostatic hydrocephalus
      3. Hydrosyringomyelia
   5. Swallowing disorders
   6. Irritability
   7. Seizures
   8. Severe muscular hypotonia
   9. Late in walking
   10. Development of genu valgum
   11. Short stature
   12. Complications
      1. Recurrent pneumonia
      2. Increased intracranial pressure
      3. Renal compromise secondary to:
         1. Hypercalcemia
         2. Hypercalcinuria
         3. Nephrocalcinosis
   13. Prognosis:
      1. Fatal in approximately 50% of cases by the age of 1 year
      2. Survivors
         1. Tend to improve symptomatically
         2. Deformities persist and often become worse

4. Childhood form (Fallon et al. 1984; Bianchi 2015)
   1. Appears normal at birth
   2. Often present after 6 months of age
   3. History of delayed walking and waddling gait
   4. Early loss of deciduous teeth (before age of 5 years): the most consistent clinical sign

5. Frequent bone pain
6. Defective bone mineralization presenting clinically as rickets in children
7. Respiratory complications due to rachitic deformities of the chest
8. Premature craniosynostosis despite open fontanelle resulting in increased intracranial pressure
9. Dolichocephalic skull
10. Enlarged joints
11. Short stature
12. Muscular hypotonia
13. Failure to thrive
14. Lack of appetite, nausea, and gastrointestinal problems
15. Delayed walking
16. Repeated bone fractures
17. Waddling gait due to bone deformities
18. Chronic lower extremity bone pain
19. Presence of hypercalcemia causes increased excretion of calcium resulting in renal damage
20. Prognosis: improving both clinically and radiographically with age in some childhood hypophosphatasia patients

5. Adult form (Fallon et al. 1984; Wendling et al. 2001; Berkseth et al. 2013; Bianchi 2015)
    1. Variable age of onset and severity
    2. Onset usually during middle age
    3. A wide spectrum of clinical manifestations: 1/3 of patients asymptomatic at the time of diagnosis
    4. The most common presenting features
        1. Musculoskeletal pain (40.9%)
        2. Fractures (18.2%)
        3. Whereas classic features of childhood forms of HPP such as dental abnormalities and a history of rickets are relatively uncommon
    5. Fractures
        1. Stress fractures of metatarsals, tibia
        2. Femur pseudofractures
        3. Fragility fractures
        4. History of delayed fracture healing in childhood; often mild "rickets"
    6. Defective bone mineralization presents clinically as osteomalacia and osteoporosis in adults
    7. Premature loss of deciduous teeth
    8. Usually presents clinically with loss of adult teeth
    9. Foot pain due to stress fractures of the metatarsals
    10. Thigh pain due to pseudofractures of the femur
    11. Delay in healing after a fracture
    12. Joint pain due to deposition of calcium pyrophosphate dihydrate (chondrocalcinosis)
    13. Pseudogout
    14. Chondrocalcinosis
    15. Osteoarthritis
    16. Myopathy/weakness
    17. Renal abnormalities
        1. Reduced GFR
        2. Nephrocalcinosis and kidney stones
    18. Psychiatric symptoms
        1. Insomnia
        2. Restlessness
        3. Anxiety
        4. Depression
6. Odontohypophosphatasic form (Bianchi 2015)
    1. Premature loss of adult teeth; the only physical finding in this form
    2. Not associated with bone, articular, or muscular problems
7. Craniosynostosis
    1. Considered a known feature in the infantile and childhood types of hypophosphatasia (Whyte 1995; Mornet 2007; Collmann et al. 2009), while it is missed in the adult and odontohypophosphatasia forms
    2. Often progressively involves all cranial sutures and poses significant functional risks to the optic nerves, as well as the spinal cord
8. Differential diagnosis of hypophosphatasia and osteomalacia (Silver et al. 2012)
    1. Osteomalacia
        1. Serum alkaline phosphatase: high

2. Serum levels of vitamin D and parathormone (PTH)
    1. low serum vitamin D
    2. Elevated PTH
3. Serum levels of calcium and phosphate
    1. Hypercalcemia
    2. Hypophosphatemia
4. Biopsy
    1. Discontinuous atrophic changes in the muscle fibers
    2. Loss of myofibrils
    3. Type II fiber atrophy

2. Hypophosphatasia
    1. Serum alkaline phosphatase: low
    2. Serum levels of vitamin D and parathormone: normal
    3. Serum levels of calcium and phosphate: normal
    4. Biopsy
        1. No atrophic signs
        2. Peripheral nucleus
        3. Type I fiber predominance
3. Both conditions
    1. Similar radiologic abnormalities
    2. Muscle hypotonia
    3. Waddling gait
    4. Diffuse bone pain worse with the cold and the exercise
    5. Proximal muscular weakness of the pelvic girdle and the lower limbs

Diagnostic Investigations

1. Laboratory tests
    1. Low serum alkaline phosphatase levels in all types of hypophosphatasia
    2. Increased levels of urinary phosphoethanolamine levels
    3. Elevated plasma levels of pyridoxal 5'-phosphate
    4. Normal serum calcium, except in infantile cases where hypercalcemia can be seen due to renal failure
    5. Normal serum phosphate: hyperphosphatemia in various forms of hypophosphatasia reported
2. Skeletal survey (James and Moule 1966; Kozlowski et al. 1976).
    1. Lethal perinatal form
        1. Near absence of skeletal mineralization
        2. Skull: tiny ossification of occipital and/or frontal bones or complete absence of ossification
        3. Teeth: very poorly formed
        4. Spine
            1. Some vertebrae frequently unossified
            2. Occasionally unossified vertebrae
            3. Abnormally shaped vertebrae: rectangular, round, flattened, sagittally cleft, or butterfly-shaped vertebrae
        5. Shortening and bowing of the long and tubular bones
        6. Diaphyseal spurs
        7. Skin-covered spurs extending from the medial and lateral aspects of the knee and elbow joints
        8. Fractures
        9. Rachitic changes
            1. Pathology most evident at metaphyses as in rickets where growth is most rapid, namely the wrists, knees, hips, and proximal humeri
            2. Defective, irregular ossification of the metaphysis: the most diagnostic feature of the disease
            3. Nearly absent provisional zone of calcification
            4. Irregular widening of the epiphyseal plate
            5. Grossly irregular ossification of metaphysis giving a “frayed” or “tufted” appearance: a distinguished feature in hypophosphatasia. In rickets, the decalcification is usually regular and may give a “ground glass” effect to the affected metaphysis (metaphyseal cupping)

2. Infantile form
    1. Deficient skeletal mineralization
    2. Congenital bowing of the long bones
    3. Bands of decreased density in metaphyses
    4. Widened cranial sutures
    5. Later craniosynostosis: premature craniosynostosis occurs despite an open fontanelle
    6. Asymmetrical, moderate to severe rickets-like metaphyseal changes
    7. Metaphyseal and epiphyseal ossification defects
    8. Distorted bone trabeculation with areas of decreased and increased transradiancy
    9. Thin cortical bone
    10. Diaphyseal spurs
3. Childhood form
    1. Mild, asymmetrical, metaphyseal changes resembling rickets or metaphyseal dysplasia
    2. Distorted bone trabeculation with areas of decreased and increased transradiancy
    3. Thin cortical bone
    4. Hypotubulation and bowing of long bones
    5. Stress fractures
    6. Radiolucent projections from the epiphyseal plate into the metaphysis
4. Adult form
    1. Pseudofractures often occur in the lateral aspect of the proximal femur: a hallmark of this form
    2. Osteomalacia
    3. An increased incidence of poorly healing stress fractures, especially of the metatarsals
5. Odontohypophosphatasic form: normal radiographic findings

3. Radiography and ultrasound screening for nephrocalcinosis
4. Whole body magnetic resonance imaging (WB-MRI) on the childhood form of HPP (Beck et al. 2011)
    1. Long bones: presence of deformities and defects
    2. All patients showed radiological lesions in the metaphyses of the long bones predominantly in the lower extremities being consistent with hyperemia and edema
5. Histology
    1. Growth plates
        1. Rachitic abnormalities
        2. Poorly mineralized and ossified columns with broad osteoid seams in metaphysis
        3. Osteoblasts lacking membrane-associated alkaline phosphatase activity on histochemical testing, disrupting incorporation of calcium into the matrix
    2. Teeth
        1. A decrease in cementum
        2. Enlarged pulp chamber
        3. Incisors tend to be affected
6. Molecular genetic diagnosis (Monet and Nunes 2016): ALPL, the gene-encoding alkaline phosphatase, tissue nonspecific isozyme (TNASALP), is the only gene known to be associated with hypophosphatasia
    1. Single-gene testing
        1. Sequence analysis of ALPL is performed first
        2. Followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found
    2. A multi-gene panel that includes ALPL and other genes of interest may also be considered: The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time
    3. More comprehensive genomic testing (when available) including whole-exome sequencing (WES) and whole-genome sequencing (WGS) may be considered if single-gene testing (and/or use of a multigene panel that includes ALPL) fails to confirm a diagnosis in an individual with features of hypophosphatasia. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a

different gene that results in a similar clinical presentation)

Genetic Counseling

1. Recurrence risk: genetic counseling is complicated by the inheritance that may be autosomal dominant or autosomal recessive, the existence of the uncommon prenatal benign form, the variable expression of the disease, and the incomplete penetrance of the trait (Mornet 2007; Simon-Bouy et al. 2008; Monet and Nunes 2016)
    1. Patient's sib
        1. Autosomal recessive: 25%
        2. Autosomal dominant: not increased unless a parent is affected in which case the recurrence risk is 50%
    2. Patient's offspring
        1. Autosomal recessive: not increased unless a spouse is a carrier in which case the recurrence risk is 50%
        2. Autosomal dominant: 50%
2. Prenatal diagnosis (Mulivor et al. 1978)
    1. Fetal radiography (Leroy et al. 1982)
    2. Prenatal ultrasonography
        1. 2D-ultrasonography
            1. Failure to visualize a well-defined skull
            2. Other fetal skeletal structures not readily discernable
        2. 3D-ultrasonography: can demonstrate specific osseous spurs in a lethal form (Sinico et al. 2007)
    3. Prenatal ultrasonography for benign prenatal hypophosphatasia (Matsushita et al. 2014)
        1. Normal skeletal mineralization
        2. Normal chest and abdominal circumferences, despite the limb bowing and shortening
    4. Fetal cordocentesis in the first trimester: undetectable fetal alkaline phosphate concentration (Tongsong and Pongsatha 2000)
    5. Assay of the alkaline phosphatase activity: a useful complementary and independent method, especially when a mutation is unidentified and DNA from the index case is unavailable
        1. Assay of the tissue nonspecific alkaline phosphatase activity in chorionic villus samples in the first trimester (Maxwell et al. 1985; Brock and Barron 1991; Mornet et al. 1999)
        2. Absent alkaline phosphatase activity in the amniotic fluid and cultured amniotic fluid cells in the second trimester
    6. Prenatal diagnosis and preimplantation genetic diagnosis: mutation analysis of fetal DNA from amniocentesis or CVS where the disease-causing mutation has been identified in the family (Monet and Nunes 2016)
3. Management
    1. No specific treatment available: efforts to effect improved mineralization in patients with hypophosphatasia have not been successful (Barcia et al. 1997)
        1. Nonsteroidal anti-inflammatory drugs for control of the bone pain
        2. Dietary phosphate restriction may be helpful (Wenkert et al. 2007)
        3. Large dose of vitamin D: reversal of improvement in the bony architecture upon withdrawal of the drug (Anderton 1979)
        4. Oral cortisone: reversal of improvement in serum alkaline phosphatase level and radiographic appearance of the bones upon withdrawal of the drug (Anderton 1979)
        5. Avoid saline solution, furosemide diuresis, steroid therapy, or a low-calcium diet because these approaches may actually worsen bone mineralization and nephrocalcinosis
        6. Inhibition of osteoclastic activity with calcitonin: continued demineralization despite returning of normal serum calcium concentration

7. Plasma infusions designed to supplement alkaline phosphatase activity or induce alkaline phosphatase production: not consistently improve bone mineralization
8. Pyridoxine and/or pyridoxal phosphate in neonates with intractable seizures (Balasubramaniam et al. 2010)

2. Benign prenatal hypophosphatasia (Matsushita et al. 2014)
   1. A treatable disease not to be missed
   2. Marked bowing of the long bones at birth but showed a relatively benign postnatal course with spontaneous improvement of bowing
3. A clinical trial of marrow cell transplantation for infantile hypophosphatasia (Whyte et al. 2003)
   1. A significant, prolonged clinical and radiographic improvement followed soon after receiving a boost of donor marrow cells
   2. Biochemical features of hypophosphatasia, however, remain unchanged to date
   3. The most plausible hypothesis for the patient's survival and progress: transient and long-term engraftment of sufficient numbers of donor marrow mesenchymal cells form functional osteoblasts and perhaps chondrocytes, to ameliorate the skeletal disease
4. Enzyme replacement therapy with asfotase alfa: associated with improved findings on skeletal radiographs and improved pulmonary and physical function in infants and young children with life-threatening hypophosphatasia (Millán and Plotkin, 2012)
5. Enzyme replacement therapy for congenital hypophosphatasia allows for surgical treatment of related complex craniosynostosis (Kosnik-Infinger et al. 2015)
6. Surgical care
   1. Rachitic deformities
   2. Gait abnormalities
   3. Adult form
      1. Rod placement for pseudofractures of the adult type results in the union and relief of the pain
      2. Primary bone grafting and plating for midshaft fractures
      3. Anticipate delayed union of fractures

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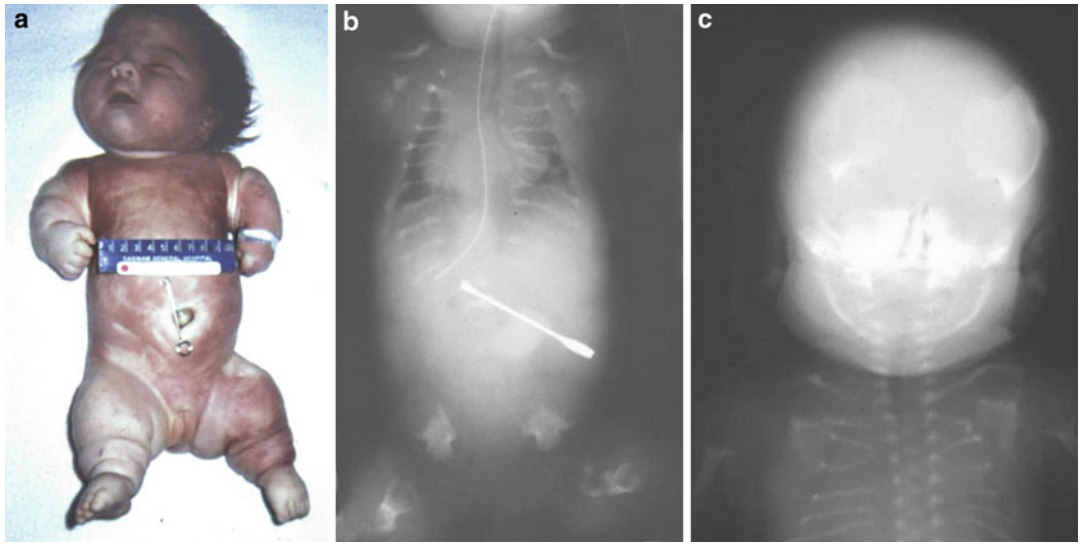

Fig. 1 (**a**–**c**) A neonate with perinatal lethal form of hypophosphatasia showing severe shortening of limbs. Radiograph shows markedly deficient ossification and abnormal bone development similar to achondrogenesis type I

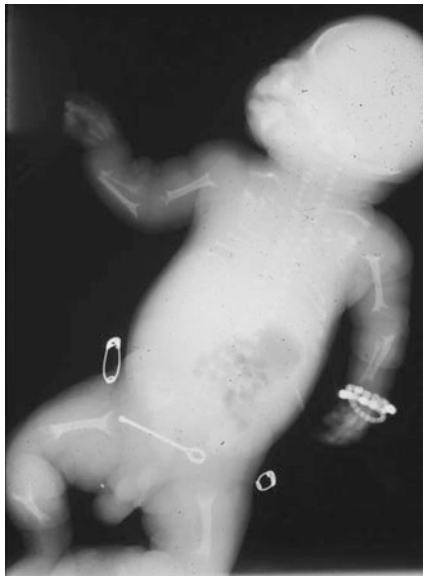

Fig. 2 Radiograph of another neonate with hypophosphatasia shows rickets-like metaphyseal cupping (spurs) and poor mineralization of cranial bones

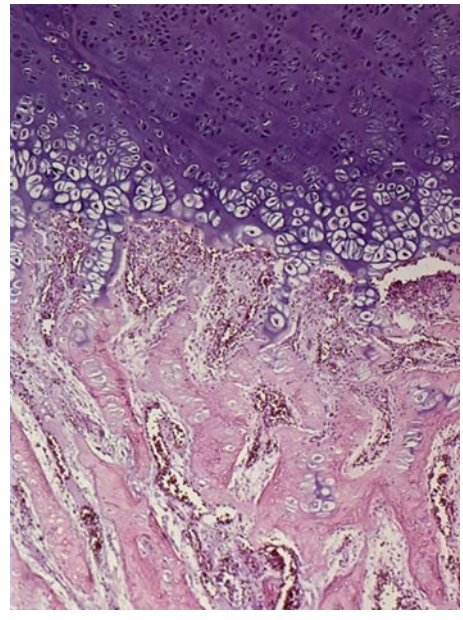

Fig. 3 Photomicrograph of a rib. Broad columns of hypertrophic chondrocytes with osteoid seams are present in the metaphysis. These columns are poorly mineralized and ossified

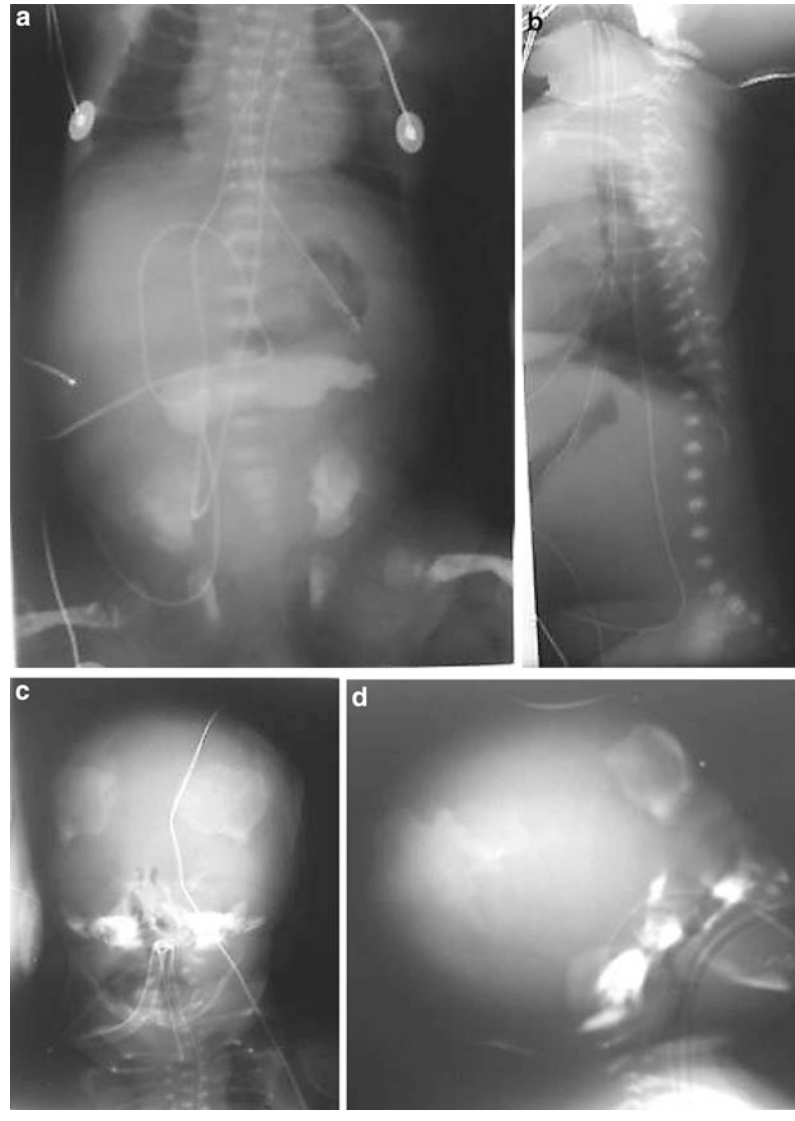

Fig. 4 (**a**–**d**) Radiographs of another neonate with perinatal lethal form of hypophosphatasia showing marked deficient skeletal mineralization, prenatal fracture of the left femur, and abnormal metaphyseal ossification of the proximal femurs

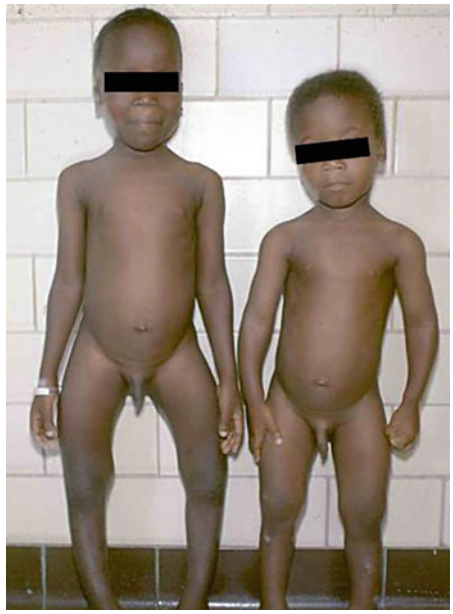

Fig. 5 Childhood hypophosphatasia in two brothers showing short stature and bowed legs

Hypopituitarism

Contents

Hypopituitarism is a term used to describe the deficiency of one or more of the hormones of the anterior or posterior pituitary gland. It can vary in severity and age at presentation. These hormonal deficits can also be present as part of a syndrome, with patients manifesting extrapituitary abnormalities such as in the eye and forebrain.

In clinical practice, panhypopituitarism is used to describe patients deficient in growth hormone (GH), gonadotropins, corticotropin, and thyrotropin in whom posterior pituitary function remains intact.

Hypopituitarism is rare, with an estimated annual incidence rate of 4.2 cases per 100,000 and with a prevalence rate of 45.5 per 100,000 (Regal et al. 2001).

Synonyms and Related Disorders

Adrenocorticotropin deficiency; Gonadotropin deficiency; Growth hormone deficiency; Pituitary hormone deficiency; Primary empty sella syndrome; Prolactin deficiency; Sheehan's syndrome; Thyrotropin deficiency

Genetics/Basic Defects

1. Pituitary cell types and hormones produced (Webb and Dattani 2011)
    1. Anterior lobe hormone produced action target tissue
        1. Somatotrophs
            1. Growth hormone: growth promotion and metabolic action
            2. Target tissue: liver, adipose tissue, bone
        2. Thyrotrophs
            1. Thyroid-stimulating hormone: stimulates thyroxine production
            2. Target tissue: thyroid gland
        3. Lactotrophs
            1. Prolactin: lactation
            2. Target tissue: breast ductal tissue
        4. Gonadotrophs
            1. Follicle-stimulating hormone and luteinizing hormone: stimulate gonadal maturation and hormonal cycling

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_130

   2. Target tissue: gonads (testis, ovary)
5. Corticotrophs
   1. Adrenocorticotropic hormone: stimulates cortisol production and promotes renal reabsorption of water
   2. Target tissue: adrenal cortex

2. Intermediate lobe: melanotrophs
   1. Pro-opiomelanocortin, the precursor to melanocyte-stimulating hormone and endorphins: increases skin pigmentation
   2. Target tissue: skin
3. Posterior lobe: axonal projections of neurons
   1. Cell bodies reside in the hypothalamus and secrete arginine vasopressin and oxytocin
   2. Vasopressin: essential for reabsorption of water in collecting ducts
   3. Oxytocin: important for parturition

2. Heterogeneous causes (Schneider et al. 2007; Kelberman and Dattani 2007; Toogood and Stewart 2008; Fernandez-Rodriguez et al. 2012; Corenblum 2014; Kim 2015)
   1. Brain damage
      1. Traumatic brain injury (trauma to hypophysis)
      2. Subarachnoid hemorrhage
      3. Neurosurgery
      4. Radiation: progressive and irreversible neuroendocrine dysfunction following radiation-induced damage to the hypothalamic–pituitary axis (Darzy 2013)
      5. Stroke
   2. Intrasellar tumors
      1. Adenomas
      2. Craniopharyngiomas
   3. Parasellar tumors
      1. Meningiomas
      2. Optic gliomas
      3. Chordomas
      4. Ependymomas
      5. Metastatic tumors: breast, lung, melanoma, renal cell carcinoma
   4. Infections
      1. Abscess
      2. Hypophysitis
      3. Meningitis
      4. Encephalitis
      5. Tuberculosis
      6. Syphilis
      7. Fungal disease
      8. Malaria
      9. HIV
   5. Vascular
      1. Infarction (postpartum): Sheehan's syndrome
      2. Diabetes mellitus
      3. Pituitary apoplexy
      4. Cavernous sinus thrombosis
      5. Aneurysms of intracranial internal carotid artery
   6. Autoimmune disorders: lymphocytic hypophysitis
   7. Infiltrative processes
      1. Hemochromatosis
      2. Granulomatous diseases
      3. Histiocytosis X
      4. Secondary amyloidosis
   8. Empty sella or arachnoidocele (Guitelman et al. 2013): herniation of the subarachnoid space within the sella turcica, associated with elongated pituitary stalk and flattening of the pituitary gland (De Marinis et al. 2005; Guinto et al. 2007).
      1. Primary empty sella: results from postpartum pituitary necrosis (Sheehan's syndrome) or lymphocytic hypophysitis
      2. Secondary empty sella: usually results from a pituitary adenoma that shrinks after different treatments (surgery, radiotherapy, or drugs) or spontaneous regression
   9. Perinatal insults
   10. Pituitary hypoplasia or aplasia
   11. Idiopathic causes (GH, ACTH, TSH, others): frequently monohormonal
3. Genetic causes (mutations) of multiple pituitary hormone deficiencies (Cohen and Radovick 2002; Dattani 2005; Mehta and Dattani 2008; Higham et al. 2016)
   1. *POU1F1* (*PIT-1*) (Andersen and Rosenfeld 2001): genetic combined pituitary hormone deficiency (CPHD) caused by mutations within the pituitary-specific transcription factor 1

1. Combine pituitary hormone deficiencies
    1. GH
    2. Thyrotropin (TSH)
    3. Prolactin
2. Inheritance
    1. Autosomal dominant (AD)
    2. Autosomal recessive (AR)
3. Phenotypes
    1. Hormone deficiencies: severe
    2. Thyrotropin secretion: initially normal, but secondary hypothyroidism inevitable
    3. Variable anterior pituitary hypoplasia

2. *PROP1* (Sornson et al. 1996): the most common cause of CPHD caused by mutations of *Prophet of PIT1*
    1. Combine pituitary hormone deficiencies
        1. GH
        2. TSH
        3. LH
        4. FSH
        5. Prolactin
        6. Occasional ACTH deficiency
    2. Inheritance: AR
    3. Phenotypes
        1. Deficiencies tend to be milder than in *POU1F1* mutations
        2. Evolving corticotropin deficiency with increasing age
        3. Enlarged pituitary size with later involution (transient anterior pituitary hyperplasia)
        4. Can be associated with a mass lesion (Turton et al. 2005)
3. *HESX1* (Dattani et al. 1998)
    1. Hormone deficiencies: range from isolated GH deficiency to CPHD (panhypopituitarism, including diabetes insipidus)
    2. Inheritance: AD, AR
    3. Phenotypes
        1. May be associated with septo-optic dysplasia, combined pituitary hormone deficiency (CPHD), and isolated growth hormone deficiency.
        2. Mutations result in a variable phenotype: anterior pituitary hypoplasia, ectopic posterior pituitary, and midline forebrain abnormalities.
        3. Environmental factors, such as drugs and alcohol, are implicated.
4. *LHX3* (Netchine et al. 2000)
    1. Combine pituitary hormone deficiencies
        1. GH
        2. TSH
        3. LH
        4. FSH
        5. Prolactin
        6. ACTH
    2. Inheritance: AR
    3. Phenotypes
        1. Elevated and anteverted shoulders giving the appearance of a stubby neck with limited rotation of the neck and head (short rigid cervical spine)
        2. Sensory neural deafness
        3. Hypoplasia of anterior pituitary gland
        4. Preservation of corticotropin secretion
5. *LHX4* (Machinis et al. 2001)
    1. Combine pituitary hormone deficiencies
        1. GH
        2. TSH
        3. Cortisol
        4. Gonadotropin deficiency
    2. Inheritance: AD
    3. Phenotypes (MRI of the brain)
        1. Small sella
        2. Persistent craniopharyngeal canal
        3. Hypoplastic anterior pituitary and ectopic posterior pituitary
        4. Pointed cerebellar tonsils

4. Genetic causes (mutations) of isolated pituitary hormone deficiencies
    1. *TBX19* (*TPIT*) (Pulichino et al. 2003)
        1. Hormone deficiencies: corticotropin
        2. Inheritance: AR
        3. Phenotypes
            1. Presentation in neonatal period with severe hypoglycemia and prolonged cholestatic jaundice
            2. Undetectable corticotropin and cortisol levels
            3. Failure to respond to corticotropin-releasing hormone

4. High incidence of neonatal death in affected families

2. *SOX2* (Maheshwari et al. 1998)
   1. Hormone deficiencies: hypogonadotropic hypogonadism
      1. LH
      2. FSH
      3. Variable GHD
   2. Inheritance: de novo mutation reported
   3. Phenotypes
      1. Anophthalmia or microphthalmia
      2. Hypothalamic hamartoma
      3. Learning difficulties
      4. Developmental delay
      5. Genital abnormalities
      6. Esophageal atresia
      7. Sensorineural hearing loss
      8. Diplegia
3. *SOX3* (Hamel et al. 1996; Laumonnier et al. 2002)
   1. Hormone deficiencies: isolated growth hormone deficiency or CPHD
   2. Inheritance: X-linked recessive
   3. Phenotypes
      1. Intellectual disability
      2. Anterior pituitary hypoplasia
      3. Ectopic posterior pituitary
      4. Infundibular hypoplasia
      5. Midline abnormalities
4. *GHRHR* (Maheshwari et al. 1998)
   1. Hormone deficiencies: GH
   2. Inheritance: AR
   3. Phenotypes
      1. Short stature
      2. Proportionate growth
      3. Anterior pituitary hypoplasia
5. *GH1* (Cogan et al. 1993)
   1. Hormone deficiencies: GH
   2. Inheritance: AR
   3. Phenotypes
      1. Short stature
      2. Abnormal facies
      3. Respond to exogenous GH treatment, but may develop antibodies
6. *KAL-1* (Legouis et al. 1991; Franco et al. 1991)
   1. Hormone deficiencies
      1. GnRH
      2. FSH
      3. LH
   2. Inheritance: X-linked
   3. Phenotypes
      1. Failed or arrested puberty
      2. Anosmia
      3. Synkinesis
      4. Unilateral renal agenesis
7. *FGFR-1* (*KAL-2*) (Dode et al. 2003)
   1. Hormone deficiencies
      1. GnRH
      2. FSH
      3. LH
   2. Inheritance: AD
   3. Phenotypes: failed or arrested puberty
8. *GNRHR1* (Beranova et al. 2001)
   1. Hormone deficiencies
      1. FSH
      2. LH
   2. Inheritance: AR
   3. Phenotypes: variable, determined by the sensitivity of the mutant receptor to GnRH
9. *DAX1* (Lin et al. 2006)
   1. Hormone deficiencies
      1. FSH
      2. LH
   2. Inheritance: AR, X-linked
   3. Phenotypes
      1. Presents initially with severe neonatal hypoadrenalism
      2. Subsequently fail to enter puberty or suffer delayed or arrested puberty
10. *GPR54* (de Roux et al. 2003)
    1. Hormone deficiencies
       1. FSH
       2. LH
    2. Inheritance: AR
    3. Phenotypes: presents with absent or delayed puberty

11. *POMC* (Krude et al. 1998)
    1. Hormone deficiencies: corticotropin
    2. Inheritance: AR
    3. Phenotypes (clinical triad)
        1. Early-onset obesity
        2. Adrenal hypoplasia
        3. Cortisol deficiency
12. *Thyrotropin-β* (Vuissoz et al. 2001)
    1. Hormone deficiencies: thyrotropin
    2. Inheritance: AR
    3. Phenotypes: severe congenital hypothyroidism if not detected and treated early on
13. *GLI2*
    1. Hormone deficiency
        1. GH
        2. TSH
        3. LH
        4. FSH
        5. ACTH
    2. Inheritance: haploinsufficiency
    3. Phenotypes
        1. Holoprosencephaly
        2. Craniofacial abnormalities
        3. Polydactyly
        4. Hypogonadotropic hypogonadism
        5. Partial agenesis of the corpus callosum
14. *FGF8*
    1. Hormone deficiency
        1. LH
        2. FSH
        3. Diabetes insipidus
    2. Inheritance: AR, AD
    3. Phenotypes
        1. Hypogonadotropic hypogonadism
        2. Anosmia
        3. Holoprosencephaly
        4. Moebius syndrome
        5. Septo-optic dysplasia
15. *OTX2*
    1. Hormone deficiency
        1. IGHD
        2. CPHD
    2. Inheritance: AD
    3. Phenotypes
        1. Anophthalmia or microphthalmia
        2. Coloboma
        3. Developmental delay

Clinical Features

1. Nonspecific symptoms (Toogood and Stewart 2008)
    1. Feeling of general ill health
    2. Being abnormally tired
    3. Increased lethargy
    4. Feeling cold
    5. Weight loss
    6. Reduced appetite
    7. Abdominal pain
2. Symptoms related to local effects of any underlying tumor
    1. Headaches
    2. Visual disturbance (typically a bitemporal hemianopia)
    3. Cerebrospinal fluid rhinorrhea
3. Clinical presentation (Higham et al. 2016)
    1. Acute hypopituitarism
        1. Pituitary apoplexy, acute pituitary inflammation, and Sheehan's syndrome can all cause acute hypopituitarism
        2. If untreated, have a high risk of mortality, usually secondary to loss of ACTH and subsequent hypoadrenalism.
        3. This presentation is rare but crucial to recognize.
    2. Chronic hypopituitarism
        1. Onset: usually insidious, and
        2. Nonspecific clinical presentation
        3. Pattern of symptoms and signs: depends on the order and extent of hormonal loss
4. GH deficiency
    1. Neonates with congenital GH deficiency (or hypopituitarism).
        1. Severe neonatal hypoglycemia often associated with convulsions, presenting

most frequently in the first 24 h of life (birth trauma)
2. Prolonged conjugated hyperbilirubinemia
3. Hypothermia
4. Possibly a micropenis (Ogilvy-Stuart 2003)

2. Neonates with midline birth defects should be considered at risk for isolated or multiple pituitary hormone deficiencies.
3. Older babies who escape early diagnosis may present with failure to thrive and poor weight gain.
4. Older children.
   1. Proportional short stature with height more than 2–3 standard deviations (SD) below the mean for the age
   2. Reduced growth velocity for their age
   3. Delayed bone maturation in the absence of an inherited skeletal dysplasia or chronic disease
   4. Characteristic craniofacial appearance in patients with severe GH deficiency: a prominent forehead and depressed midface development caused by the lack of GH effect on endochondral growth at the base of the skull, occiput, and sphenoid
   5. Delayed dentition
   6. Presence of other features attributable to the underlying etiology of the GH deficiency
5. Adults
   1. Multiple symptoms and pathophysiologic changes affecting a variety of biologic systems (none are pathognomonic) are attributed to GH deficiency in adult life (Molitch et al. 2006).
   2. Impaired quality of life (Burman et al. 1995; Holmes and Shalet 1995)
      1. Complaining of tiredness.
      2. Lack of energy.
      3. Emotional lability.
      4. Reduced sleep quality.
      5. A degree of disability consistent with psychiatric illness requiring treatment (up to 30% of patients) (McGauley et al. 1990).
      6. Patients who have childhood-onset GH deficiency do not seem to suffer the same degree of impairment in quality of life as those who have adult-onset GH deficiency (Attanasio et al. 1997).
5. Gonadotropin (LH, FSH) deficiency
   1. Male infants with congenital hypogonadotropic hypogonadism: effect of relative androgen deficiency occurring during the third trimester
      1. Unilateral or bilateral cryptorchidism
      2. Microphallus
   2. Adolescent boys
      1. Pubertal development
         1. Fail to initiate or abnormal with failure to progress normally
         2. Testicular volumes vary between prepubertal boys (<4 cm^3) and normal adult size
         3. Pubic hair (mediated by testicular or adrenal androgens): present but unlikely to be normal
   3. Adolescent girls
      1. Gonadotropin deficiency becoming apparent in teenage years
      2. Delayed breast development
      3. Primary amenorrhea
   4. Isolated gonadotropin deficiency
      1. Normal growth during childhood.
      2. Slow growth during adolescence when the growth spurt fails to occur.
      3. Epiphyses, however, fail to fuse at the usual age, and the long bones continue to grow, ultimately resulting in tall stature and a eunuchoid habitus.
   5. Men with acquired gonadotropin deficiency during adult life
      1. Usually achieve a normal height with proportionate growth.
      2. Adult secondary sexual characteristics are present, although the testes may become soft and reduced in size because the FSH deficiency causes atrophy of the seminiferous tubules.
      3. Slowing of beard growth with less frequent shaving.
      4. Loss of body hair.

5. Skin becoming thin with development of thin wrinkles if the gonadotropin deficiency is severe and prolonged.
6. Libido may be reduced, and the ability to achieve and maintain an erection may be compromised.
7. Testosterone deficiency can lead to nonspecific symptoms, for example:
    1. Tiredness
    2. Reduced muscle bulk
    3. Reduced exercise capacity
8. Decreased bone mineral density with a risk for:
    1. Osteopenia or osteoporosis
    2. Increased fractures
9. Azoospermia: usually present in prolonged gonadotropin deficiency, although there are exceptions.
10. Symptoms of hypogonadotropism: nonspecific and may not become evident for many years, particularly if fertility is not an issue.

6. Women with secondary gonadotropin deficiency
    1. Diagnosed quickly when oligomenorrhea or amenorrhea develops.
    2. Symptoms of estrogen deficiency.
        1. Vaginal dryness
        2. Dyspareunia
        3. Hot flashes
        4. Breast atrophy
    3. Pubic and axillary hair remains unless there is coexistent corticotropin deficiency with adrenal androgen deficiency.

6. Adrenocorticotropin (ACTH) deficiency
    1. Results in secondary hypoadrenalism.
    2. The most serious of anterior pituitary hormone deficits.
    3. During an intercurrent illness.
        1. May develop an adrenal crisis with severe hyponatremia and hypovolemic shock
        2. Can result in death if not diagnosed and treated appropriately
    4. Decompensation and shock occur during periods of illness or physical stress, such as surgery.
    5. Other symptoms of cortisol deficiency.
        1. Lethargy.
        2. Fatigue.
        3. Weight loss.
        4. Nonspecific abdominal pain.
        5. Hypoglycemia.
            1. Feelings of hunger
            2. Light-headedness
            3. Sweating
            4. Hypotension and complain of postural symptoms
        6. Absence of the pigmentation associated with primary adrenal failure in patients with corticotropin deficiency: the skin may be pale with an alabaster-like appearance (Arlt and Allolio 2003).
    6. Patients who have hypopituitarism are protected somewhat from developing severe, acute hypoadrenalism compared with patients who have primary adrenal failure, as the angiotensin–aldosterone axis remains intact.

7. Thyrotropin (TSH) deficiency
    1. Symptoms and signs
        1. Similar to those of primary hypothyroidism but usually are less severe, as there often is some residual thyrotropin secretion.
        2. Tiredness.
        3. Cold intolerance.
        4. Weight gain.
        5. Constipation.
        6. Dry skin and hair are common features.
    2. With the exception of traumatic brain injury (TBI), thyrotropin deficiency usually occurs late in the evolution of hypopituitarism and often is seen with other anterior pituitary hormone deficits.
    3. In children, secondary hypothyroidism contributes to poor growth, delayed bone age, and failure of secondary dentition.

8. Prolactin deficiency
    1. Prolactin is inhibited predominately by dopamine; as a consequence, prolactin levels frequently are raised in the presence of hypothalamic–pituitary disease because of compression or transection of the pituitary stalk.

2. Hypoprolactinemia is found in patients who have mutations of the transcription factors, PIT1 and PROP1.
3. However, in patients with structural pituitary disease, prolactin deficiency is a marker of severe pituitary damage (Mukherjee et al. 2003; Toledano et al. 2007).
4. In women, prolactin deficiency can cause failure of lactation in the postpartum period.
5. Although prolactin is an important hormone in the animal world with multiple identified roles in growth, water homeostasis, reproduction, behavior, and growth and immune modulation (Bole-Feysot et al. 1998), a phenotype attributable to prolactin deficiency in man has yet to be established.

9. *PROP1*-related combined pituitary hormone deficiency (De Graff 2014)
   1. Most affected individuals are ascertained because of growth failure and failure to thrive starting in infancy or early childhood.
   2. Hypothyroidism.
      1. Usually mild
      2. Occurs in later infancy and childhood
   3. Absent or delayed and incomplete secondary sexual development with infertility.
      1. Males: usually have a small penis and small testes.
      2. Females: some experience menarche but subsequently require hormone replacement therapy.
   4. GH deficiency.
      1. Neonatal hypoglycemia
      2. Proportionate short stature
      3. Delayed bone age
   5. TSH deficiency.
      1. Suspected in children with growth failure, poor weight gain, and delayed bone maturation
      2. Large posterior fontanelle
      3. Jaundice lasting more than 1 week after birth
      4. Macroglossia
      5. Hoarse cry
      6. Distended abdomen
      7. Umbilical hernia
      8. Hypotonia
   6. LH and FSH deficiency.
      1. Newborn males
         1. Micropenis without hypospadias
         2. With or without cryptorchidism
      2. Adolescent males
         1. Delayed onset of puberty (after age 14)
         2. Cessation of secondary sexual development
      3. Adolescent females: lack of breast development or menses by age 14
   7. Prolactin deficiency: suspected in females with impaired lactation.
   8. ACTH deficiency.
      1. Less common
      2. Usually occurs in adolescence or adulthood
      3. Suspected in children with persistent weakness, abdominal pain, anorexia, and weight loss
      4. Signs of acute ACTH deficiency
         1. Acute hypotension
         2. Dehydration
         3. Shock accompanied by hyponatremia, hyperkalemia, and hypoglycemia

10. *POU1F1* combined pituitary hormone deficiency (De Graff et al. 2014)
    1. Normal birth weight and birth length and uncomplicated perinatal course
    2. Growth failure in early infancy in most affected individuals
    3. Growth hormone deficiency: usually severe
    4. Proportional short stature
    5. Hypothyroidism
       1. Can be congenital
       2. Can be mild and later onset
       3. Progressive loss of TSH occurring over time
    6. Distinctive facies (Aarskog et al. 1997)
       1. Prominent forehead
       2. Marked midface hypoplasia
       3. Depressed nasal bridge
       4. Deep-set eyes
       5. Short nose with anteverted nostrils

7. MRI of the brain: pituitary usually appears hypoplastic

Diagnostic Investigations

1. Brain MRI (Toogood and Stewart 2008).
    1. To exclude tumors and other lesions of the sellar and parasellar region after confirmation of hypopituitarism.
    2. Normal MRI of the sellar and parasellar region cannot exclude hypopituitarism.
2. Hypopituitarism is diagnosed based on baseline blood sampling for thyroid stimulating hormone, gonadotropin, and prolactin deficiencies, whereas for ACTH, growth hormone, and antidiuretic hormone deficiency dynamic stimulation tests are usually needed. Repeated pituitary function assessment at regular intervals is needed for diagnosis of the predictable but slowly evolving forms of hypopituitarism (Higham et al. 2016).
3. Growth hormone deficiency.
    1. The definition of GH deficiency in adulthood differs from that in childhood.
        1. In children, the diagnosis of GH deficiency is made in the presence of a reduced growth velocity.
        2. In adults, the clinical features attributed to GH deficiency are numerous and nonspecific; there is no single pathognomonic feature that alerts clinicians to the diagnosis.
        3. Diagnosis of GH deficiency should be considered only in adults who have a history of pituitary disease, secondary to neoplastic disease, surgery, or cranial radiation or in those who have had a history of treatment with GH during childhood and adolescence (Growth Hormone Research Society 1998).
        4. Results of dynamic tests of GH status are affected by obesity (all stimuli) (Shalet et al. 1998) and age (Toogood et al. 1998) and could lead to an inappropriate diagnosis.
    2. The insulin tolerance test (ITT).
        1. Considered the gold standard used to diagnose GH deficiency in adults, using a diagnostic threshold of 3 mg/L.
        2. Not suitable for use in all patients and is contraindicated in patients who have a history of seizures or ischemic heart disease.
        3. Consequently, the majority of endocrinologists do not use the ITT in patients over 65 in case undiagnosed heart disease is present.
    3. Insulin-like growth factor (IGF-1).
        1. A GH-dependent peptide, although the level of dependence seems to diminish with increasing age.
        2. In young adults who have childhood-onset GH deficiency, 95% (de Boer et al. 1994) have serum IGF-1 below the normal range, whereas 82% of GH-deficient patients over 60-year-old have a normal IGF-1 (Toogood et al. 1998).
4. Gonadotropin deficiency.
    1. Women with gonadotropin deficiency
        1. In women of postmenopausal age, low or undetectable levels of FSH and LH are sufficient to make a diagnosis.
        2. In younger women, amenorrhea with low estradiol levels and low or normal gonadotropins is consistent with the diagnosis of gonadotropin deficiency.
        3. Failure to induce a withdrawal bleed after a progesterone challenge confirms the presence of a hypoestrogenic state.
    2. Men with gonadotropin deficiency
        1. Diagnosed in the presence of low or normal serum gonadotropin levels and a low serum testosterone.
        2. Semen analysis is useful when considering fertility and may demonstrate oligospermia or azoospermia.
5. Adrenocorticotropin deficiency.

1. The activity of the hypothalamic–pituitary–adrenal (HPA) axis exhibits a diurnal rhythm; serum cortisol levels often are undetectable at midnight during sleep, rising and reaching peak at approximately 5:00 a.m. and declining gradually over the course of the day.
2. The insulin tolerance test (ITT).
    1. A peak response to hypoglycemia (blood glucose 2.2 mmol/L) of greater than 20 mg/dL: considered a normal response (Tuchelt et al. 2000; Nelson and Tindall 1978).
    2. Tests the integrity of the whole HPA axis and has the advantage of simultaneously assessing the GH status of patients.
3. Short Synacthen test (SST): an alternative test to ITT
    1. Measures the serum cortisol response after an intramuscular injection of cosyntropin (Synacthen) (250 mg) (Stewart et al. 1988; Clayton 1996; Kane et al. 1995).
    2. Based on the premise that corticotropin deficiency results in atrophy of the adrenal cortex and subsequently becomes unresponsive to a single pulse of corticotropin.
    3. A serum cortisol value of 22 mg/dL (550 nmol/L) or higher 30 min after administration of Synacthen: consistent with normal corticotropin reserve.
    4. Risk for a false-negative result (a perception that patients have normal corticotropin reserve): the SST should not be performed until at least 6 weeks after surgery or an apoplectic event.
6. Thyroid-stimulating hormone deficiency.
    1. Diagnosed based on the presence of a low or normal serum thyrotropin measurement with a low serum free thyroxine (fT4) level.
    2. Measurement of serum fT3: not required but may be low or normal.
    3. In patients treated with radiotherapy, sequential falls in the serum fT4 toward the lower end of the normal range associated with evolving symptoms of hypothyroidism may be sufficient to warrant instigation of levothyroxine.
    4. The thyrotropin response to thyrotropin-releasing hormone: used less frequently since the introduction of sensitive thyrotropin assays.
7. *PROP1*-related combined pituitary hormone deficiency (CPHD) (De Graff et al. 2014).
    1. Testing for deficient secretion of GH, TSH, LH, FSH, prolactin, and ACTH: establishes the diagnosis
    2. *PROP1* is the only gene associated with *PROP1*-related CPHD
        1. Targeted mutation analysis for the common recurring deletion in which three AG repeats are reduced to two repeats: available clinically
        2. This mutation accounts for 55% of familial cases and 12% of nonfamilial cases

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal dominant inheritance
            1. Recurrence risk of 50% if a parent is affected
            2. Low recurrence risk if both parents are normal
        2. Autosomal recessive inheritance: risk of recurrence 25%
        3. X-linked recessive: 50% of male sibs affected if the mother is a carrier
    2. Patient's offspring
        1. Autosomal dominant inheritance: a 50% risk of offspring affected.
        2. Autosomal recessive inheritance: low recurrence risk unless the spouse is affected or a carrier.
        3. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal.
2. Prenatal diagnosis (De Graff 2014)
    1. Prenatal diagnosis is possible for pregnancies at increased risk for various conditions such as *PROP1* or *POU1F1* CPHD when

the disease-causing mutation in the family is known.
2. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member.

3. Management (Toogood and Stewart 2008)
   1. Replacement treatment exists in the form of thyroxine, hydrocortisone, sex steroids, growth hormone, and desmopressin. If onset is acute, cortisol deficiency should be replaced first. Modifications in replacement treatment are needed during the transition from pediatric to adult endocrine care and during pregnancy (Higham et al. 2016).
   2. Pituitary hormone replacement therapy
      1. Growth hormone replacement
         1. GH replacement in children who have GH deficiency results in an increase in linear growth, and its use for that purpose is accepted universally.
         2. Recombinant human GH has allowed GH replacement to be used in adults.
         3. In the event of side effects (peripheral edema, arthralgia, and headaches) during the titration phase, the dose of GH should be reduced or, if severe, treatment should be withdrawn.
      2. Sex steroid and gonadotropin replacement
         1. The aim of androgen replacement in men: to maintain secondary sexual characteristics, restore a sense of well-being, prevent loss of and optimize bone mass, and improve sexual function (Bhasin et al. 2006).
         2. Women who have gonadotropin deficiency require sex steroid replacement to alleviate the symptoms of estrogen deficiency and to optimize bone health.
         3. Induction of fertility can be achieved in men and women using exogenous gonadotropins. In men, human chorionic gonadotropin can be used initially to stimulate spermatogenesis (Vicari et al. 1992). In women, ovulation induction is initiated with FSH or human menopausal gonadotropin.
      3. Adrenocorticosteroid replacement
         1. Cortisol: hydrocortisone is the glucocorticoid of choice for patients who have secondary adrenal insufficiency
         2. Optimize and monitor glucocorticoid replacement therapy
      4. Dehydroepiandrosterone
         1. In addition to cortisol, the adrenal cortex produces androgens regulated by corticotropin.
         2. Patients who have corticotropin deficiency also are deficient in dehydroepiandrosterone (DHEA) (Arlt et al. 1999).
      5. Thyroxine replacement
   3. Long-term consequences of hypopituitarism
      1. Patients who have hypothalamicpituitary disease and are receiving a combination of sex steroids, glucocorticoids, and thyroxine, but not GH replacement, for a range of anterior pituitary hormone deficiencies have an approximately twofold increase in mortality compared with the general population (Rosen and Bengtsson 1990; Bates et al. 1996; Tomlinson et al. 2001).
      2. In the largest study to date, there was an increase in deaths from cardiovascular, cerebrovascular, and respiratory disease (Tomlinson et al. 2001).
      3. GH replacement therapy improves short-term individual cardiovascular risk profiles.
   4. Long-term follow-up of patients with hypopituitarism
      1. Continued follow-up under the care of a physician (endocrinologist) who has expertise in the field
      2. Annual assessment to determine their cardiovascular risk once hormone replacement treatments are optimized
      3. Attention to blood pressure and cholesterol levels and treatment with

antihypertensives and cholesterol lowering agents instigated as appropriate

5. Adult GH deficiency and hypopituitarism (Crespo et al. 2015)
    1. Untreated
        1. Abnormal body composition: decreased bone and muscle mass, greater body fat
        2. Decreased exercise capacity and muscle strength with increased fatigue
        3. Increased insulin resistance
        4. Unfavorable lipid profile
        5. Impaired quality of life
        6. Cognitive problems: decreased memory and concentration and increased irritability
    2. Replacement therapy with recombinant GH
        1. Quality of life improvement
        2. Decreased use of healthcare resources
        3. Increased vitality, energy, and emotional state
        4. Recovery of physical performance
        5. Decreased waist circumference
        6. Improved metabolic profile

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Fig. 1 A 16-year-old female was evaluated for pituitary hormone deficiency. She had short stature for which she received growth hormone therapy since 3 years of age. MRI scan of the brain showed a very small (hypoplastic) pituitary gland. Endocrine investigations revealed the following: low serum IGF-1 (somatomedin-C): <10 ng/mL (normal 11–206 ng/mL); low free T4: 0.67 ng/dL (normal 0.71–1.85 ng/dL); low TSH: 0.02 μU/mL (normal 0.47–5.01 μU/mL); normal cortisol: 7.5 μg/dL (normal 3.0–21 μg/dL); low ACTH-ICMA: 9.0 pg/mL (normal 10.0–60.0 pg/mL); low estradiol: < 0.5 ng/dL (normal 0.7–6.0 ng/dL); low FSH: 1.3 mIU/mL (normal 1.5–12.8 mIU/mL); normal LH: 0.38 mIU/mL (normal 0.10–12.0 mIU/mL). Molecular genetic testing for *POU1F1* gene mutation revealed no sequence variants. However, a different genetic basis for combined pituitary hormone deficiency cannot be ruled out

Fig. 2 A 6-year-old boy was evaluated for pituitary hormone deficiency. He had a history of hypoglycemia and a micropenis. He was noted to be very short, for which he received growth hormone shots daily. He was also treated for hypothyroidism. Past lab results: TSH: 3.16 μU/mL; low free T4: 0.56 ng/dL; normal IGF-1: 66 ng/mL; low IGFBP-3: 0.7 mg/L; normal cortisol: 5.5 μg/dL; normal ACTH-ICMA: 17 pg/mL. Molecular genetic testing for *POU1F1* gene mutation showed no sequence variation

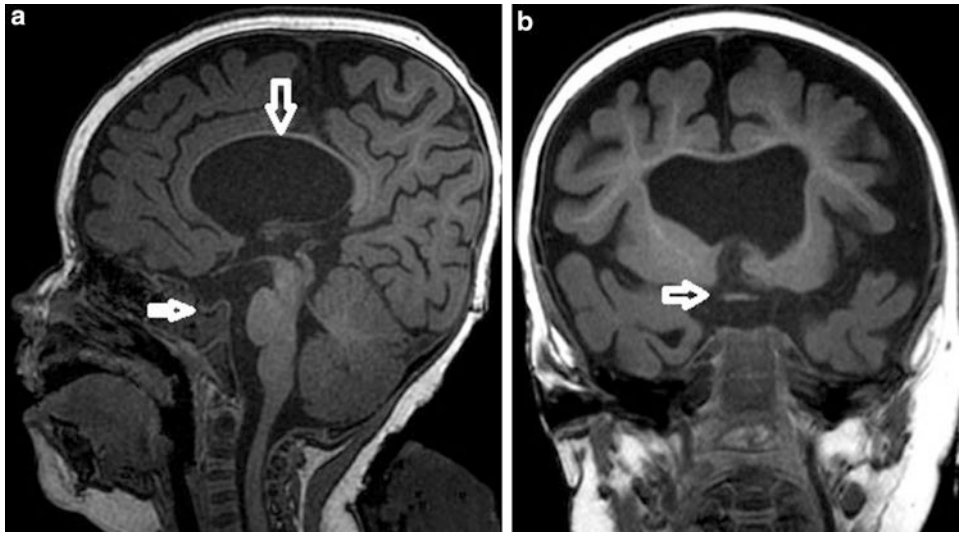

Fig. 3 (**a**, **b**) A 9-month-old boy with a history of encephalopathy and epilepsy. The molecular genetic study identified a 143 kilobyte interstitial duplication of an Xp11.4. MRI of the brain demonstrates the complete absence of the septum pellucidum with ventriculomegaly and white matter thinning. There is absence of the normal posterior pituitary bright spot (**a**, *small arrow*) and diffuse thinning of the corpus callosum (**a**, *large arrow*). The optic nerves, optic chiasm, and optic tracts are markedly atrophic (**b**, *arrow*). The above dysmorphic changes are compatible with septo-optic dysplasia and hypopituitarism (Courtesy of Dr. Grace Guo)

I(1p), I(1q) Syndrome

Contents

In 1999, Chen et al. (1999) first described uniparental (paternal) isodisomy, resulting from 46,XX,i(1p),i(1q) in a woman with short stature, ptosis, micro-/retrognathia, myopathy, deafness, and sterility.

Synonyms and Related Disorders

I(1p), I(1q) uniparental (paternal) isodisomy: isochromosome 1p and isochromosome 1q syndrome

Genetics/Basic Defects

1. Uniparental disomy (UPD): inheritance of both homologues from one parent. Several types of errors in chromosome segregation during gamete formation may be responsible for uniparental disomy (Spence et al. 1988).
2. Uniparental isodisomy: caused by isochromosome formation from misdivision of the centromere (Bernasconi et al. 1996; Eggerding et al. 1994; Lindenbaum et al. 1991; Shaffer et al. 1997). Although maternal UPD (Pulkkinen et al. 1997; Turner et al. 2007) and paternal UPD (Gelb et al. 1998; Takizawa et al. 2000) of chromosome 1 have been reported previously, none of these involved an isochromosome.
3. Cytogenetic analysis from the peripheral blood of the patient demonstrated one i(1p) and one i(1q) without normal chromosome 1 homologues (Figs. 1, 2, 3, and 4, Table 1).
4. The most likely mechanism of formation of the rearranged chromosomes in our patient (Fig. 5) is as follows:
    1. The zygote contained a chromosome 1 from the father and none from the mother due to nondisjunction resulting in a monosomy 1 conceptus.
    2. Subsequently, misdivision at the centromere may have occurred, leading to two isochromosomes, one of each chromosome arm.
    3. At the next mitotic division, both went into the same daughter cell.
    4. In the following cell cycle, normal replication took place. This would produce two isochromosomes, made up of one i(1p) and one i(1q), with uniparental isodisomy.
5. Additionally, many mechanisms could account for the finding of isochromosomes, as put forward by Bernasconi et al. (1996) regarding two isochromosomes and UPD 2. Except for the possibility of homozygosity for recessive mutations, maternal uniparental disomy 2 appears to have no adverse impact on the phenotype.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_131

6. Mechanisms of formation of the two isochromosome, maternal i(2q) and paternal i (2p) Albrecht et al. 2001; (Baumer et al. 2007):
   1. The initial maternal meiotic I error may have been a nondisjunction event of chromosome 2.
   2. Trisomy rescue may have occurred during the recombination event that led to the isochromosomes, or, alternatively, the formation of the maternal i(2q) preceded that of the paternal i(2p). In this case, the formation of the paternal i(2p) would rescue the trisomy 2q and monosomy 2p.
   3. A third possibility: the initial meiotic I rearrangement consisted in the formation of the maternal isochromosome; rescue of the trisomy 2q/monosomy 2p would have occurred postzygotically through the formation of a paternal i(2p).
7. To the best of our knowledge, our patient is the first case of uniparental isodisomy resulting from i(1p) and i(1q):
   1. Our patient, therefore, has allelic homozygosity for all paternal chromosome 1 loci, demonstrated in part by our molecular studies.
   2. However, the possibility of areas of heterodisomy through meiotic recombination likely exists.
   3. The patient's abnormal phenotype is most likely due to unmasking of rare recessive mutations through isodisomy, but the possibility of genomic imprinting and the presence of mosaicism cannot be ruled out.
   4. The presence of myopathy in this patient suggests the possibility that the potential gene(s) involved may be localized on chromosome 1.

Clinical Features

1. Short stature
2. Bilateral conductive hearing loss
3. Facial features
   1. Downward slant of palpebral fissures
   2. Bilateral ptosis
   3. Malar hypoplasia
   4. Severe micro-/retrognathia
   4. High-arched palate
   5. Cervical vertebral anomaly
   6. Slightly short fingers
   7. Scoliosis
   8. Normal intelligence
   9. Normal secondary sex characteristics
10. Menarche at 11 years with regular menstruation but never conceived in three marriages with different partners

Diagnostic Investigations

1. Cytogenetic analyses: to demonstrate one i (1p) and one i(1q) without normal chromosome 1 homologues by:
   1. GBG banding
   2. CBG banding
   3. FISH analysis using whole-chromosome 1 probe
2. Molecular investigations to demonstrate isochromosomes with complete homozygosity of either paternal or maternal markers

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased
   2. Patient's offspring: the presence of two isochromosome 1 s would virtually exclude viable offspring since either duplication of the long arm with deletion of the short arm or duplication of short arm with deletion of long arm would be lethal to the fetus.
2. Prenatal diagnosis: demonstration of i(1p) and i(1q) without two normal chromosome 1 s by either CVS or amniocentesis
3. Management: supportive

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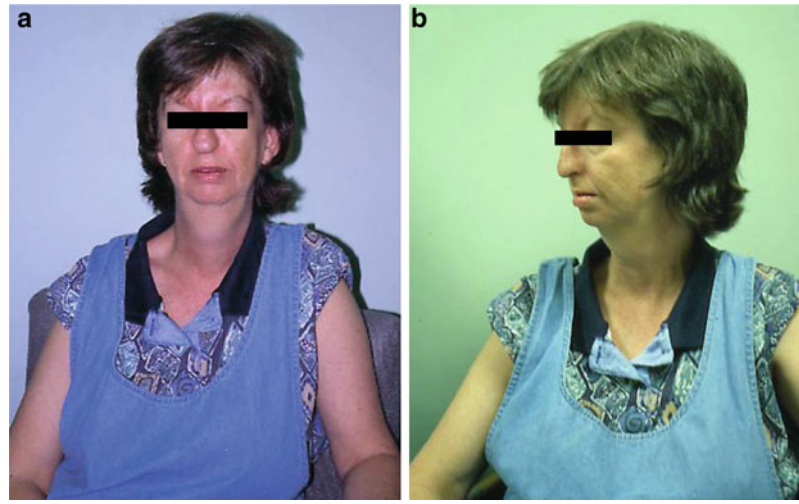

Fig. 1 (**a**, **b**) A 43-year-old woman was referred for evaluation because of minor facial anomalies, myopathy, sterility, short stature, hearing loss, downward slant of palpebral fissures, bilateral ptosis, severe micro-/retrognathia, high-arched palate, and scoliosis

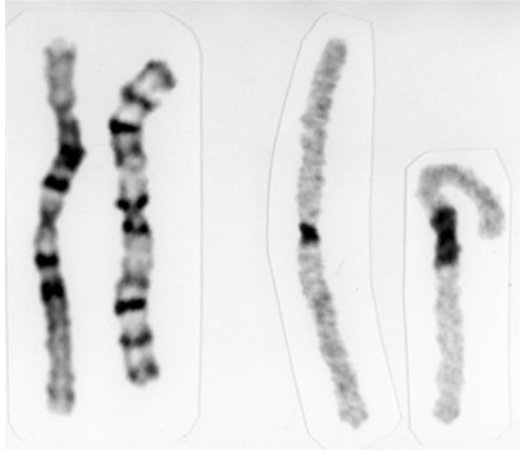

Fig. 2 Cytogenetic analyses utilizing GTG and CBG bandings showed the presence of one i(1p) and one i (1q) without normal chromosome 1 homologues

Fig. 3 Fluorescence in situ hybridization analysis showed hybridization to only two chromosomes, consistent with the G-banded interpretation of i(1p) and i(1q). To the best of our knowledge, this is the first case of isochromosomes 1p and 1q replacing the two normal chromosome 1 s

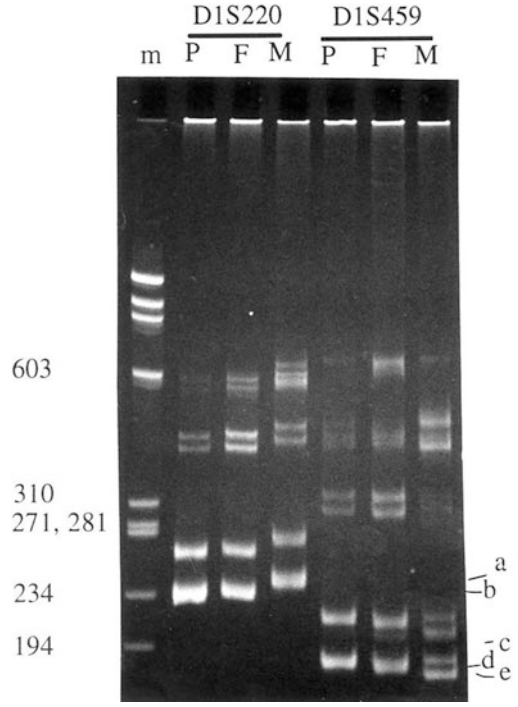

Fig. 4 PCR analyses of chromosome 1 markers (D1S220, D1S459) indicated that the patient (P) inherited b allele (using D1S220) and d allele (using D1S459) from the father (F) but none (a, c, or e alleles) from the mother (M) (D1S214, D1S550, D1S162, D1S188, D1S248, D1S514, and D1S2347 data not shown). The numbers on the left are standard marker size in bp

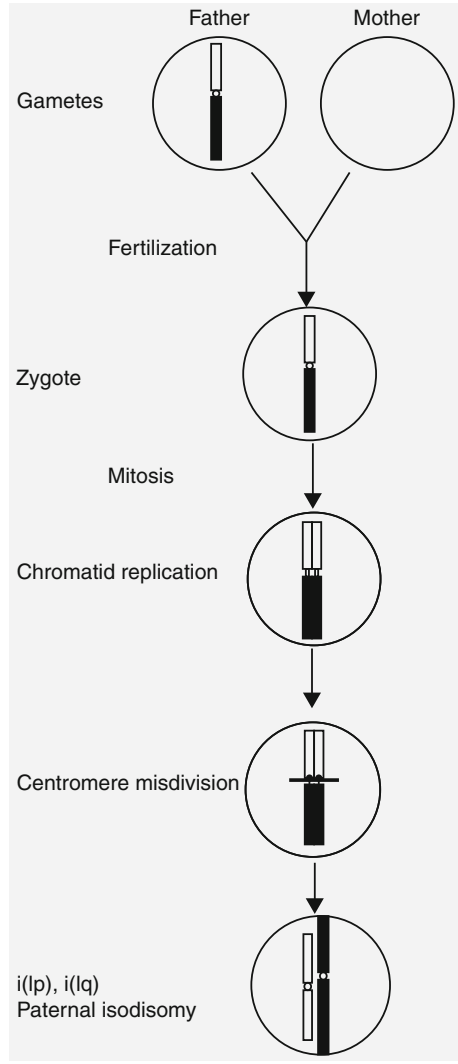

Fig. 5 Mechanism of i(1p) and i(1q) formation resulting in uniparental (paternal) isodisomy

Table 1 Genotype analysis of the patient and her parents with chromosome 1 markers*

Markers	Location	Mother	Patient	Father	Informative
D1S214	1p36.23-p36.33	13	24	24	*
D1S186	1p34	12	12	12	
D1S220	1p33-p31.3	24	13	13	*
D1S550	1p31	13	24	24	*
D1S162	1p32	24	13	13	*
D1S188	1p22	12	22	22	
D1S248	1p13-1p21	22	11	11	*
D1S514	1p13	13	24	24	*
D1S2347	1q21	13	24	24	*
D1S1589	1q25	12	12	12	
D1S422	1q31.3	12	12	12	
D1S103	1q32	12	12	12	
D1S102	1q32-q44	12	12	12	
D1S459	1q42.12	13	22	22	*

*The polymorphic markers used in the analysis are shown on the left, with fully informative ones indicated by *asterisks* (*) on the right and their cytogenetic locations noted in the second column.

Idic(Yq) Syndrome

Contents

Dicentric chromosomes are among the most common structural changes of the Y chromosome (deletions, rings, Y-autosomal or Y-X translocations, isochromosomes, and dicentrics). Among these structural abnormalities, dicentric Y chromosomes are the most commonly found (Hsu 1994; Yoshida et al. 1997).

The dicentric Y chromosomes have two different types: dic(Yq), resulting from the fusion between the short arms of two Y chromosomes in which some Yp material is maintained, and dic (Yp) in which only the Yq arms fuse (Codina-Pascual et al. 2004). If the dicentric has completely symmetric arms, it is considered an isodicentric chromosome. The sites of breakage and fusion at Yp and Yq are variable (Robinson et al. 1999).

Isodicentric Y chromosomes are one of the most commonly reported structural abnormalities of the Y chromosome (Hsu 1994), consisting of two identical arms that are positioned as mirror images to one another, with an axis of symmetry lying between two centromeres. Due to the presence of two centromeres, these chromosomes are often unstable during cell division (Daniel et al. 1980; Buchanan et al. 1976). As a result, chromosomal mosaicism is common and most patients have a 45,X cell line (Hsu 1994; Tuck-Muller et al. 1995).

Synonyms and Related Disorders

Isodicentric chromosome Yq syndrome

Genetics/Basic Defects

1. Isochromosome (DesGroseilliers et al. 2006)
    1. A chromosome with identical chromosome material in which two arms are mirror images and are of equal length
    2. An isochromosome can be monocentric or dicentric
2. Isodicentric chromosomes (dicentric isochromosomes)
    1. Likely resulting from a single break in the paracentric region followed by chromatid duplication and the joining of chromatids from one side of the break (Guevarra et al. 2009)
    2. Usually unstable during cell division and remain so until one of their centromeres is inactivated (Daniel et al. 1980; Therman

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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et al. 1986), resulting in various types of cell lines (Kohn et al. 1997)
3. Consequently, most reported patients have alternate cell lines, including 45,X (95% of cases) (Bouayed Abdelmoula and Amouri 2005a)
4. The resulting phenotype depends on the proportion of each cell line and on the localization of the breakpoints (Alvarez-Nava et al. 2003; Bouayed Abdelmoula and Amouri 2005b)
5. The most likely mechanism of formation of the isodicentric chromosome (Bouayed Abdelmoula and Amouri 2005a)
    1. An isochromatid break, followed by a U-type exchange
    2. Breakpoints in the short arm lead to a duplication of the entire long arm and a part of the short arm
    3. Breakpoints in the long arm lead to the duplication of the entire short arm and part of the long arm

3. Isodicentric Y chromosome [idic(Y)]
    1. Isodicentric Y chromosome: formed by homologous crossing over between opposing arms of palindromes on sister chromatids (Lange et al. 2009)
        1. These ectopic recombination events occur at nearly all Y-linked palindromes
        2. Intrapalindrome sequence identity is maintained via noncrossover pathways of homologous recombination
        3. DNA double-strand breaks that initiate these pathways can be alternatively resolved by crossing over between sister chromatids to form idic (Y) chromosomes, with clinical consequences ranging from spermatogenic failure to sex reversal and Turner syndrome
    2. Isodicentric Yq (Guevarra et al. 2009)
        1. Refers to a dicentric Y chromosome with two complete long arms and two symmetric incomplete portions of the short arms, arranged in a mirror image
        2. The breakpoints are in the short arm of Y
        3. When two centromeres are not closely located, only one is active; the other is suppressed
    3. Most dicentric Y chromosomes (90%) are present in mosaic form due to the instability of isodicentric chromosomes during cell division (Kohn et al. 1997)
        1. The mosaicism may be more or less complex depending on its meiotic or postzygotic origin and on its mitotic stability, and it usually includes a 45,X, in addition to idic(Y), idic(Y)*x*2, del(Y), or 46,XY cell lines (Ying and Ives 1971; Daniel et al. 1980; Chandley et al. 1986; Stankiewicz et al. 2001; Codina-Pascual et al. 2004; Bouayed Abdelmoula and Amouri 2005a)
        2. Errors occurring during gametogenesis, before the spermatid stage, or in the first mitotic division after fertilization would result in a mosaicism without a normal 46,XY cell line
        3. Errors occurring after the first zygotic division, a normal 46,XY cell line can be present (Fernandez et al. 2002)
        4. Patients carrying a dicentric Y chromosome have a wide range of somatic, genital, and gonadal phenotypic manifestations, depending on the structure of the dicentric Y chromosome, the Yp and Yq breakpoints, and the types of mosaicism (Tuck-Muller et al. 1995)
        5. Of affected individuals, 40.9% were phenotypical females, 31.8% were phenotypical males, and 27.3% had different degrees of intersexuality (Hsu 1994)
    4. The absence or mutation of SRY (sex-determining region on the Y chromosome) gene on the isodicentric Y chromosome: another factor adding to diversity of the phenotype, illustrated by case studies by DesGroseilliers et al. (2006)
        1. In one case of idic(Y), the female phenotype and Turner stigmata can be explained by the localization of the breakpoint, which is proximal to the SRY gene, in Yp11.2 or p11.31

2. In three patients, who do not have a predominant 45,X cell line but possess two copies of SRY (as breakpoints are in the long arm) usually develop as males: They are often infertile due to the absence of one of the azoospermia factor (AZF) regions or the incorrect pairing between the rearranged Y and the X chromosome during meiosis I (Chandley et al. 1986)

5. Nonmosaic 46,X,idic(Y) with breakpoints in the long arm has been reported in rare cases of females: dicentric chromosome Y associated with Leydig cell agenesis and sex reversal (female phenotype) (Genuardi et al. 1995)
6. A complex mosaic karyotype, 48,XX,+idic (Yq)*x*2/47,XX,+idic(Yq)/46,XX has been reported in twin girls (Hipp et al. 2016)
    1. Fluorescence in situ hybridization (FISH): negative for SRY located at Yp11.3 and positive for two copies of the centromeric probe DYZ3, confirming the dicentric structure
    2. A SNP microarray performed on twin A with a focus on further delineating Y chromosome breakpoints to determine gonadoblastoma risk: A 39.3 Mb gain of material from region Yq11.222-q12 was identified, with no detection of genomic material from Yp or the pericentromeric region of Yq extending to Yq11.221, suggesting a final isodicentric Yq structure with incomplete duplication of the q arm. No additional copy number variants or large regions of homozygosity were detected

4. The putative gonadoblastoma locus (GBY) (Page 1987)
    1. Thought to correspond to the TSPY (testis-specific protein, Y-linked) gene (Lau et al. 2003), which has clusters in several loci on both the short and the long arms of the Y chromosome (Tsuchiya et al. 1995; Rottger et al. 2002)
    2. Presence of multiple GBY loci on the Y chromosome could explain why such tumors have been reported in both idic with breakpoints in the long and short arms (Hsu 1994; Tuck-Muller et al. 1995)

Clinical Features

1. Extremely variable physical and genital features (52 cases with dicentric Yq, studied by Guevarra et al. 2009) (Hsu 1994; Tuck-Muller et al. 1995; Bouayed Abdelmoula and Amouri 2005b; DesGroseilliers et al. 2006)
    1. Twelve phenotypic males (23%)
        1. Age/presenting symptoms
            1. Six adults: infertility (5), short stature (1)
            2. Six children: short stature (6)
        2. Gonads
            1. Normal testes (10)
            2. Not reported (2)
            3. Gonadoblastoma (0)
        3. Stature
            1. Short (6)
            2. Normal (3)
            3. Borderline (1)
            4. Not reported (2)
        4. Turner syndrome stigmata (3)
    2. 17 phenotypic ambiguities (33%)
        1. Age/presenting symptoms
            1. Two adults: inguinal mass/gynecomastia (1), ambiguous genitalia (1)
            2. Sixteen children: short stature (4), ambiguous genitalia (12)
        2. Gonads
            1. Normal testes (2)
            2. Abdominal testes (2)
            3. Mixed gonadal dysgenesis (10)
            4. Not reported (3)
            5. Gonadoblastoma (3)
        3. Stature
            1. Short (9)
            2. Normal (3)
            3. Not reported (5)
        4. Turner syndrome stigmata (2)

3. Twenty-three phenotypic females (44%)
    1. Age/presenting symptoms
        1. Six adults: short stature (1), primary amenorrhea (5)
        2. Thirteen children: short stature (9), primary amenorrhea (3), not reported (1)
    2. Gonads
        1. Normal ovaries (0), mixed gonadal dysgenesis (15)
        2. Gonadoblastoma (6)
    3. Stature
        1. Short (16)
        2. Normal (3)
        3. Not reported (4)
    4. Turner stigmata (10)
2. Karyotype-phenotype correlations
    1. Sexual differentiation of patients: depends on the distribution of the 45,X cell line in various tissues, including gonads
        1. Three cases reported by Alvarez-Nava et al. (2003):
            1. 45,X/46,X,idic(Y) positive for the same Y chromosome molecular markers, with various degrees of abnormal sexual differentiation
            2. A predominant 45,X cell line was found in the streak gonads of the female with Turner stigmata, while the dysgenetic testes of the male had a predominant 46,X,idic(Y) cell line
            3. The individual with sexual ambiguity had a streak gonad with a predominant 45,X cell line on one side and a dysgenetic testis with a predominant 46,X,idic(Y) cell line on the other side
        2. Nine female patients studied by DesGroseilliers et al. (2006)
            1. An increase in the proportion of 45,X cells in the gonads compared to blood in four patients (93% vs. 64%, 80–100% vs. 39%, 82% vs. 60%, and 79% vs. 8%), thus could explain their female or ambiguous phenotypes
            2. A similar increase of the 45,X cell line was found in fibroblasts compared to blood in three patients (96% vs. 39%, 92% vs. 8%, and 95% vs. 23%)
    2. Great phenotypic variations observed in patients with an isodicentric Y chromosome greatly limit the genotype-phenotype correlation
        1. The variability is explained by the degree of mosaicism in different tissues and the various locations of the breakpoints
        2. To improve the genotype-phenotype correlation
            1. Analyze more than one tissue, as significantly different proportions of various cell lines can be found
            2. Perform histological studies of the gonads
            3. Molecular definition of the breakpoints (Stuppia et al. 1996) will provide more information, allowing for a better genetic counseling
3. Differential diagnosis of idic(Yp) (Bruyere et al. 2006)
    1. Adult males with idic Yp invariably present with a history of infertility
        1. Likely, a result of loss or disruption of all or part of the Yq11.2 AZF gene cluster, which is crucial for spermatogenesis (Siffroi et al. 2000; Stankiewicz et al. 2001; Marrocco et al. 2003; Yoshitsugu et al. 2003; Patsalis et al. 2005)
        2. Pairing dysfunction between the X and Y chromosomes during meiosis: proposed as an alternate mechanism for azoospermia in these men (Yoshida et al. 1997)
        3. All idic Yp cases in which paternal chromosome testing has been performed have been de novo (Schintzel 2001; Bruyere et al. 2006). This further supports the concept that males with an idic Yp are usually infertile. With the exception of cases, whose mosaicism included the presence of a structurally normal Y chromosome in a significant proportion of cells, normal fertility in these boys is unlikely

2. Phenotype
    1. Normal male phenotype with sterility with rare exception
    2. Rare ambiguous genitalia

Diagnostic Investigations

1. Cytogenetic analysis by high-resolution banding techniques (Q-, G-, and C-bandings)
    1. Blood
    2. Skin fibroblasts
    3. Gonadal tissues
2. Fluorescence in situ hybridization (FISH) and SKY (spectral karyotyping), using DNA probes specific for Y chromosome sequences present in Yp, in Yq, and in the centromeric Y region, allow the structural characterization of abnormal Y chromosomes (Robinson et al. 1999)
3. Molecular studies
    1. Use of PCR to determine the presence or absence of specific Y chromosome sequences: may not provide enough information to determine the structure of the abnormal Y chromosome
        1. Amplify genes or chromosome regions (SRY, ZFY, DYZ1) which are needed for the male development
        2. Y centromere sequence (DYZ3) (Tuck-Muller et al. 1995; Robinson et al. 1999)
    2. Comparative genomic hybridization (CGH)
4. Hormonal investigations (Udler et al. 2001)
    1. Estradiol level
    2. Follicle-stimulating hormone level
    3. Luteinizing hormone level
    4. Testosterone level
5. Abdominal ultrasonography and MRI (Mizuno et al. 2009): suspect the presence of a testicular component and the possibility of mixed gonadal dysgenesis or true hermaphroditism in a phenotypic girl without gonad (especially with a history of a high testosterone level, enlargement of the clitoris, response to human chorionic gonadotropin stimulation test, and the presence of SRY), followed by laparoscopic evaluation and biopsy of the specimen: laparoscopic bilateral gonadectomy when dysgenetic gonad is found

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Since reported cases so far have been de novo, recurrence risk to sib is not likely increased.
        2. However, several sets of affected identical twins have been reported.
            1. Monozygotic twins with 47,X,idic(Y)(q11.2),idic(Y)(q11.2)/46,X,idic(Y)(q11.2)/45,X from peripheral blood: twin A (phenotypic female with 42% of Y-containing cells); twin B (phenotypic male with 94% of Y-containing cells) (Nonomura et al. 2002)
            2. Monozygotic twins with 45,X/46,X,idic(Y)(p11) from peripheral blood and skin fibroblasts: twin A (phenotypic female with 0–57% Y-containing cells); twin B (phenotypic male with 22–60% Y-containing cells) (Fujimoto et al. 1991)
    2. Patient's offspring: not likely increased since affected individuals are infertile
2. Prenatal diagnosis: possible via amniocentesis or CVS (Wu et al. 2007)
    1. Cytogenetic analysis
    2. FISH
    3. SKY
    4. Molecular studies using specific Y chromosome sequence
3. Management
    1. Gender assignment after careful evaluation of the patient when there is a genital ambiguity
    2. Advise surgery to remove gonads in women with gonadal dysgenesis and Y material at young age since they are at higher risk (15–20%) of developing gonadoblastoma and seminoma (Verp and Simpson 1987; Fallat and Donahoe 2006)

3. A boy with 45,X/46,XidicY(p11) mosaicism and short stature who has shown an improved final adult height as a result of long-term growth hormone treatment (Guevarra et al. 2009)

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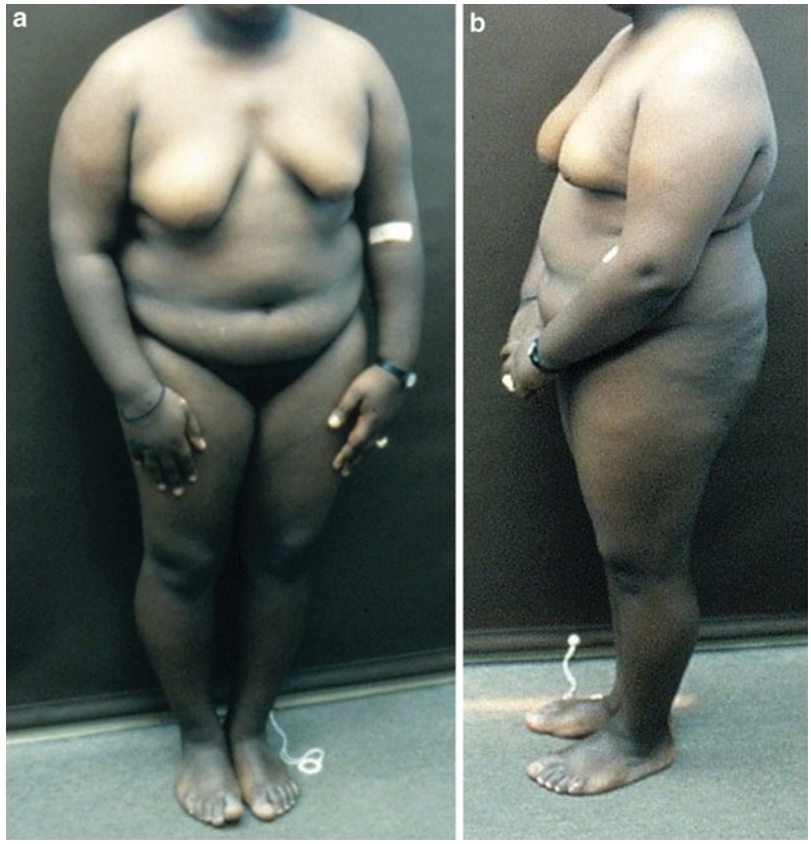

Fig. 1 (**a**, **b**) An 18-year-old female was evaluated for primary amenorrhea and short stature (Tuck-Muller et al. 1995). She was noted to be obese. Laboratory findings included prepubertal female levels of estradiol (below 10 pg/mL) and high levels of luteinizing hormone (72 mU/mL with normal of 4–30 mU/mL), follicle-stimulating hormone (53 mU/mL with normal of 4–30 mU/mL), and testosterone (103 ng/dL with normal adult female value of 6.0–86 ng/dL). Laparoscopic exploration revealed an infantile uterus, a left streak gonad, and a right gonadal enlargement. Histological examination of the right gonad showed gonadoblastoma merged with a diffuse germ cell component diagnosed as dysgerminoma. The specimen leveled as left streak ovary consisted of vestigial Wolffian ducts. The analysis of genomic DNA from the patient indicated that sequences derived from the short arm (using SRY and ZFY mapped at Yp11.32), centromere (using Y97 mapped at Y centromere), and the middle and terminal portions of the long arm of the Y chromosome (using eD6 mapped at Yq11; 1 F5 mapped at Yq11.2; pY3.4 mapped at Yq12) were present

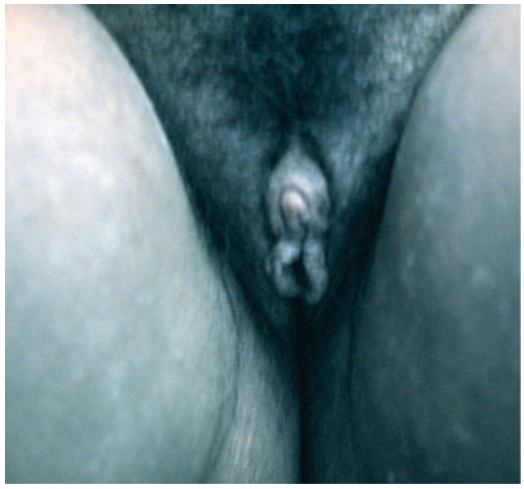

Fig. 2 Her external genitalia was characterized by clitoromegaly, rudimentary labia minora, hypoplastic labia major, and a narrow but patent vagina

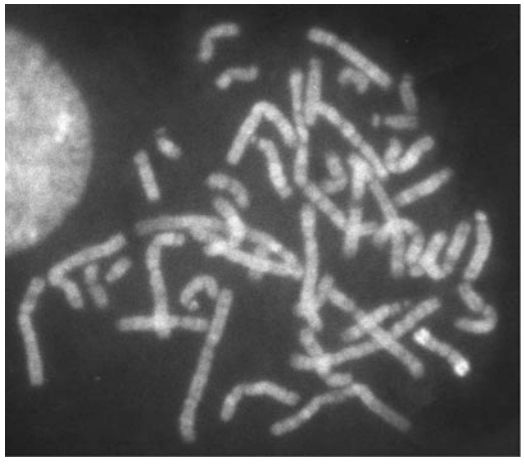

Fig. 3 The predominant cell line in the patient's blood (29 of 40 cells), skin (33 of 35 cells), and right (31 of 33 cells) and left (25 of 25 cells) gonadal tissues had monosomy X. The second cell line had 46 chromosomes with one X and one abnormal Y chromosome, illustrated in this Q-banded spread showing isodicentric Y chromosome. Brightly fluorescent bands were present at the terminus of both arms of the abnormal chromosome, which stained darkly by C-banding (Fig. 4). The abnormal chromosome was interpreted to be a dicentric isochromosome composed of two copies of the long arm, centromere, and proximal portion of the short arm of the Y chromosome. Both parents were karyotypically normal

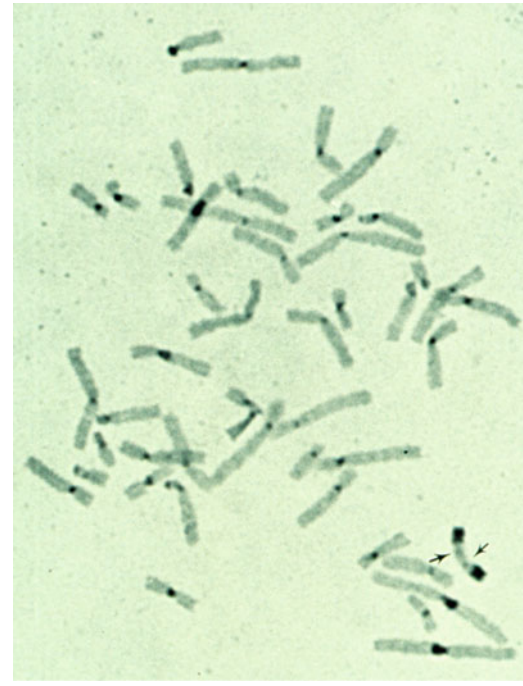

Fig. 4 The isodicentric Y chromosome (*arrows*) is illustrated in this C-banded spread

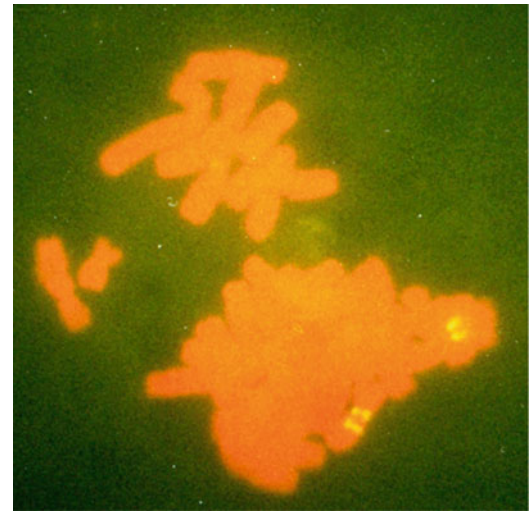

Fig. 5 The Y-specific α-satellite probe hybridized to the two centromeric regions of the abnormal Y chromosomes. The chromosome spread illustrates the presence of two idic(Y)

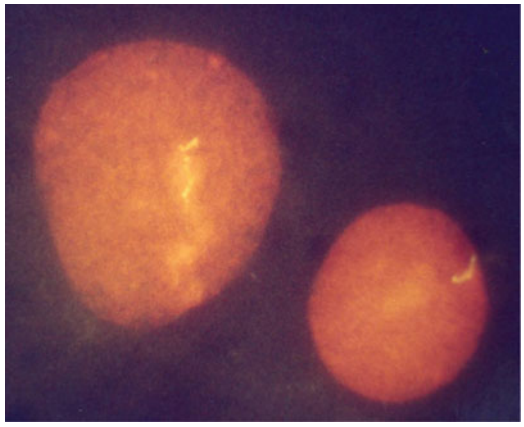

Fig. 6 FISH on interphase cells using Y probe shows idic (Yq) signals

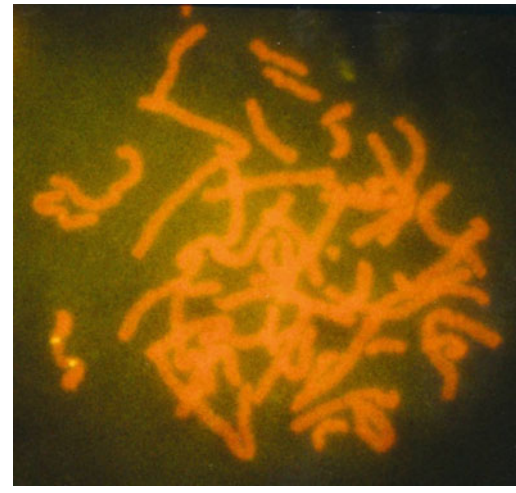

Fig. 7 FISH on a metaphase spread using Y centromeric probe shows idic(Yq) chromosome

Incontinentia Pigmenti

Contents

Bloch and Sulzberger, in 1926 and 1928, respectively (Bloch 1926; Sulzberger 1928), were credited for the first description of the clinical syndrome of incontinentia pigmenti (IP), known as Bloch-Sulzberger syndrome. It is a rare genodermatoses occurring in approximately 1 in 50,000 newborns (Aradhya et al. 2001b).

Synonyms and Related Disorders

Bloch-Sulzberger syndrome

Genetics/Basic Defects

1. Inheritance (Berlin et al. 2002):
    1. X-linked dominant transmission, usually prenatally lethal in males (Devriendt et al. 1998), suggested by pedigree analyses (Curth and Warburton 1965; Wiklund and Weston 1980; Wettke-Schäfer and Kanter 1983)
    2. A high affected female/affected male ratio
    3. Instances of female-to-female transmission
    4. 1:1:1 affected female/normal female/normal male ratio in the offspring of an affected mother
    5. Increased incidence of miscarriages in patients with incontinentia pigmenti, presumably representing affected male conceptuses that typically fail to survive past the second trimester
2. Female patients with IP mutations:
    1. Dizygosity for the X chromosome
    2. Skewed X-inactivation (Happle 1985)
        1. Cells expressing the mutant X chromosome are eliminated selectively around the time of birth so that females with IP exhibit extremely skewed X-inactivation, based on the Lyon hypothesis (random inactivation of one X chromosome in each cell of the female at an early developmental stage, resulting in an X-chromosomal mosaic for each female with one X functioning in some of the cells and the other X functioning in the rest of the cells).
        2. Female heterozygous for an X-linked incontinentia pigmenti gene: the pigmented areas on the skin represent cell populations in which the abnormal

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gene is active and the areas of normal skin tissue in which the normal gene is active.
3. Highly variable phenotype explainable by the chance variability in the number and position of the cells carrying the active incontinentia pigmenti gene.

3. The gene for IP: linked genetically to the *factor VIII* gene in Xq28 (Sefiani et al. 1989; Smahi et al. 1994).
4. Molecular pathophysiology (Fryssira et al. 2010):
   1. Attributed to mutations in the gene of nuclear factor kappa B (*NF-kB*) essential modulator (*NEMO*) currently known as *IKBKG* (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase gamma) (Aradhya et al. 2001a; Smahi et al. 2000; Jain et al. 2001; Jentarra et al. 2006; Fusco et al. 2008).
   2. The *IKBKG* gene is located on chromosome X, band q28. It spans 23 kb and consists of 10 exons.
   3. An intrachromosomal rearrangement that deletes exons 4–10 of the gene accounts for approximately 90% of new mutations (Aradhya et al. 2001a).
   4. The *IKBKG* gene encodes a protein which is essential for the activation of NF-jB transcription factor, which protects cells against tumor necrosis factor-induced apoptosis.
   5. The *IKBKG* gene also regulates the expression of various cytokines, chemokines, and adhesion molecules (Smahi et al. 2000; Berlin et al. 2002).
5. Mechanisms for occasional survival of affected males (Kenwrick et al. 2001; Berlin et al. 2002):
   1. Presence of an extra X chromosome (47, XXY Klinefelter syndrome) (Ormerod et al. 1987; Garcia-Dorado et al. 1990)
   2. Skewed X-inactivation
   3. Hypomorphic alleles
   4. Mosaics for common mutations (somatic mosaicism). Somatic mosaicism of a novel *IKBKG* mutation (nonsense mutation) has been reported in a male IP patient (Hull et al. 2015)
   5. A parent with gonadal mosaicism (Kirchman et al. 1995)
6. Anhidrotic/hypohidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) (Zonana et al. 2000; Doffinger et al. 2001):
   1. A disorder allelic to incontinentia pigmenti but with different phenotype due to various natures of genetic mutations underlying the two disorders
   2. A rare X-linked recessive disorder affecting only males
   3. Caused by mutations in the *NEMO* gene
   4. Possible family history of IP in boys with EDA-ID
   5. Presentation with severe recurrent infections caused by common encapsulated bacterial pathogens, suggesting functional defects in the immune response
   6. Rare opportunistic diseases
      1. Mycobacterial infections
      2. Cytomegaloviral infections
      3. *Pneumocystis carinii* pneumonitis
   7. Immunologic studies
      1. Normal or increased levels of B cells
      2. Normal T-cell counts
      3. Normal to low levels of IgG
      4. Elevated levels of either IgM or IgA
7. Eosinophil recruitment through eotaxin release by activated keratinocytes.
8. Incontinentia nomenclature: the localization of the gene for IP to Xq28, coupled with reports of children with "incontinentia pigmenti" and X-autosome translocations with breakpoints at Xp11 (Hodgson et al. 1985), resulting in a nomenclature differentiation of IP1 (sporadic) and IP2 (familial). However, IP1 and IP2 designation should be abandoned (Happle 1998):
   1. IP1
      1. Disorder applied to cases associated with X-autosome translocations with Xp11 breakpoints (Gilgenkrantz et al. 1985; Kajii et al. 1985; Cannizzaro and Hecht 1987; Sybert 1998) and r(X) (de Grouchy et al. 1985; Bitoun et al. 1992; Shastry 2000)
      2. Skin changes different from patients to patients

3. Serves no useful purpose either causally or clinically
4. More appropriately using descriptive phrase "X-autosome translocation associated with pigmentary abnormalities" (Sybert 1994)

2. IP2: applied to cases of familial IP mapped to Xq28

Clinical Features

1. Highly variable clinical presentations among affected female family members (Berlin et al. 2002)
    1. Attributed to lyonization in females, resulting in functional mosaicism
    2. Clonal expansion of the progenitor cell along lines of embryonic development in that each cell determines which X chromosome to express during the first weeks of gestation
        1. Manifesting along the curvilinear lines of Blaschko in the skin (Jackson 1976; Harre and Millikan 1994)
        2. Percentage of progenitor cells that express the mutated X chromosome reflecting the extent of expression
        3. Mutation in a high percentage of ectodermal cells in severe cases
2. Clinical expression among small number of live-born male patients
    1. Generally not severer than that in affected females
    2. Many male patients with disease expression limited to cutaneous involvement of one or two limbs
3. Cutaneous manifestations: most often the first observed sign of IP and are present in nearly all patients. They are classically subdivided into the following four classic cutaneous stages (Minić et al. 2014):
    1. Vesicular, vesiculobullous, or inflammatory stage
        1. Frequency: about 90% of cases
        2. Age of onset: within first 2 weeks of life (92%), by 6 weeks of age (4%), starting after the first year of life (several cases)
        3. Age at resolution: blisters generally clearing by 4 months, recurrence usually short-lived and less severe than the original eruption
        4. Clinical features: erythema, superficial vesicles in linear distribution on torso and extremities (64%) and extremities alone (33%)
        5. Differential diagnosis: dermatoses with blistering in early infancy (e.g., different types of epidermolysis bullosa and bullous bacterial infection), herpes simplex, and varicella/herpes zoster
    2. Verrucous (wartlike) stage
        1. Frequency: about 70% of cases
        2. Age of onset: peak of onset between 2 and 6 weeks of age
        3. Age at resolution: clearance by 6 months (80%)
        4. Clinical features: verrucous hyperkeratotic papules and plaques (Bessems et al. 1988), almost exclusively involving extremities
        5. Differential diagnosis: verrucae vulgares (simple warts), nevus verrucosus, molluscum contagiosum, X-linked-dominant chondrodysplasia punctata, and linear epidermal nevi
    3. Hyperpigmented stage
        1. Frequency: nearly all patients with IP (98%)
        2. Age of onset: 12–26 weeks of age
        3. Age at resolution: puberty
        4. Clinical features: whorls and streaks of brown pigmentation following lines of Blaschko (multiple lines on the human body corresponding to the distribution of linear nevi and dermatoses) on torso and extremities (65%) and torso alone (27%)
        5. Differential diagnosis: hypomelanosis of Ito, Naegeli syndrome, and pigment mosaicism
    4. Atrophic/hypopigmented (dermal scarring) stage

1. Frequency: 42%
2. Age of onset: early teens to adulthood
3. Age at resolution: permanent lesion
4. Clinical features: pale, hairless, atrophic patches, and/or hypopigmentation
5. Differential diagnosis: vitiligo with localized alopecia and different types of ectodermal dysplasia

4. Hair abnormalities (50%)
   1. Vertex alopecia
      1. The most common hair manifestation
      2. Most commonly mild and unnoticed
      3. Follows inflammation and vesiculation
      4. May be associated with scarring
   2. Agenesis of eyebrows and eyelashes: infrequent
5. Nail abnormalities (7–40%)
   1. Ridging, pitting, or nail disruption
      1. Starting early childhood and involving all or most of the fingernails and toenails
      2. Tends to regress and disappear with age
   2. Subungual and periungual keratotic tumors (Mascaro et al. 1985; Adeniran et al. 1993)
      1. Appear at a later stage.
      2. Affect fingers more than toes.
      3. Continued growth results in pain, nail dystrophy, and destruction of the underlying bone of the terminal phalanx.
      4. Bone lytic lesions caused by pressure from the overlying tumor.
6. Dental anomalies (>80%) (Russell and Finn 1967)
   1. Partial adontia or adontia (43%)
   2. Pegged and conical teeth (30%)
   3. Late eruption of teeth (18%)
   4. Enamel hypoplasia
7. Ophthalmologic anomalies (35%)
   1. Blindness (7.5%)
   2. Nonretinal manifestations
      1. Strabismus (18–33%)
      2. Optic atrophy (4%)
      3. Cataracts (4%)
      4. Pseudoglioma (3.5%)
      5. Microphthalmia (3%)
      6. Rare conjunctival pigmentation (McCrary and Smith 1968), iris hypoplasia, nystagmus, and uveitis
   3. Retinal manifestations (Francois 1984; Goldberg and Custis 1993)
      1. Foveal hypoplasia.
      2. Mottled or hypopigmented retinal pigment epithelium.
      3. Avascular retina.
      4. Neovascularization (Rosenfeld and Smith 1985).
      5. Vitreous hemorrhages.
      6. Fibrovascular proliferation.
      7. Retinal detachment (3%).
      8. Asymmetric retinal disease between eyes in the same individual and variable retinal findings within the kindred. These differences may be explained by random inactivation of the X chromosome or other epigenetic modifications (Chen et al. 2015).
8. Neurologic deficits (30%)
   1. Infantile spasms and seizure disorder (13%)
   2. Learning disability (12%) (Pizzamiglio et al. 2014)
   3. Spastic paralysis (11%)
   4. Motor retardation (7.5%)
   5. Microcephalus (5%)
   6. Infrequent manifestations
      1. Cerebellar ataxia
      2. Congenital hearing loss
      3. Muscle paresis
      4. Aseptic encephalomyelitis
9. Other associated anomalies
   1. Nipple anomalies
      1. Supernumerary nipple
      2. Nipple hypoplasia
      3. Breast hypoplasia/aplasia
   2. Oral anomalies
      1. High-arched palate
      2. Cleft lip/palate
   3. Skeletal anomalies
      1. Dwarfism
      2. Chondrodysplasias
      3. Short stature
      4. Spina bifida
      5. Skull defects
      6. Club foot
   4. Increased risk of serious and unusual infection in some patients

5. Occasional hypohidrosis with increased rates of bacterial skin infections: may be evidence of the continuum between IP and the allelic anhidrotic ectodermal dysplasia-immune deficiency
6. Cardiovascular abnormalities (Miteva and Nikolova 2001)
    1. Tricuspid insufficiency
    2. Pulmonary vein-to-superior vena cava shunt

10. Diagnostic criteria for incontinentia pigmenti (Landy and Donnai 1993; Minić et al. 2014)
    1. Negative family history (no evidence of IP in a first-degree female relative): at least one major criterion is necessary to make a firm diagnosis of sporadic incontinentia pigmenti. The minor criteria, if present, will support the diagnosis. Because of their high incidence, complete absence of minor criteria should induce a degree of uncertainty:
        1. Major criteria: typical IP skin stages distributed along Blaschko's lines
            1. Vesiculobullous stage
            2. Verrucous stage
            3. Hyperpigmented stage
            4. Atrophic/hypopigmented stage
            5. Landry and Donnai's original major criteria: typical neonatal rash (erythema, vesicles, eosinophilia), typical hyperpigmentation (mainly trunk, Blaschko's lines, fading in adolescence), and linear, strophic, hairless lesions
        2. Minor criteria (supportive evidence)
            1. Dental anomalies
            2. Ocular anomalies including retinal disease
            3. CNS anomalies
            4. Alopecia
            5. Abnormal hair (sparse hair, wooly hair, anomalies of eyebrows and eyelashes)
            6. Abnormal nails
            7. Palate anomalies
            8. Nipple and breast anomalies
            9. Multiple male miscarriages
            10. Typical skin pathohistological findings
    2. Positive family history (evidence of IP in a first-degree female relative)
        1. Any single major or at least two minor criteria.
        2. In all cases, eosinophilia and skewed X chromosome inactivation support diagnosis.

Diagnostic Investigations

1. Major histopathologic features from skin biopsy samples (Berlin et al. 2002):
    1. Vesicular, vesiculobullous, or inflammatory stage
        1. Spongiotic dermatitis
        2. Dermal and epidermal eosinophilia
        3. Eosinophil-filled vesicles
    2. Verrucous stage
        1. Papillomas
        2. Epidermal hyperplasia
        3. Hyperkeratosis
        4. Dyskeratotic cells
    3. Hyperpigmented stage
        1. Dermal melanophages
        2. Vascular changes in basal layer of epidermis
    4. Atrophic stage
        1. Loss of rete ridges
        2. Loss of dermal sweat coils
        3. Skin biopsy helpful for the diagnosis of IP at late stage (IV) (Fraitag et al. 2009)
            1. Slight atrophy and some scattered apoptotic cells in the epidermis, epidermal hypopigmentation, and reduced melanocyte number.
            2. The dermis appeared thickened and homogeneous and revealed a complete absence of hair follicles (23/26) and sweat glands (22/26).
            3. There was no melanin incontinence or inflammatory cells, and the elastic network was normal.
2. Light microscopy (Zillikens et al. 1991):
    1. Hypopigmented streaks with slight epidermal atrophy

2. A reduced number of melanocytes and skin appendages
3. Electron microscopy (Schaumburg-Lever and Lever 1973):
   1. Dyskeratosis
   2. Phagocytosis of dyskeratotic cells and of melanosomes by macrophages
   3. Presence of melanophages in the upper dermis
   4. Abnormal cutaneous nerves (Worret et al. 1988)
   5. Amorphous material resembling colloid, suggesting degeneration of basal keratinocytes (Zillikens et al. 1991)
4. CBC: marked peripheral blood leukocytosis and eosinophilia (Cohen 1994)
5. Abnormal immune system (Jessen et al. 1978; Menni et al. 1990): not a consistent finding
6. CT/MRI imagings of the brain:
   1. Optic atrophy
   2. Retinal vasculopathy
   3. Hypoplasia of the corpus callosum (Pascual-Castroviejo et al. 1994)
   4. Ventriculomegaly
   5. Periventricular white matter lesions
   6. Ischemic strokes
   7. Hemorrhagic necrosis (Chatkupt et al. 1993)
   8. Porencephalic cyst
   9. Brain atrophy (Avrahami et al. 1985)
7. Magnetic resonance angiography/spectroscopy for cerebral ischemia and a vaso-occlusive phenomenon (Lee et al. 1995)
8. Single photon emission computed tomography: detection of cerebral infarction (Kasai et al. 1997)
9. Fluorescein angiography for retinal vascular abnormalities
10. EEG for seizures
11. Chromosome analysis in male patients with IP (Scheuerle 1998)
12. Molecular genetic testing: mutation detection for the majority of families, facilitated by the high frequency of specific deletion, using Southern blotting, PCR amplification, or DNA sequencing:
    1. X-inactivation assay and Xq28 marker studies: X-inactivation analysis is indicated wherever a recombination event between Xq28 markers and the disease locus is suspected. The absence of recombination between the disease locus and Xq28 loci suggests that mosaicism is responsible for the discrepancy where Xq28 marker studies are at odds with the clinical assessment.
    2. Identification of the *IKBKG* (also known as *NEMO*) gene mutation as a biological marker for a molecular diagnosis of IP (Scheuerle and Ursini 2015):
       1. Deletion/duplication analysis.
       2. Sequence analysis.
       3. Targeted mutation analysis for common deletions.
       4. Carrier testing for the mother who has an affected daughter with a known mutation.
       5. Determine whether the miscarried or stillborn male fetus has IP.
       6. Prenatal testing of a fetus at risk.

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Recurrence risk: $<1\%$, provided that the mother is not a carrier of the gene: a small increased risk due to either a new mutation in a second child or germ line mosaicism in a parent
      2. Recurrence risk of 50% for sisters to be affected when the mother is a carrier of the gene
      3. Recurrence risk of 50% for brothers to be affected (prenatally aborted fetuses or stillborns) when the mother is a carrier of the gene
   2. Offspring of an affected female
      1. Daughters: 50% affected, 50% normal
      2. Sons: 50% affected (prenatally aborted fetuses or stillborns), 50% normal (all the live-born sons will be normal)
   3. Offspring of an affected male
      1. All daughters affected

   2. All sons normal
2. Prenatal diagnosis possible if the disease-causing mutation has been detected in the families at risk (Scheuerle and Ursini 2015)
   1. Determination of the fetal sex by amniocentesis or CVS.
   2. An increased risk of miscarriage or stillborn for an affected male fetus (fetal karyotype 46,XY).
   3. If the fetal karyotype is 47,XXY: more severe IP phenotype in males and of Klinefelter syndrome.
   4. Molecular genetic testing of a female fetus: if the fetal karyotype is 46,XX, there is 50% of fetuses that are likely to be affected with IP.
   5. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified previously: a healthy delivery of twins by assisted reproduction followed by preimplantation genetic screening was reported in a woman with X-linked dominant incontinentia pigmenti (Kim et al. 2014).
3. Management
   1. Reduce the risk of secondary infection of blisters.
   2. Keep lesions dry.
   3. Avoid trauma to blisters.
   4. Dental care.
   5. Early photocoagulation or cryotherapy in cases of retinal involvement.
   6. Laser treatment of the ischemic peripheral retina: good outcome, resulting in stability of vision (Neto et al. 2014).
   7. Intervention programs for learning disabilities and developmental delay.
   8. Antiseizure medications for seizures

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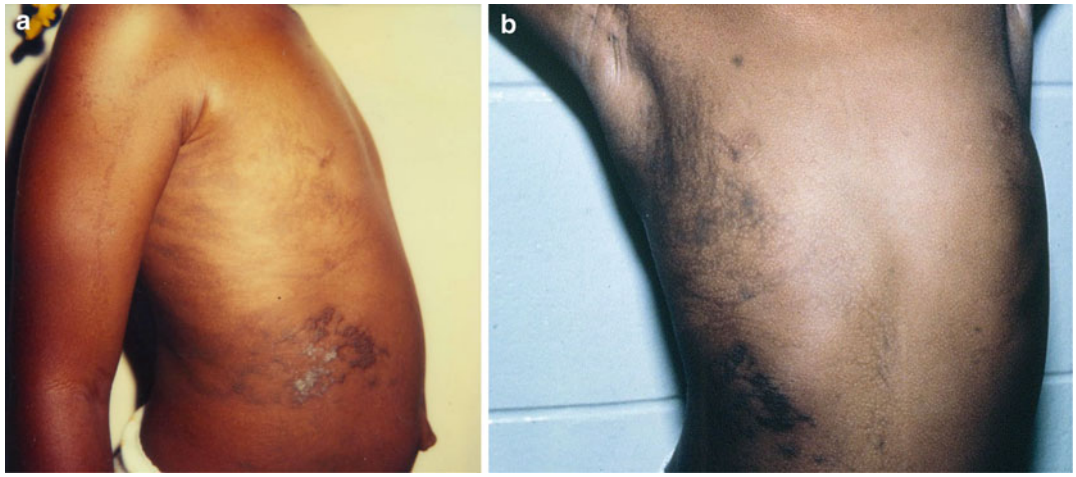

Fig. 1 (**a**, **b**) Two girls with incontinentia pigmenti showing classical hyperpigmentation on the trunk following Blaschko's lines

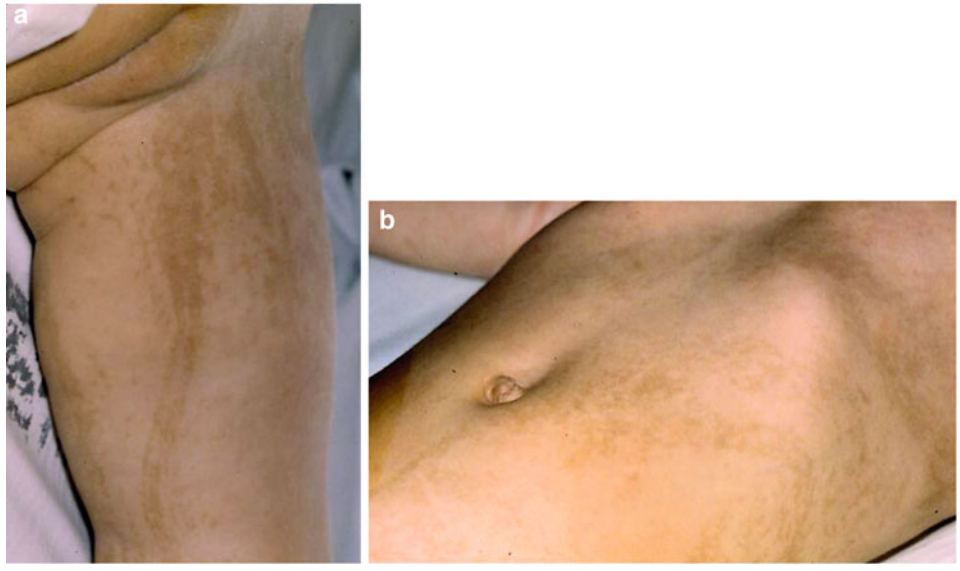

Fig. 2 (**a**, **b**) A girl with incontinentia pigmenti showing streaks and whorls of brown pigmentation on the leg (**a**) and trunk (**b**)

Infantile Myofibromatosis

Contents

Infantile myofibromatosis, previously known as congenital generalized fibromatosis, is the most common fibrous tumor of infancy (Wiswell et al. 1988). It is characterized by the formation of tumors, either in a solitary or in a multicentric fashion, in the skin, muscle, viscera, bone, and subcutaneous tissue.

Synonyms and Related Disorders

Congenital generalized fibromatosis; Juvenile myofibromatosis

Genetics/Basic Defects

1. Etiology: Unknown but appears to originate in utero. Fetal estrogenic hormone stimulation or hamartomas of myofibroblasts have been considered.
    1. Sporadic in most cases.
2. Several reports of familial cases (Bračko et al. 1992; Zand et al. 2004):
    1. Autosomal dominant (Jennings et al. 1984) with variable penetrance (Kulkarni et al. 2012)
    2. Autosomal recessive (Baird and Worth 1976; Venencie et al. 1987; Narchi 2001)
3. Recently, mutations in platelet-derived growth factor receptor β gene (*PDGFRB* located on chromosome 5q31-q32) have been identified in familial autosomal dominant forms of infantile myofibromatosis (infantile myofibromatosis 1) (Cheung et al. 2013; Martignetti et al. 2013). The role of a second gene, *NOTCH3* located on chromosome 19p13.12, is suspected in one family (infantile myofibromatosis 2) (Martignetti et al. 2013), suggesting genetic heterogeneity. Long arm and interstitial deletion of chromosome 6 (q12q15) and a published translocation between chromosomes 9 and 16 confirm the genetic heterogeneity of infantile fibromatosis (Stenman et al. 1999; Sirvent et al. 2004).
4. Homozygous variant in *NDRG4* (identified by exome sequencing) may be the causative variant of the autosomal recessive form of infantile myofibromatosis in the studied family (Linhares et al. 2014).
5. CD34-positive infantile myofibromatosis with hemangiopericytoma-like pattern tumors reported (Kiyohara et al. 2016).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Three types of infantile myofibromatosis (Larralde et al. 2010):
    1. Solitary infantile myofibroma
        1. A single lesion affecting mainly the skin or muscle of the head, neck, or trunk
        2. More common in males (approximately 75% of all cases)
    2. Multiple infantile myofibromatosis without visceral involvement (multicentric lesions limited to skin and muscle)
    3. Multiple infantile myofibromatosis with visceral involvement or generalized (multicentric lesions arising not only on the skin and muscle but also on the bone, lung, heart, and most frequently gastrointestinal tract)
3. Spontaneous regression of tumors (Teng et al. 1963; Schaffzin et al. 1972; Brill et al. 1982), possibly due to apoptotic cell death (Fukasawa et al. 1994).

Clinical Features

1. Affects almost exclusively infants and young children
    1. Sixty percent noted at birth or shortly thereafter
    2. Eighty percent occurred before the age of 2 years
2. Characteristics of tumors
    1. Superficial
        1. Palpable, rubbery, firm, and freely moveable nodules
        2. Fibrotic, plaque-like, indurated, and crusted lesions
    2. Deeper lesions: generally immovable
    3. Nontender and painless
3. Overlying skin
    1. Erythema or a purple discoloration resembling a hemangioma
    2. Ulceration and atrophic scar
4. Dermatological presentations (Stanford and Rogers 2000)
    1. Most lesions were dermal or subcutaneous, although some were intramuscular and intraosseous.
    2. The clinical appearance was nonspecific leading to frequent misdiagnosis.
    3. While most patients presented with nodules, atrophic depressed lesions and warty pedunculated lesions were also seen.
5. Affected bones
    1. Radiolucent lytic lesions (cystic defects)
    2. Most commonly involved skeletal locations (Inwards et al. 1991)
        1. Cranium (Hasegawa et al. 1995; Shnitka et al. 1958; Duffy et al. 1997; Söylemezoglu et al. 2001)
        2. Femurs
        3. Tibias
        4. Spine (Wada et al. 1998)
        5. Ribs
    3. Circumscribed lytic tumors not present at birth but develop quickly over the first few days or weeks of life
6. Solitary form (myofibroma)
    1. About 80% of the cases
    2. Boys more commonly affected
    3. Mostly involves the skin and bones (Hasegawa et al. 1993), and rarely the CNS (Kaplan 2002) and viscera
    4. A good outcome provided there is no visceral involvement
    5. Natural history of myofibromas of the CNS without visceral involvement: frequently characterized by a period of initial rapid growth, subsequent stabilization, and spontaneous regression in many cases
7. Multicentric form (myofibromatosis)
    1. Without visceral involvement
        1. Girls more commonly affected
        2. Typically undergoing spontaneous regression within the first 1 or 2 years of life when limited to the skin or bone
        3. A good outcome
    2. With visceral involvement (Roggli et al. 1980; Wiswell et al. 1985; Coffin et al. 1995)
        1. One-fourth of cases of multicentric cases
        2. Multiple nodules distributed throughout the body
            1. Soft tissues such as multicentric myofibromatosis presenting as a large congenital eyelid myofibroma (Macintosh et al. 2016)

2. Bone
3. Skeletal muscle
4. Viscera (kidney, pancreas, retroperitoneum, lungs, gastrointestinal tract (Alberti et al. 2012), peritoneum, diaphragm, heart, tongue, lymph nodes, peripheral nerves, liver, ovary (Ng et al. 2001) uterus (Bhatkule et al. 2015))

3. Fatal outcome with visceral involvement usually within 4 months of life
   1. Localized mass effect on the lung, gastrointestinal tract, or within the conduction system of the heart.
   2. Mortality rate approaches 75%.
4. Possible survival: spontaneous resolution of visceral lesions within the first year of life
5. Disseminated pathologic process including proliferation of multiple nodules of collagen-forming fusiform cells
6. Likely origin of proliferating cells: myofibroblast (displaying both smooth muscle and fibroblast features)

8. Differential diagnosis (Johnson et al. 1997)
   1. Bone lesions
      1. Fibrous dysplasia
      2. Neurofibromatosis
      3. Metastatic neurofibroma
      4. Hemangiomatosis
      5. Lymphangiomatosis
      6. Letterer-Siwe disease
      7. Eosinophilic granuloma
      8. Familial multiple osteogenic fibromas
   2. Soft tissue lesions (Schrodt and Callen 1999)
      1. Leiomyomas
      2. Neurofibroma
      3. Soft tissue sarcomas
      4. Metastatic neuroblastomas
      5. Hyaline fibromatosis
      6. Deep hemangiomas
      7. Other fibromatoses of infancy
9. Prognosis depending on the extent of involvement and location of the lesions (Orozco-Covarrubias et al. 2002)
   1. Solitary forms usually cause little morbidity and virtually no mortality. However, a solitary nodule involving the central nervous system (CNS) may be fatal.
   2. Lesions confined to soft tissue and bone are usually self-limited with good prognosis.
   3. Good prognosis with frequent spontaneous regression when viscera are not involved (Bellman et al. 1991; Zeller et al. 1997).
   4. Poor prognosis with infantile myofibromatosis with multiple visceral involvement.
      1. May cause significant morbidity
      2. Progression to death: usual outcome
      3. Fatal in neonates (up to 75% of cases) (Wiswell et al. 1998)
      4. Death resulting from complications due to cardiopulmonary or gastrointestinal involvement

Diagnostic Investigations

1. Radiography, US, CT, and MRI (Johnson et al. 1997)
   1. Soft tissue lesions: round and well defined on US and MRI
   2. Invaluable in assessing the extent and progression or regression of the disease
      1. Soft tissue lesions (multiple subcutaneous and intramuscular tumors)
      2. Bone lesions
      3. Visceral lesions
   3. Radiography: lesions appearing as multiple areas of osteolysis with a sclerotic margin (Inwards et al. 1991)
   4. Ultrasonography: hyperechoic nodules with peripheral hyperperfusion on color Doppler
   5. CT scan
      1. Masses: isoattenuating with muscle or as low attenuating with slight enhancement in the periphery (Koujok et al. 2005)
      2. Brain (Tamburrini et al. 2003)
         1. Partially calcific masses or isodense cystic lesions with intense peripheral contrast enhancement and smoothly marginated bone erosion
         2. The typical absence of sclerosis of the margins

6. MRI: intramuscular, subcutaneous, and visceral (liver, lungs) lesions (Counsell et al. 2002; Tamburrini et al. 2003; Koujok et al. 2005)
    1. Low signal on T1-weighted images
    2. High or low signal of the center on T2-weighted images
    3. All masses showed peripheral enhancement after gadolinium administration (Spadola et al. 2002)
    4. Intraparenchymal brain lesions, epidural spinal masses, and/or vertebra plana or lytic lesions of the calvarium and spine (Holzer-Fuehwald et al. 2012)
2. Histology (biopsy of tumors) (Chung and Enzinger 1981; Fletcher et al. 1987)
    1. Gross appearance of tumors is well demarcated.
    2. Lesion consisting of bundles of elongated cells with features of both fibroblasts and smooth muscle cells.
    3. Staining characteristics are intermediate between fibroblasts and smooth muscle.
    4. Central part of the tumors is often necrotic.
    5. Ultrastructurally, the localized form of congenital generalized fibromatosis is composed of myofibroblasts (Liew and Haynes 1981).
3. Electron microscopy
    1. Characteristic intracytoplasmic myofilaments
    2. Dense bodies
    3. Focal basal lamina and macula adherens

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Sporadic form: not increased
        2. Autosomal recessive form: 25% risk
        3. Autosomal dominant form: not increased unless a parent is affected
    2. Patient's offspring
        1. Sporadic form: not increased
        2. Autosomal recessive form: not increased unless the spouse is a carrier
        3. Autosomal dominant form: 50% risk
2. Prenatal diagnosis by ultrasonography
    1. Solitary or multicentric tumors in soft tissue (Kubota et al. 1999; Meizner et al. 2000), bones, or viscera
    2. A superficial head tumor at 13 weeks' gestation (Arabin et al. 2009)
    3. A splenic mass (Muraoka et al. 2008)
    4. An upper arm mass (Kubota et al. 1999)
    5. A solid paraspinal mass (Meizner et al. 2000)
    6. A mass on the lung parenchyma (Yeniel et al. 2013)
3. Management
    1. Observation.
        1. Spontaneous regression
        2. Possible sequelae (tissue loss or damage) resulting from spontaneous regression
    2. Surgical excision (Stanford and Rogers 2000).
        1. To prevent complications and improve prognosis.
        2. Sometimes required for obstructive or locally destructive tumors.
        3. Reserved for symptomatic lesions or if vital organs are compromised, in view of the tendency to spontaneous regression.
        4. Radical resection reserved for those lesions posing an immediate threat due to their locations or massive size and those showing obvious progression.
        5. Seven to ten percent of lesions recurred after excision (Tamburrini et al. 2003).
        6. Decompressive surgery of the spinal cord may improve the neurological outcome in patients with infantile myofibromatosis involving the spinal cord (Kim et al. 2013).
        7. While solitary infantile myofibromatosis may be cured surgically, multicentric/generalized forms require ongoing clinical evaluation (Mashiah et al. 2014).
    3. Chemotherapy with or without radiotherapy.
        1. Necessary for recurrent or unresectable lesions.
        2. A combination of chemotherapy with vincristine, adriamycin-D, and

cyclophosphamide produces regression of fibromatosis in some children with recurrent or unresectable lesions (Raney et al. 1987).

3. Well-tolerated, successful outcomes in a series of patients with high-risk infantile myofibromatosis in need of life sustaining interventions treated with a combination of vincristine and dactinomycin (Weaver et al. 2015).
4. The successful use of a combination of vinblastine and low-dose methotrexate in an infant with generalized infantile myofibromatosis (Day et al. 2002; Azzam et al. 2009).

4. Limited success has been achieved with radiation treatment, steroid injection, and chemotherapy in aggressive cases (Johnson et al. 1997).

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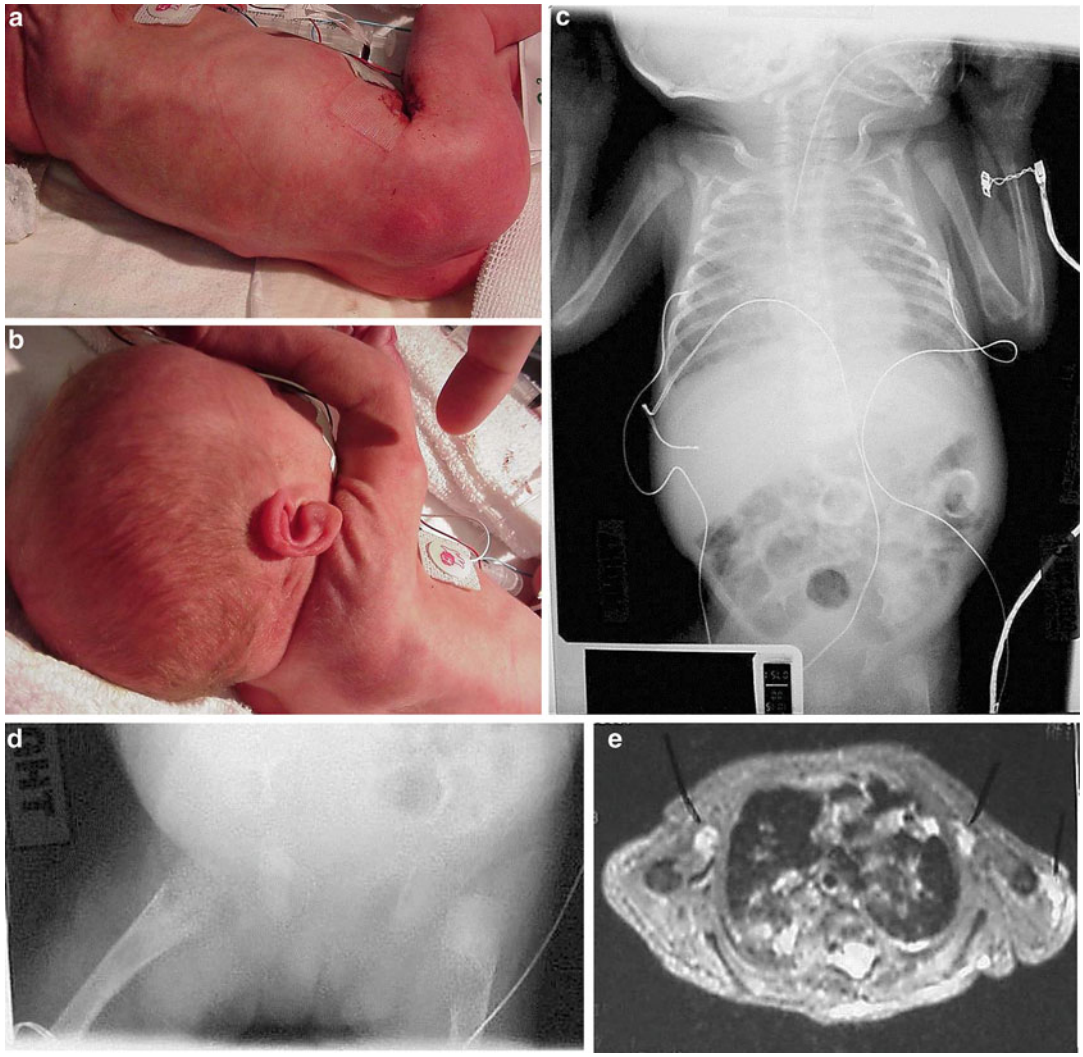

Fig. 1 (**a**–**e**) An infant with multicentric myofibromatosis showing subcutaneous nodules in the back (**a**), arm (pointed by a finger) (**b**), cystic lytic lesions in the humeri (**c**) and femora (**d**) (radiographs), and multicentric nodules (identified by *dark lines*) in the chest wall by MRI (**e**)

Isolated Growth Hormone Deficiency in Children

Contents

Among children with significant short stature (height of ≤ -2.5 standard deviations (SD)), 16–20% have growth hormone deficiency (GHD), which may be isolated (IGHD) or combined (CGHD) with deficiency of other pituitary hormones (Desai et al. 1991). Congenital IGHD occurs in 1 in 4,000 to 1 in 10,000 live births, with prevalence of 1 in 3,500 in school-age population (Lindsay et al. 1994). It is often sporadic and nonfamilial (NFIGHD) but may be familial (FIGHD) in 3–30% (Mullis 2007; Rimoin and Phillips 1997) (Figs. 1, 2, and 3).

Synonyms and Related Disorders

Dwarfism of Sindh; Hypogammaglobulinemia and isolated growth hormone deficiency, X-linked; Isolated growth hormone deficiency, Types IA, IB, II, and III; Pituitary dwarfism due to isolated growth hormone deficiency, autosomal dominant; Pimordial dwarfism

Genetics/Basic Defects

1. Causes of IGHD (Dattani and Preece 2004; Wit et al. 2011; Alatzoglou and Dattani 2012; Desai et al. 2013)
    1. Congenital: often due to genetic mutations
        1. Associated with structural defects of the brain
            1. Agenesis of the corpus callosum
            2. Septo-optic dysplasia
            3. Holoprosencephaly
            4. Encephalocele
            5. Hydrocephalus
        2. Associated with midline facial defects
            1. Cleft lip or palate
            2. Single central incisor
    2. Acquired
        1. Trauma
        2. Infections
        3. CNS tumors
        4. Langerhans cell histiocytosis
        5. Postcranial irradiation
        6. Postchemotherapy
        7. Pituitary infarction
        8. Neurosecretory dysfunction
        9. Psychosocial deprivation
        10. Hypothyroidism
2. Gene implicated in the etiology of IGHD
    1. Growth hormone 1 gene (*GH1*)
        1. Located on chromosome 17q22-q24
        2. Mutating the coding region and/or either entire or partial deletions of the *GH1* gene lead to IGHD

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Mutations in the receptor of growth hormone–releasing hormone gene (*GHRHR*)
3. Mutations caused by other genetic factors
    1. Genetic defects associated with multiple pituitary deficiencies: e.g., PROPHET OF PIT1 gene (*PROP1*) and POU Domain, Class 1, Transcription Factor 1 gene (*POU1F1*)
    2. Rare causes: mutations in the transcription factors
        1. Homeobox Gene Expressed in Es Cells gene (*HESX1*): associated with septo-optic dysplasia (McCabe et al. 2011) or may cause IGHD with or without optic nerve hypoplasia
        2. SRY-Box 2 gene (*SOX2*): usually associated with anophthalmia/severe microphthalmia and part of the endocrine spectrum (hypogonadotrophic hypogonadism), a hypoplastic anterior pituitary, and growth hormone deficiency (Kelberman et al. 2006)
        3. Homologue of Orthodenticle, Drosophila, two gene (*OTX2*): variable phenotype ranging from IGHD to hypopituitarism with or without ocular malformations (Ashkenazi-Hoffnung et al. 2010; Dateki et al. 2010; Tajima et al. 2009)
    4. Mutations in known genes account only for a small percentage of cases; other as yet unidentified factors may be implicated in its etiology
3. Classification of four genetic forms of IGHD
    1. Autosomal recessive type IA
        1. Gene: *GH1* (17q23.3)
        2. Phenotype
            1. Undetectable GH
            2. Anti-GH antibodies on treatment
    2. Autosomal recessive type IB
        1. Gene: *GH1*, *GHRHR* (7p14.3), Growth Hormone Secretagogue Receptor gene (*GHS*R), *HESX1*
        2. Phenotype
            1. Low detectable GH
            2. No antibodies to recombinant human GH (rhGH) treatment
    3. Autosomal dominant Type II
        1. Gene: *GH1*
        2. Phenotype
            1. Less severe short stature
            2. Variable phenotype
    4. X-linked recessive Type III
        1. Gene: *SOX3*, Bruton tyrosine kinase gene (*btk*) (Xq22.1), or other yet unknown genes (Stewart et al. 2008)
        2. Phenotype
            1. With or without mental retardation
            2. Ectopic posterior pituitary

Clinical Features

1. Principal mode of presentation of IGHD: proportional short stature and a low/decreased growth velocity for age and pubertal stage (Pinto et al. 1999; Shalet et al. 1998; Alatzoglou and Dattani 2012)
2. Additional criteria
    1. Absence of bone dysplasias
    2. Absence of chronic disease
    3. Skeletal maturation: usually delayed in proportion to height retardation
3. Age of presentation
    1. Highly variable from the first few months of life to adolescence
    2. Highly influenced by the time of onset and the degree of GFD (Adan et al. 1994)
4. IGHD Type IA
    1. At birth: may or may not have short length
    2. By the first 6 months of life: present with severe growth failure (height SD < -4.5)
    3. Infancy: may or may not have hypoglycemia
    4. Puppet (baby doll) facies
5. IGHD Type IB
    1. Less severe and more variable phenotype compared to those with type IA
    2. Marked short stature
    3. Poor growth velocity
6. IGHD Type II
    1. Commonest genetic form of IGHD
    2. Exhibiting significant variability in time of presentation and severity of GHD

7. IGHD Type III
    1. Variable phenotype: ranging from IGHD to hypopituitarism
    2. With or without mental retardation
    3. Infections
        1. Sinusitis
        2. Chronic otitis media leading to hearing loss
        3. Conjunctivitis
        4. Pneumonia
        5. Enteroviral hepatitis
        6. Diarrhea
        7. Epididymitis
        8. Prostatitis
        9. Urinary tract infections
        10. Septic arthritis
        11. Pyoderma
        12. Meningitis/encephalitis
    4. Immunology
        1. Frequent bacterial infections
        2. Severe enteroviral infections
        3. Absent B lymphocytes in all organs
        4. Absent antibody production
        5. Small tonsils
        6. Panhypogammaglobulinemia
        7. Susceptive to infections starting in the first week of life
8. Consensus statement criteria to initiate evaluation for GHD (Consensus Guidelines for the Diagnosis and Treatment of GHD in Childhood and Adolescence from the GH Research Society (2000))
    1. "Severe" short stature [height < -3 standard deviation (SD) below mean]
    2. Height less than -1.5 SD below midparental height
    3. Height less than -2 SD below mean and either height velocity less than -1 SD below mean over past year or decrease in height SD of more than 0.5 SD over past year
    4. In the absence of short stature, height velocity less than -2 SD below mean over 1 year OR less than -1.5 SD below mean over 2 years
    5. Signs of an intracranial lesion
    6. Signs of multiple pituitary hormone deficiency
    7. Neonatal signs and symptoms of GHD, including hypoglycemia, prolonged jaundice, microphallus, or craniofacial midline abnormalities

Diagnostic Investigations

1. Consensus Guidelines for the Diagnosis and Treatment of GHD in Childhood and Adolescence from the GH Research Society (2000)
    1. The degree of short stature
    2. Growth velocity
    3. Radiographic assessment of bone age
        1. Bone age: delayed
        2. Degree of delay: related to the severity and duration of GHD
    4. Measurement of insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3)
        1. Considerable overlap between IGF-I and IGFBP-3 values in children with GHD compared to normal children
        2. These measures have reasonable specificity and are useful in conjunction with other diagnostic criteria
    5. Provocative growth hormone (GH) testing (postexercise, L-DOPA, insulin tolerance, arginine, insulin–arginine, clonidine, glucagon, and propranolol protocols): The results are poorly reproducible and dependent on
        1. The assay used
        2. The pubertal and nutritional status of the child
        3. The GH secretion pattern prior to testing
    6. Testing for concomitant deficiencies of LH, FSH, TSH, and ACTH
2. If growth hormone deficiency is congenital and complete, the diagnosis is relatively easy to confirm (Rogol 2014)
    1. Affected children present with severe growth failure and very low serum concentrations of growth hormone, insulin-like growth factor I (IGF-I), and its major binding protein, IGFBP-3.
    2. If diagnosed in infancy, they may also manifest hypoglycemia, prolonged jaundice,

microphallus in males, and giant cell hepatitis.
3. In those diagnosed late, delayed bone age is characteristic.

3. MRI of the hypothalamic–pituitary region: detects anomalies in about 12% of patients with IGHD
   1. Abnormal findings on pituitary MRI indicate
      1. A relatively high likelihood that GHD will persist in adulthood
      2. That subsequent pituitary deficiencies may develop
   2. Anterior pituitary may appear aplastic or hypoplastic
   3. Posterior pituitary may be ectopically sited
   4. Septo-optic dysplasia
4. Genetic testing for children with isolated GHD and a family history of GHD (Stanley 2012)
   1. Screening for growth hormone 1 (GH1) and growth-hormone-releasing hormone receptor (GHRHR) mutations (Wit et al. 2011; Kempers et al. 2013)
   2. Other genetic testing is not yet widely applicable in the diagnosis of GHD but may contribute to the diagnosis in the future
5. If there is no clue for a specific gene, consider a whole genome approach, using an SNP array or Array CGH

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Acquired: not increased
      2. Autosomal recessive: 25% of siblings affected, 50% of siblings carriers, and 25% of siblings normal
      3. Autosomal dominant: not increased unless a parent is affected, in which case the recurrence risk is 50%
      4. X-linked recessive
         1. If the mother is a carrier: 50% of brothers affected and 50% of sisters carriers
         2. If the mother is not a carrier: the recurrence risk is probably low
   2. Patient's offspring
      1. Acquired: not increased
      2. Autosomal recessive: not increased unless the spouse is also a carrier, in which case the recurrence risk is 50%
      3. Autosomal dominant: 50%
      4. X-linked recessive: None of the sons will be affected; all daughters will be carriers.
2. Prenatal diagnosis by molecular genetic analysis
   1. Prenatal testing for pregnancies at increased risk is possible if the family's specific disease-causing mutation is known
   2. Molecular characterization in a case of isolated growth hormone deficiency leading to prenatal diagnosis of an unknown sibling (Nadar et al. 2013)
3. Management (Rogol 2014)

1. Growth hormone promotes linear growth in children by stimulating cartilage growth, particularly at the epiphyseal plate. In addition, growth hormone increases lean body mass and bone mass and reduces fat mass while increasing plasma and liver lipid content.
2. Replacement using exogenous, biosynthetic (recombinant) growth hormone
3. A majority of children with idiopathic isolated growth hormone deficiency (67–78%) with partial growth hormone deficiency initially had normal serum growth hormone responses to insulin-induced hypoglycemia at the completion of their growth hormone therapy (Wacharasindhu et al. 1996; Tauber et al. 1997).

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Fig. 1 A 10-year-old Caucasian boy was originally evaluated for unusual facies, small for age, and tight hamstrings and heel cords. He has been seen by an endocrinologist and received growth hormone short daily. Chromosome microarray showed Arr cgh 3q22.1 (RP11-883MS) × 1 variant

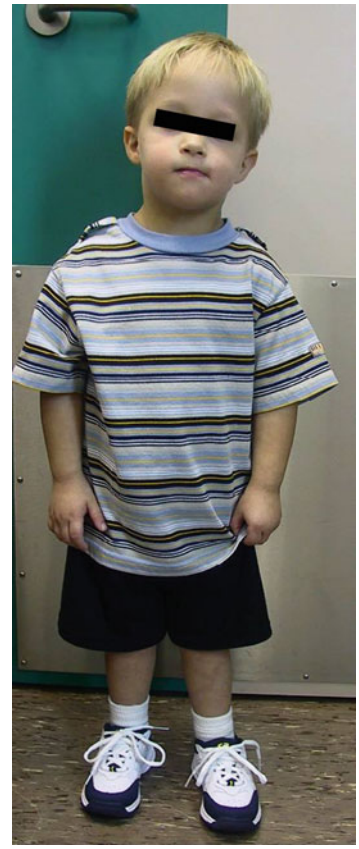

Fig. 2 This 2 year and 8 month old Caucasian boy was evaluated for growth hormone deficiency. He received Humatrope 0.5 mg IM/day since 2 years and 3 month. At 11 years of age, He was receiving 2.4 MG a day (growing at 8 cm a year) and Lupron 15 MG/28 days for his early puberty. His bone age was 13.5 years and IGF-1 was 962NG/ML. He also had acanthosis nigricans

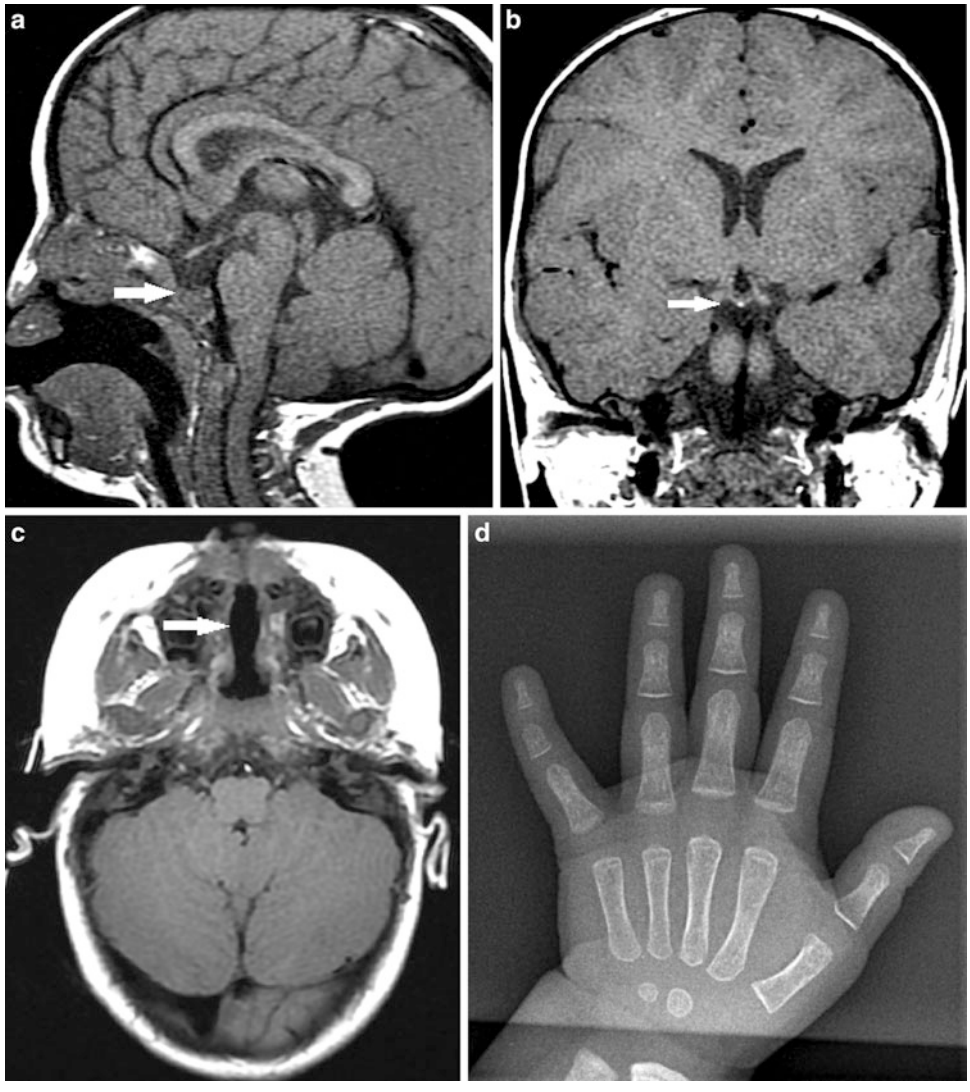

Fig. 3 (**a**–**d**) A 3-years-old girl was diagnosed with isolated growth hormone deficiency. She initially presented for small stature and abnormal MRI of her pituitary gland. Her height was 66.9 cm, which is less than the 3rd percentile. The weight was 7.3 kg, which is less than the 3rd percentile. Blood pressure 88/56, pulse 86. Systemic review was unremarkable for any systemic symptoms. There is decreased level of Insulin-like growth factor 1 (*IGF-1*) and IGF binding protein (*IGFBP-3*). Chromosomal study was reported as normal. MRI images showed hypoplasia of the pituitary lobes which lies within a shallow/small pituitary fossa (*arrow*) (**a**). Marked thinning of the pituitary stalk was noted with ectopic posterior pituitary which is located at the level of the infundibular recess of the third ventricle (*arrow*) (**b**). These findings are compatible with the pituitary stalk interruption syndrome. Cleft lip and cleft palate were also seen (*arrow*) (**c**). PA view of the left hand (**d**) was performed for bone age evaluation. It showed markedly delayed bone age (female standard for 9 months) (Courtesy of Dr. Grace Guo)

Ivemark Syndrome

Contents

Ivemark syndrome consists of visceroatrial heterotaxia associated with asplenia (Ivemark 1955). It is also known as asplenia syndrome, heterotaxy syndrome, cardiosplenic syndrome, right atrial isomerism (two morphologically right atrial appendages), or bilateral right-sidedness. The incidence of the syndrome is estimated to be 1/10,000–1/40,000 live births (Rose et al. 1975; Noack et al. 2002). Ivemark syndrome accounts for 1–3% of all congenital heart defects (Cesko et al. 1997).

Synonyms and Related Disorders

Asplenia syndrome; Asplenia with cardiovascular anomalies; Cardiosplenic syndrome; Familial isolated congenital asplenia; Heterotaxy syndrome; Right atrial isomerism

Genetics/Basic Defects

1. Inheritance.
    1. Autosomal recessive (Simpson and Zellweger 1973; Hurwitz and Caskey 1982; McChane et al. 1989) suggested by
        1. Reports of multiple affected siblings, both males and females, born to normal parents
        2. Reports of several instances of parental consanguinity
        3. Report of mutations in the gene encoding connexin 43 (Cx43) (Britz-Cunningham et al. 1995)
    2. Autosomal dominant: familial isolated congenital asplenia (Lindor et al. 1995; Gilbert et al. 2002)
2. Genes associated with human heterotaxy syndrome (Shiraishi and Ichikawa 2012).
    1. *ZIC3* (Zhu et al. 2007)
    2. *NODAL* (Mohapatra et al. 2007)
    3. *CFC1* (Bamford et al. 2000)
    4. *ACVR2B* (Kosaki et al. 1999a)
    5. *LEFTY2* (Kosaki et al. 1999b)
    6. *CITED2* (Bamforth et al. 2004)
    7. *GDF1* (Kaasinen et al. 2010).
3. Other possible cause: maternal diabetes.
4. Heterotaxy syndrome: heterotaxy results from failure of the embryo to establish normal left-right asymmetry (Bartram et al. 2005).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. A rare congenital disorder occurring in approximately 0.8% of patients with congenital heart disease
2. Often associated with complex cyanotic heart disease and an abnormal cardiac conduction system
3. Consisting of the following two groups of disease: two syndromes are causally and pathogenetically related to each other (Niikawa et al. 1983)
    1. Right isomerism (asplenia syndrome)
        1. Commonly has a combination of complete atrioventricular canal defect, total anomalous pulmonary venous return, double-outlet right ventricle, and pulmonary stenosis
        2. Often has paired atrioventricular nodes that may serve as the substrate for a special reentrant tachycardia ("nodal-to-atrioventricular nodal tachycardia")
    2. Left isomerism (polysplenia syndrome)
        1. Tends to have few complex cardiac anomalies and therefore a better prognosis
        2. Likely to have defective sinus and atrioventricular nodes that may result in sinus node dysfunction, junctional escape rhythm, and atrioventricular block
5. Morphological characteristics of heterotaxy syndrome (Shiraishi and Ichikawa 2012).
    1. Right isomerism
        1. Cardiovascular malformations
            1. Common atrium with bilateral right atrial appendages
            2. Mesocardia/dextrocardia
            3. Atrioventricular (AV) discordance
            4. Single right ventricle
            5. AV septal defect
            6. Common AV connection associated with AV valve regurgitation
            7. Double-outlet right ventricle
            8. Malposition of the great arteries
            9. Pulmonary stenosis or atresia
            10. Total anomalous pulmonary venous drainage (with/without pulmonary venous obstruction)
            11. Right aortic arch
            12. Bilateral superior vena cava
            13. Bilateral sinus node
            14. Paired (anterior/posterior) AV nodes with sling formation
        2. Extracardiac malformations/dysfunctions
            1. Bilateral right-sided lungs and bronchi
            2. Asplenia (susceptibility to *Streptococcus pneumoniae*)
            3. Symmetrical liver
            4. Right-sided stomach
            5. Malrotation of the intestine
            6. Bronchial cilia dysfunction
    2. Left isomerism
        1. Cardiovascular malformations
            1. Bilateral left atrial appendages
            2. Complete/incomplete AV septal defect
            3. Unbalanced ventricles
            4. Persistent left superior vena cava sometimes draining into the left atrium
            5. Interrupted hepatic portion of the inferior vena cava
            6. Partial anomalous pulmonary venous drainage
            7. Hypoplastic sinus node (sick sinus syndrome)
            8. Single/paired AV nodes
            9. Interruption between AV node and His bundles (congenital AV block)
        2. Extracardiac malformations
            1. Bilateral left-sided lungs and bronchi
            2. Bilateral hyparterial bronchi
            3. Polysplenia
            4. Midline liver
            5. Extrahepatic portal vein atresia

Clinical Features

1. Congenital absence of the spleen (asplenia) and associated anomalies (Putschar and Manion 1956)
2. Congenital heart malformations (Durairaj et al. 1976)

1. Cardiac malpositions (44%)
    1. Dextrocardia
    2. Right-sided aortic arch/aortic valve anomaly (Freedom 1974)
2. Venous system
    1. Systemic veins: bilateral superior vena cava (53%)
    2. Pulmonary veins
        1. Total anomalous pulmonary venous drainage (72%)
        2. Partial anomalous pulmonary venous drainage (6%)
3. Great vessels
    1. Transposition of the great arteries (Marino et al. 2002) (72%)
    2. Pulmonary stenosis or atresia (78%)
4. Coronary arteries: single coronary artery (19%)
5. Intracardiac defects
    1. Single ventricle (44%)
    2. Single AV valve (87%)
    3. Absent coronary sinus (85%)
    4. Endocardial cushion defect
    5. Double-inlet ventricle
    6. Discordant ventriculoarterial connection
6. Systemic and pulmonary venous connections in visceral heterotaxy with asplenia (Rubino et al. 1995)
7. Acute pulmonary embolism in an adult (Petitpierre et al. 2013)

3. Maldevelopment of the abdominal organs (Freedom 1972; Mishalany et al. 1982)
    1. Abnormalities of the mesenteric attachment (intestinal malrotation) (Ditchfield and Hutson 1998), a major predisposing cause of midgut volvulus
    2. Situs inversus (heterotaxia)
    3. A midline (central) liver
    4. Tubular stomach
    5. Imperforate anus
    6. Annular pancreas and obstructing duodenal bands
    7. Esophageal varices
    8. Duplication of stomach
    9. Congenital pancreatic cyst (Chahed et al. 2012)
    10. Agenesis of gallbladder
    11. Rudimentary pancreas
    12. Meckel diverticulum
    13. Esophageal atresia and TE fistula
    14. Hiatus hernia
    15. Gastric hypoplasia
    16. Malrotation/volvulus of bowel (Moller et al. 1971; Markowitz et al. 1977)
    17. Acute gastric volvulus (Nakada et al. 1997): a rare complication
    18. Cleft palate
    19. Duplication of the hindgut
    20. Aganglionosis
4. Bronchopulmonary isomerism
    1. Abnormal lobation of the lungs
        1. Bilaterally trilobed
        2. Bilaterally bilobed
    2. Bilateral eparterial bronchi
    3. Pulmonary hypoplasia
5. CNS malformations: uncommon
    1. Agenesis of the corpus callosum
    2. Porencephalic cyst
    3. Cerebellar cysts
    4. Focal cerebellar dysplasia
    5. Hydrocephalus
    6. Septum pellucidum abnormality
6. Genitourinary anomalies
    1. Horseshoe kidney
    2. Cystic kidney
    3. Bilobed urinary bladder
    4. Hydroureter
    5. Posterior urethral valves
    6. Ureteral valve with hydronephrosis
    7. Double collecting system
    8. Rectourethral fistula
    9. Bicornuate uterus
    10. Ovarian cysts
7. Endocrine abnormalities
    1. Fused or horseshoe adrenal
    2. Absent adrenal
8. Musculoskeletal abnormalities
    1. Equinovarus deformity
    2. Overlapping toes
    3. Clubbing of hands
    4. Absent radii
9. Miscellaneous
    1. Microphthalmia
    2. Single umbilical artery
10. Prognosis (Tkebuchava et al. 1997)
    1. Prognosis related to cardiac malformations

1. Severe and incompatible with life (as a rule).
2. Anoxia.
3. Cyanotic neonates die from cardiac insufficiency.
4. Most die from cardiac disease during the first year of life (usually the first month).
5. Complications of surgery.
6. Hemorrhage.

2. Prognosis related to asplenia (Gilbert et al. 2002)
   1. Greater risk from infection for those who survive the first 12 months (Waldman et al. 1977).
   2. Persistent thrombocytosis is present in patients with asplenia syndrome (Yamamura et al. 2013). It may greatly contribute to the development of thromboembolism during the management of congenital heart disease than expected.
   3. Sudden death in infancy (Kiuchi et al. 1988) from sepsis and impaired resistance to infection.
3. Long-term prognosis of heterotaxy patients (Shiraishi and Ichikawa 2012)
   1. Protein-losing enteropathy: one of the most severe manifestation of the failing Fontan circulation, occurring in 5–10% of the total postoperative cases
   2. Arrhythmias
   3. Heart failure
   4. Hepatic dysfunction
4. Perinatal and infant outcomes of prenatal diagnosis of heterotaxy syndrome (Escobar-Diaz et al. 2014)
   1. Bradyarrhythmia: the only predictor of fetal death
   2. Pulmonary vein stenosis and noncardiac anomalies: predictors of postnatal death

Diagnostic Investigations

1. Echocardiography for delineating congenital heart defects (Biggar et al. 1981)
2. Diagnosis of asplenia
   1. No splenic uptake on technetium sulfur colloid scan
   2. The presence of Howell-Jolly bodies in a peripheral blood smear after the first week of life
3. Radiography of visceral patterns (Freedom and Fellows 1973)
4. Immunologic assessment in congenital asplenia
   1. Quantitation of serum immunoglobulins
   2. Most common pathogens
      1. In children less than 6 months of age
         1. *Escherichia coli*
         2. *Klebsiella*
      2. In children surviving past 6 months of age
         1. *Haemophilus influenzae*
         2. *Pneumococci* (Gilbert et al. 2002)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis of right atrial isomerism by fetal echocardiography (Colloridi et al. 1994; Noack et al. 2002)
   1. No identifiable spleen (the fetal spleen can usually be detected at 20 weeks of gestation in the left gastrorenal angle) (Chitayat et al. 1988)
   2. Visceral heterotaxy
   3. Visualization of the pulmonary venous return and outflow obstruction and characterization of the rhythm disturbances (Lin et al. 2002)
   4. Levocardia
   5. Complete atrioventricular septal defect
   6. Double-outlet right ventricle
   7. Dextro-malposition of the great arteries
   8. Pulmonary atresia/stenosis
   9. Other cardiac anomalies
3. Management
   1. Although the leading causes of death in fetuses and children with heterotaxy

syndromes are cardiac, a small subset of fetuses has extracardiac anomalies with significant impact on the outcome. These anomalies often escape prenatal detection; therefore, neonates at risk have to be monitored for bowel obstruction, biliary atresia, and immune dysfunction in order to allow timely intervention in a multidisciplinary approach (Gottschalk et al. 2015).

2. In asplenic children, early diagnosis, antibiotic prophylaxis, and immunization for encapsulated bacteria can decrease the risk of morbidity and mortality due to invasive infections (Erdem et al. 2015).
3. Palliative cardiac surgery for congenital heart defects (Ando et al. 1976).
4. Surgical intervention for gastrointestinal malformations and other anomalies (Aoyama and Tateishi 1986).
5. Cardiac transplantation may be the only option for patients with severe heart failure, intractable arrhythmias, or recurrent protein-losing enteropathy (Shiraishi and Ichikawa 2012).

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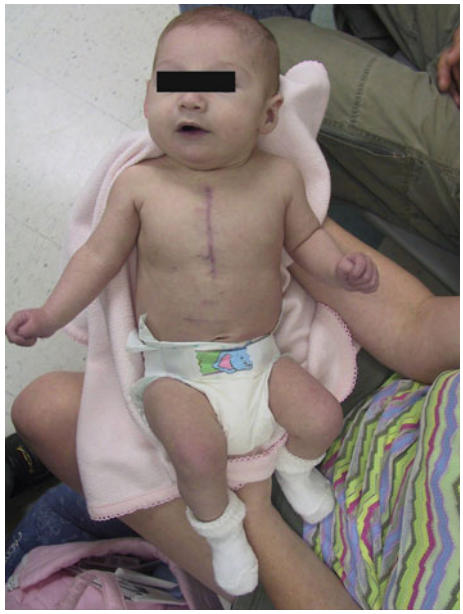

Fig. 1 A 3-month-old with Ivemark syndrome who has asplenia with complex cardiovascular malformations (AV canal, single ventricle, transposition of the great vessels, pulmonary atresia, and total anomalous pulmonary venous return). She also has malrotation of intestine

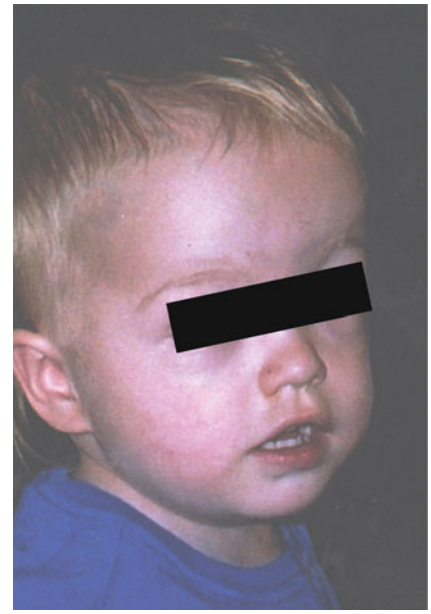

Fig. 2 A 19-month-old boy with Ivemark syndrome. He had heterotaxy syndrome with asplenia, situs inversus, and complex congenital heart defects consisting of a single ventricle, atrioventricular septal defect with small ostium primum ASD, pulmonary stenosis, interrupted IVC with azygous continuation to a left SVC, right aortic arch, and congenital complete heart block

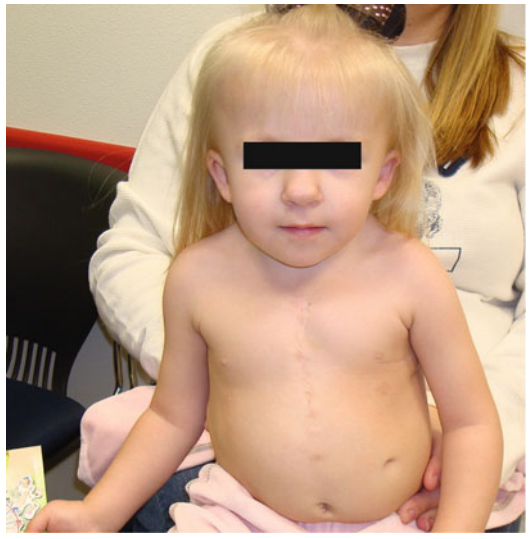

Fig. 3 A 25-month-old girl with Ivemark syndrome. She had dextrocardia, situs inversus, complete AV canal, interrupted inferior vena cava, trachea compression by aorta, and status post pulmonary artery banding. Her complete AV canal was surgically repaired. Chromosome analysis was normal with normal FISH for DiGeorge syndrome

Jarcho-Levin Syndrome

Contents

In 1938, Jarcho and Levin (1938) first described a syndrome of malformations with abnormal fusion of thoracic vertebrae and ribs associated with a short trunk and respiratory insufficiency. At present, Jarcho-Levin syndrome is an eponym used to describe a variety of clinical phenotypes, consisting of short-trunk dwarfism associated with rib and vertebral anomalies. Two phenotypic subtypes of spondylothoracic dysostosis and spondylocostal dysostosis have recently been proposed.

Synonyms and Related Disorders

Costovertebral dysplasia; Costovertebral segmentation anomalies; Spondylocostal dysostosis/dysplasia (Jarcho-Levin syndrome); Spondylothoracic dysostosis/dysplasia (Lavy-Moseley syndrome)

Genetics/Basic Defects

1. Inheritance and molecular defects (Cornier et al. 2003)
    1. The presence of considerable genetic heterogeneity with varied clinical presentations and associated abnormalities (Roberts et al. 1988)
    2. Spondylothoracic dysostosis or Lavy-Moseley syndrome
        1. Autosomal recessive inheritance (Romeo et al. 1991; Bautista et al. 1997)
        2. Linked to chromosome 2q32.1
        3. More severe respiratory compromise
        4. Largely linked to Puerto Rican cohorts and is thought to be associated to the *MESP2* gene, also a Notch pathway gene
    3. Spondylocostal dysostosis or Jarcho-Levin syndrome (Whittock et al. 2004; Turnpenny and Young 2013)
        1. Inheritance: either autosomal recessive (Turnpenny et al. 1991; Turnpenny and Young 2013) or autosomal dominant (Rimoin et al. 1968).
        2. Mutations in the delta-like three gene (*DLL3*) on chromosome 19q13.1-q13 (Bulman et al. 2000; Turnpenny et al. 1999, 2003; Bonafe et al. 2003).
            1. As the major cause of autosomal recessive spondylocostal dysostosis.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. *DLL3* (Dunwoodie et al. 2002) encodes a ligand in the Notch gene signal pathway. When mutated, defective somitogenesis occurs resulting in a consistent and distinctive pattern of abnormal vertebral segmentation affecting the entire spine.
3. Mutated mesoderm posterior two homolog gene (*MESP2*) that codes for a basic helix-loop-helix transcription factor was found to cause spondylocostal dysostosis in one consanguineous family with two affected children (linkage to 15q21.3-15q26.1) (Whittock et al. 2004; Cornier et al. 2008).
4. Mutation of the Lunatic Fringe gene in humans causes spondylocostal dysostosis with a severe vertebral phenotype (Sparrow et al. 2006).
5. Autosomal dominant spondylocostal dysostosis is caused by mutation in *TBX6* (Sparrow et al. 2013a).
6. Mutation of HES7 in a large extended family with spondylocostal dysostosis and dextrocardia with situs inversus (Sparrow et al. 2013b)

2. Pathogenesis
   1. Vertebral anomalies: probably attributed to defective segmentation of the somite at about the fourth or fifth week of intrauterine life.
   2. Costal anomalies: probably secondary to the vertebral anomalies.
   3. *Pax1* and *Pax9* might be required for the phenotypic expression of Jarcho-Levin syndrome (Bannykh et al. 2003).

Clinical Features

1. Spondylothoracic dysostosis (Herold et al. 1988; Karnes et al. 1991; Mortier et al. 1996; Cornier et al. 2004)
   1. Vertebral segmentation and formation defects throughout cervical, thoracic, and lumbar spine
      1. Hemivertebrae
      2. Block vertebrae
      3. Unsegmented bars
   2. Fusion of all the ribs at the costovertebral joints bilaterally
   3. Absence of intrinsic rib anomalies
   4. Other clinical features
      1. Short-trunk dwarfism
      2. Craniofacial features
         1. Brachycephaly
         2. Low posterior hairline
         3. Prominent nasal bridge
         4. High-arched palate
      3. Short and rigid neck
      4. Short thorax
      5. Protuberant abdomen
      6. Inguinal and umbilical hernias
      7. Urinary tract abnormalities
      8. Talipes equinovarus
   5. Prognosis: poor but not an invariably lethal condition with 56% of survival among the prospectively evaluated patients
      1. Normal intelligence
      2. Progressive kyphosis and neurologic compromise complicating spondylothoracic dysplasia in infancy (Jarcho-Levin syndrome) (Mooney and Emans 1995; Martinez-Frias and Urioste 1994)
      3. Respiratory complications such as pneumonia
      4. Congestive heart failure
      5. Pulmonary hypertension
2. Spondylocostal dysostosis (Karnes et al. 1991; Mortier et al. 1996)
   1. Constitutes a heterogeneous group of radiologic phenotypes with axial skeletal malformations
   2. Generally milder phenotype
   3. Multiple vertebral segmentation and formation defects
   4. Typical findings
      1. Intrinsic asymmetric rib anomalies
         1. Broadening
         2. Bifurcation
         3. Fusion
      2. No symmetric fusion of the ribs
      3. Do not display a fanlike configuration of the thorax
      4. No cervical spine anomalies in some patients

5. Short-trunk dwarfism
5. Associated anomalies
    1. Congenital heart disease
    2. Urogenital and anal anomalies
    3. Limb abnormalities
    4. Torticollis
    5. Diaphragmatic, umbilical, and inguinal hernias
6. Prognosis (Hayek et al. 1999)
    1. A good prognosis, due in part to the asymmetry of the thoracic anomalies resulting in a less restrictive thorax
    2. Long survival
    3. Normal intelligence

Diagnostic Investigations

1. Radiography (Cornier et al. 2003)
    1. Spondylothoracic dysostosis
        1. Bilateral fanning of the ribs with posterior fusion, giving the appearance of a common origin of ribs at the posterior thoracic spine
        2. A decreased number of cervical, thoracic, and lumbar vertebrae
        3. Multiple vertebral segmentation and formation defects
            1. Block and wedge vertebrae
            2. Unsegmented bars
            3. Hemivertebrae
            4. Anterior-posterior-lateral failure of closure
        4. Symmetric posterior fusion of the ribs: characteristic radiographic finding (Berdon et al. 2011)
    2. Spondylocostal dysostosis
        1. Multiple vertebral formations and segmentation defects along the entire spine
            1. A decreased number of cervical, thoracic, and lumbar vertebrae
            2. Block and wedge vertebrae
            3. Agenesis of the coccygeal region
            4. Progressive scoliosis of the thoracic spine due to tethering effect secondary to the rib anomalies
        2. Asymmetric intrinsic rib malformations
            1. Broadening
            2. Bifurcation
            3. Fusion
            4. Do not display a fanlike configuration of the thorax as in spondylothoracic dysostosis
        3. Asymmetrical abnormalities of the vertebral bodies and ribs: characteristic radiographic finding (Berdon et al. 2011)
2. Reconstructed tridimensional CT scan of the chest
    1. Spondylothoracic dysostosis
        1. Bilateral rib fusion at the costovertebral junction.
        2. Segmentation and formation defects in all cervical, thoracic, and lumbar vertebrae. Sacrococcygeal regions are spared from any abnormality.
        3. Increase in the coronal diameter of the thoracic and lumbar vertebrae which acquire a sickle-like appearance.
    2. Spondylocostal dysostosis
        1. Varying extent of the thoracic fusion
        2. Thoracic fusion always asymmetric with respect to each side of the thorax
        3. Increase in the coronal diameter of the thoracic and lumbar vertebrae which acquire a sickle-like appearance
3. Pulmonary function tests for restrictive lung disease
4. Molecular genetic analysis (Turnpenny and Young 2013)
    1. *DLL3* mutations in spondylocostal dysostosis (homozygous or compound heterozygous mutations).
    2. Other subtypes are defined by identification of two mutant alleles in other three genes known to be associated with autosomal recessive spondylocostal dysostosis: *MESP2*, *LFNG*, and *HES7*.

Genetic Counseling

1. Recurrence risk
    1. Autosomal recessive inheritance (spondylothoracic dysostosis and spondylocostal dysostosis)

1. Patient's sib: 25%
2. Patient's offspring: not increased unless the spouse is also a carrier; in which case, there is a 50% risk of having an affected offspring

2. Autosomal dominant inheritance (spondylocostal dysostosis)
   1. Patient's sib: not increased unless a parent is affected; in which case, there is a 50% risk of having an affected sibling
   2. Patient's offspring: 50%

2. Prenatal diagnosis by ultrasonography
   1. Ultrasonography (Tolmie et al. 1987; Marks et al. 1989; Eliyahu et al. 1997; Lawson et al. 1997; Kauffmann et al. 2003).
      1. Grossly distorted thoracic and lumbar spine
      2. Marked kyphoscoliosis
      3. Multiple vertebral segmentation anomalies
      4. Fanned ribs from fused thoracic vertebral bodies (Wong and Levine 1998)
      5. A small chest with foreshortened spine
      6. Increased fetal nuchal translucency thickness (Hull et al. 2001)
      7. Inguinoscrotal hernia in a fetus with vertebral anomalies: a clue for Jarcho-Levin syndrome and other pathologies that increase abdominal pressure (Basaran et al. 2010)
   2. Three-dimensional computed tomography of fetal spondylothoracic dysostosis at 23 weeks' gestation (Ranes et al. 2012).
   3. Prenatal diagnosis by molecular genetic analysis of *DLL3* (Whittock et al. 2003), *MESP2* (Whittock et al. 2004), *LFNG*, or *HES7* gene mutations by sequencing entire coding region of fetal DNA obtained from amniocentesis or CVS, provided the disease-causing allele has been previously identified.
   4. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have identified previously.

3. Management (Cornier et al. 2003)
   1. Minimize positive end-expiratory pressure to avoid bronchopulmonary dysplasia.
   2. Continuous feeding instead of in boluses to avoid stomach distension that will lead to increase diaphragmatic pressure.
   3. Aggressive treatment of infections.
   4. Treat the spinal deformities.
   5. Management of thoracic insufficiency syndrome in patients with Jarcho-Levin syndrome using VEPTRs (vertical expandable prosthetic titanium ribs): improves thoracic symmetry, control spinal deformity, and was associated with improved clinical respiratory function (Karlin et al. 2014).

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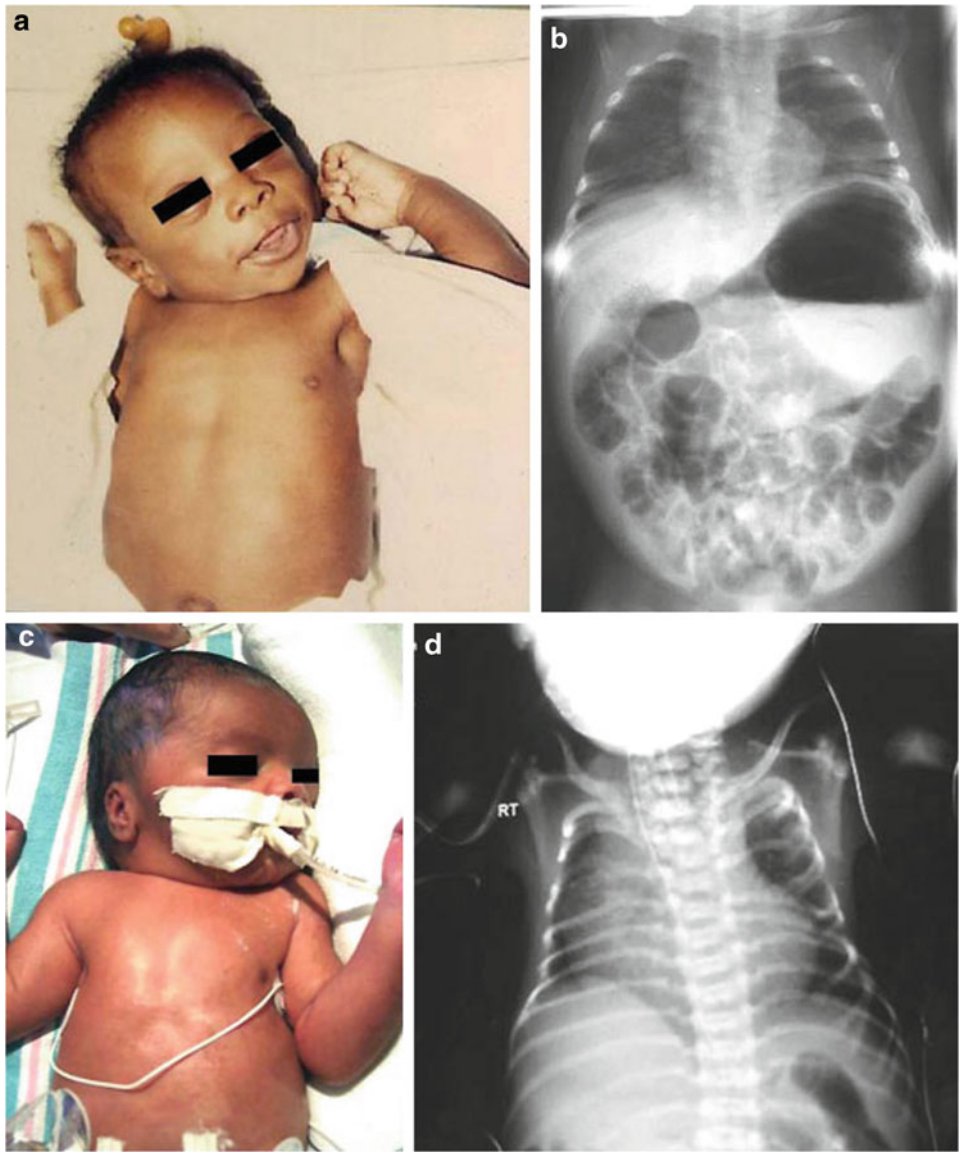

Fig. 1 (**a**–**d**) Two infants (**a**, **c**) with spondylocostal dysostosis with typical crablike deformities of the chest with fused ribs (radiographs) (**b**, **d**)

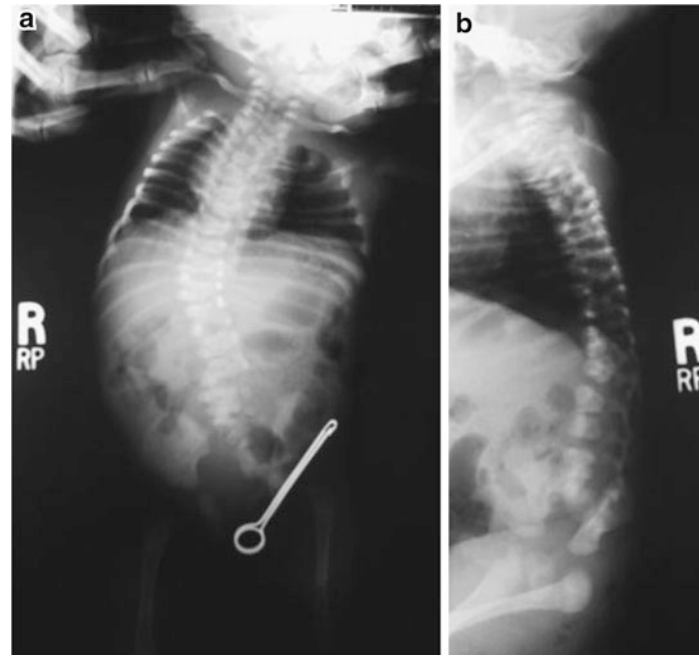

Fig. 2 (**a**, **b**) Radiographs of another infant with spondylocostal dysostosis showing fused ribs and fused vertebrae

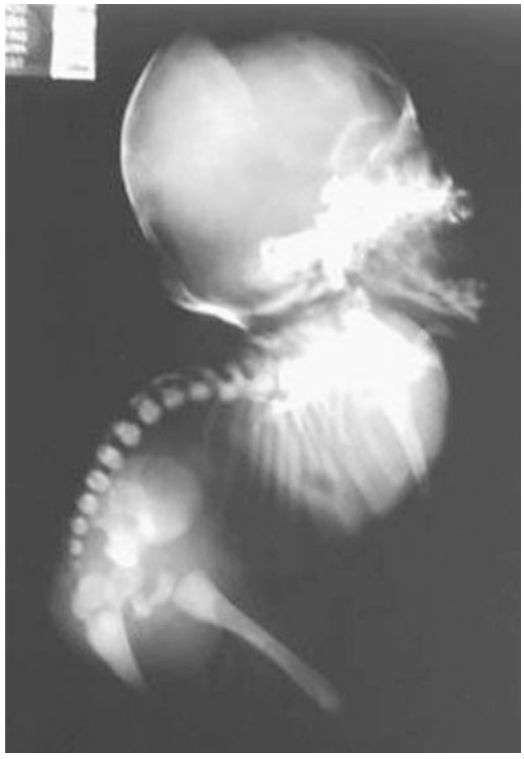

Fig. 3 Radiographs of another infant with spondylothoracic dysostosis showing severe chest deformity

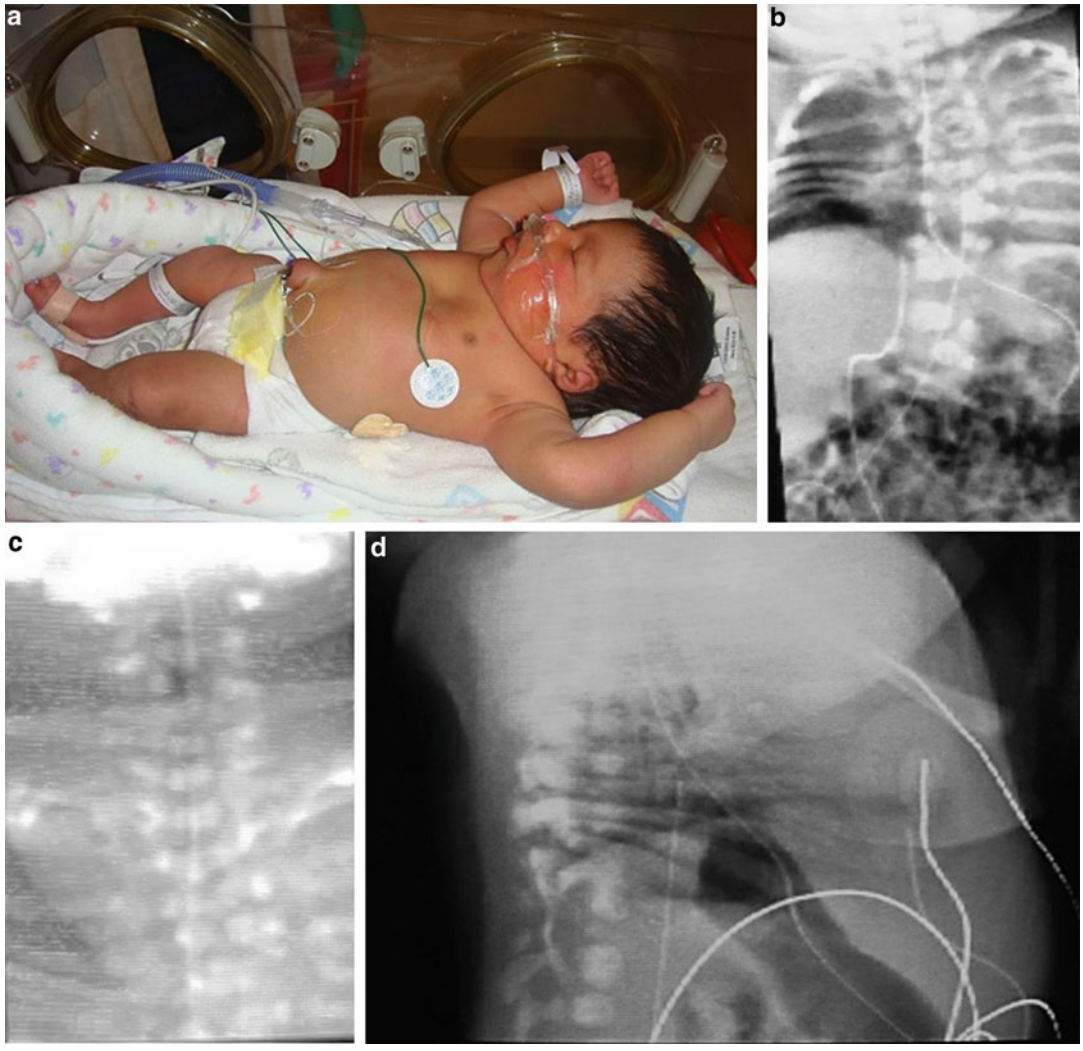

Fig. 4 (**a**–**d**) An Arabic female newborn (**a**) was evaluated for multiple vertebral and rib anomalies. Her prenatal ultrasound showed vertebral anomalies, hydramnios, and possible TE fistula. Postnatally, she was noted to have short neck, short chest, and protuberant abdomen. The postnatal radiographs (**b**–**d**) showed vertebral segmentation and formation defects throughout cervical, thoracic, and lumbar spine. Fusion of the ribs was present. Clinical diagnosis of Jarcho-Levin syndrome was made. The parents are first cousins. Molecular genetic diagnosis showed positive *DLL3* mutation. This patient is apparently homozygous in the *DLL3* gene for a frameshift mutation defined as c.329delT which is predicted to result in premature protein termination (p.Val110GlyfsStope22). This particular mutation has not been reported previously. However, it is the type expected to be pathogenic (e.g., Turnpenny et al. 2003). The homozygous c.329delT mutation is very likely the cause of recessive spondylocostal dysostosis

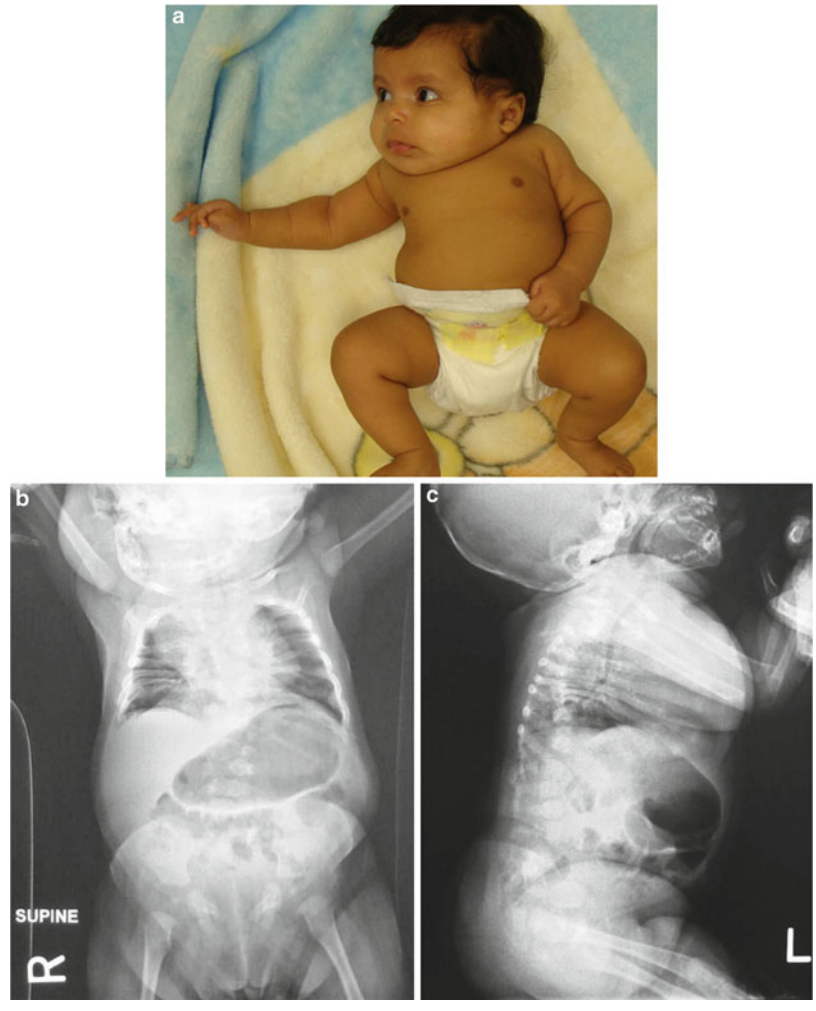

Fig. 5 (**a**–**c**) The previous infant (**a**) at 3 months of age with follow-up X-rays (**b**, **c**)

Joubert Syndrome

Contents

In 1969, Joubert et al. (1969) first documented three brothers and one sister who had episodic hyperpnea, abnormal eye movements, ataxia, mental retardation, and cerebellar vermian hypoplasia and aplasia. Later in 1977, Boltshauser and Isler (1977) reported three more cases with variable degrees of clinical symptoms and suggested the syndrome be called Joubert syndrome.

The prevalence in the United States has been estimated at approximately 1:100,000 (Parisi et al. 2006). This is likely to be an underestimate due to lack of recognition of the clinical signs or MRI findings and failure to diagnose the condition in more mildly affected individuals (Parisi et al. 2007).

Synonyms and Related Disorders

Cerebello-oculo-renal syndrome; Cerebelloparenchymal disorder; Joubert syndrome and related disorders (JSRD); Joubert-Boltshauser syndrome

Genetics or Basic Defects

1. Predominantly inherited in an autosomal recessive manner
2. JSRD caused by mutation of *OFD1*: inherited in an X-linked recessive manner
3. Causative gene defects (genetic complexity) in individuals with Joubert syndrome and related disorders (JSRD) (Parisi et al. 2006; Harris 2007)
    1. *NPHP1* (nephronophthisis 1, 2q13) gene homozygous deletion associated with juvenile nephronophthisis present in a subset of individuals with Joubert syndrome (Parisi et al. 2004; Castori et al. 2005) (1–2%)
    2. *AHI1* (Abelson helper integration site, 6q23.11) gene mutations (Dixon-Salazar et al. 2004; Parisi et al. 2006) (10–15%)
    3. *CEP290* (encoding centrosomal protein, 12q21.3) gene mutations causing pleiotropic forms of Joubert syndrome (Valenti et al. 2006) (approximately 10%)
    4. *NPHP6* (encoding centrosomal protein nephrocystin-6, 12q21.3) gene mutations in Joubert syndrome (Sayer et al. 2006)
    5. *ARL13B* cilia gene mutation leading to classical form of Joubert syndrome (Cantagrel et al. 2008)
    6. Mutations in three genes (MKS3, CC2D2A, and RPGRIP1L) in COACH syndrome (Joubert syndrome with congenital hepatic fibrosis) (Doherty et al. 2010)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_137

7. Mutations in *CSPP1* lead to classical Joubert syndrome (Akizu et al. 2014)
8. Overall, sequence variants in one of the *TCTN* genes (*TCTN1*, *TCTN2*, and *TCTN3*) represent rare causes for Joubert syndrome and Meckel-Gruber syndrome. Interestingly, all patients have a clear neurological phenotype with either vermis hypoplasia or occipital encephalocele (Huppke et al. 2015)
9. Mutations in *B9D1* and *MKS1* cause mild Joubert syndrome: expanding the genetic overlap with the lethal ciliopathy Meckel syndrome (Romani et al. 2014)

Clinical Features

1. Clinical features often cited as necessary for the diagnosis of classic Joubert syndrome (Joubert et al. 1969; Saraiva and Baraitser 1992; Steinlin et al. 1997; Maria et al. 1999a, b; Parisi et al. 2006, 2007).
    1. Cranial MRI findings of molar tooth sign (100%)
        1. Midline cerebellar vermis hypoplasia
        2. Deepened interpeduncular fossa
        3. Thick, elongated superior cerebellar peduncles
    2. Hypotonia in infancy (100%)
    3. Developmental delay or mental retardation, of variable severity (100%)
    4. Autism and autistic behavior (Holroyd et al. 1991; Ozonoff et al. 1999; Takahashi et al. 2005)
    5. One or both of the following (not absolutely required but supportive of the diagnosis):
        1. Irregular breathing pattern in infancy (episodic tachypnea and/or apnea)
        2. Abnormal eye movements (including nystagmus, jerky eye movements, and oculomotor apraxia or difficulty with smooth visual pursuits) (Sturm et al. 2010)
2. Typical facial features during childhood (Maria et al. 1999a; Braddock et al. 2007).
    1. Long face
    2. Frontal prominence
    3. Bitemporal narrowing
    4. High rounded eyebrows
    5. Broad nasal bridge
    6. Mild epicanthus
    7. Anteverted nostrils
    8. Triangular-shaped open mouth with the tongue frequently resting on the lower lip
    9. Lower lip eversion
    10. Low-set and coarse ears
3. Joubert syndrome may be considered a cerebello-oculo-renal syndrome because of the coincident involvement of all three organ systems (Valente et al. 2003).
4. JSRD: disorders sharing the MRI molar tooth sign (Gleeson et al. 2004; Brancati et al. 2010). Clinical features in JSRD with the molar tooth sign (MTS) (Maria et al. 1997; Chance et al. 1999; Parisi et al. 2007) are:
    1. Other central nervous system anomalies
        1. Hypotonia
        2. Mental retardation
        3. Oculomotor apraxia
        4. Breathing abnormalities
        5. Encephalocele
        6. Polymicrogyria (Dixon-Salazar et al. 2004; Glordano et al. 2009)
    2. Ocular abnormalities (Tusa and Hove 1999)
        1. Ocular coloboma
        2. Retinal dystrophy
        3. Leber congenital amaurosis (Ivarsson et al. 1993)
    3. Renal diseases
        1. Cystic dysplastic kidneys
        2. Nephronophthisis
    4. Hepatic fibrosis
    5. Polydactyly
    6. Tongue hamartomas/oral frenula
5. Proposed classification system for Joubert syndrome and related disorders (Zaki et al. 2008).
    1. Primary criteria include:
        1. Neurological signs
            1. Hypotonia/ataxia
            2. Developmental delay
            3. Oculomotor apraxia
        2. Radiological hallmark of molar tooth sign
        3. Occasional features (seen in all forms)

1. Mental retardation
2. Breathing abnormalities
3. Postaxial polydactyly
4. Mild retinopathy
5. Polymicrogyria
6. Corpus callosum abnormality

2. Secondary criteria.
   1. Joubert syndrome may include
      1. Mild ocular sign (retinopathy)
      2. Mild renal sign
      3. Postaxial polydactyly
   2. Cerebellar vermis hypo-/aplasia-oligophrenia-ataxia-ocular coloboma-hepatic fibrosis (COACH syndrome): at least one (typically both)
      1. Hepatic fibrosis
      2. Coloboma (choroidal or retinal)
   3. Cerebello-oculo-renal syndrome (CORS): at least one ocular sign and at least one renal sign
      1. Ocular signs: retinopathy (typically congenital blindness), coloboma
      2. Renal signs: cysts, nephronophthisis, and renal failure
   4. Orofaciodigital syndrome type VI (OFD-VI): at least one orofacial sign and at least one digital sign
      1. Orofacial signs: cleft lip/palate, tongue tumors, and notched upper lip
      2. Digital signs: mesoaxial polydactyly (most specifically), preaxial polydactyly, and bifid digits
3. The presence of the primary criteria and the secondary criteria is used to support the diagnosis of a specific type of JSRD.

Diagnostic Investigations

1. Molar tooth sign, demonstrated by a high-quality MRI scan of the brain (Zaki et al. 2008) (Parisi et al. 2007)
   1. Result from images of cerebellar vermis hypoplasia, thick and maloriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa (Maria et al. 1999b)
   2. Disorders presenting as "molar tooth sign" (Brancati et al. 2010; Dirik et al. 2013)
      1. Jubert syndrome
      2. Cerebello-oculo-renal syndrome (Satran et al. 1999)
      3. Dekaban-Arima syndrome (chorioretinal coloboma with cerebellar vermis aplasia)
      4. COACH syndrome (coloboma, oligophrenia (mental retardation), ataxia, cerebellar vermis hypoplasia, and hepatic fibrosis) (Verloes and Lambotte 1989; Satran et al. 1999)
      5. Varadi-Papp syndrome (orofaciodigital type VI): tongue hamartomas, mesoaxial hand polydactyly, and preaxial foot polysyndactyly with bifid hallux
      6. A minority of cases with Senior-Loken syndrome (nephronophthisis and Leber congenital amaurosis)
   3. Extraordinarily useful in differentiating JSRD conditions from other hindbrain malformations
      1. Dandy-Walker malformation (Maria et al. 2001)
      2. Isolated cerebellar vermis hypoplasia
      3. Pontocerebellar hypoplasia
      4. Rhombencephalosynapsis
2. High-resolution diffusion tensor imaging and tractography (Hsu et al. 2015)
   1. The absence and/or thinning of the dorsal pontocerebellar tract
   2. Abnormal thickening of the ventral pontocerebellar tract
   3. Abnormal decussation of superior cerebellar peduncles and the absence of red dot sign: a further indication that they represent a spectrum of abnormal midline axonal migration
3. Medical genetics evaluation
   1. Family history
   2. Demonstration of congenital anomalies
      1. Micro-/macrocephaly
      2. Facial dysmorphism
      3. Clefts
      4. Lingual nodules

5. Polydactyly
6. Genital anomalies
7. Others

4. Developmental assessment
5. Neurologic evaluation for cerebellar function
6. EEG for seizures
7. Polysomnogram for abnormal sleep history (apnea/hyperpnea)
8. Ophthalmological evaluation
   1. Eye malformations such as coloboma
   2. Retinopathy or blindness
   3. Abnormal eye movement such as nystagmus or oculomotor apraxia
9. Abdominal ultrasonography
   1. Renal cystic disease
   2. Liver fibrosis
10. Clinical laboratory tests
    1. BUN
    2. Creatinine
    3. CBC for anemia
    4. First-morning void urinalysis with specific gravity
11. Liver function tests
    1. Transaminases
    2. Albumin
    3. Bilirubin
    4. Prothrombin time
12. Chromosome analysis: no consistent chromosomal aberrations identified
13. Molecular genetic testing
    1. FISH or microsatellite marker analysis for homozygous deletion of the *NPHP1* gene associated with juvenile nephronophthisis (Hildebrandt et al. 2001; Parisi et al. 2004) identified in only 1–2% of subjects with JS (Parisi et al. 2006).
    2. Molecular testing for mutations in the *AHI1* gene and the *CEP290* gene: clinically available. Each of these genes is estimated to account for about 10% of cases of JSRD. Mutations in both *AHI1* and *CEP290* are more likely to be associated with retinal disease, with *CEP290* implicated in some cases with congenital blindness or Leber amaurosis (den Hollander et al. 2006; Sayer et al. 2006).
    3. Other tests used in JSRD (Parisi and Glass 2013). To date, biallelic pathogenic variants in one of the following 19 genes are identified in about 50% of individuals with a JSRD: *TMEM67* (*MKS3*), *RPGRIP1L*, *CC2D2A*, *ARL13B*, *INPP5E*, *OFD1*, *TMEM216*, *KIF7*, *TCTN1*, *TCTN2*, *TMEM237*, *CEP41*, *TMEM138*, *C5orf42*, *TMEM231*, and *TCTN3*.
    4. In rare families with a large number of affected children and/or known consanguinity, linkage analysis may be feasible on a research basis.
    5. Using a combination of linkage mapping and massively parallel sequencing of the X-chromosome exome, an 18-bp deletion was identified in exon 8 of the orofaciodigital syndrome type 1 (*OFD1*) gene in a family with X-linked Joubert syndrome (Field et al. 2012).
    6. The diagnostic utility of whole-exome sequencing in Joubert syndrome and related disorders (Tsurusaki et al. 2013).

Genetic Counseling

1. Recurrence risk (Parisi and Glass 2013).
   1. Autosomal recessive inheritance
      1. Patient's sib: a 25% risk
      2. Patient's offspring: low recurrence risk unless the partner is a carrier or affected
   2. X-linked recessive inheritance
      1. Patient's sib: If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant are unlikely to be affected; however, no carrier females have been identified. If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than

that of the general population because of the possibility of maternal germline mosaicism.
    2. Offspring of a male proband: No affected male has reproduced. Males with X-linked JSRD will pass the pathogenic variant to all of their daughters and none of their sons.
2. Prenatal diagnosis.
    1. Possible for pregnancy at risk, provided the disease-causing mutations have been identified in the affected individual
    2. Prenatal imaging for all other at-risk pregnancies
        1. Prenatal diagnosis of Joubert syndrome has been accomplished as early as the first trimester on the basis of extracranial anomalies, such as polydactyly or renal cysts, and major structural CNS malformations such as encephalocele (Wang et al. 1999).
        2. Early diagnosis: more challenging when extracranial abnormalities are not present, because cerebellar vermis hypoplasia cannot be reliably diagnosed until 18–20 weeks gestation (Bromley et al. 1994) and the MTS has not been observed before 27 weeks gestation (Fluss et al. 2006).
    3. Prenatal diagnosis: suspected at 32 weeks gestation in the absence of a family history by observation of vermian agenesis, bilateral ventriculomegaly, postaxial polydactyly, and episodes of tachypnea (Aslan et al. 2002)
    4. Sensitivity and specificity of prenatal imaging findings for JSRD: not known (Doherty et al. 2005)
3. Preimplantation genetic diagnosis may be an option for some families in which the pathogenic variant(s) have been identified.
4. Management.
    1. No specific treatments for Joubert syndrome exist.
    2. Supportive treatments with interventions for individuals with developmental disabilities:
        1. Special education programs
        2. Physical, occupational, and speech therapy
        3. Adaptive equipments as needed
        4. Seizure control
    3. Dialysis and renal transplantation for nephronophthisis.
    4. Specific surgical interventions for esophageal varices or portal hypertension in liver fibrosis.
    5. Liver transplantation for COACH syndrome.

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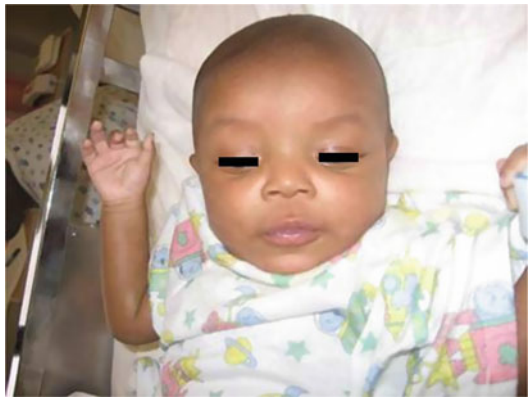

Fig. 1 Patient 1 with Joubert syndrome. This 6-week-old boy presented with respiratory distress, tachypnea with episodes of apnea, and abnormal eye movement. Ultrasound revealed multiple bilateral renal cysts

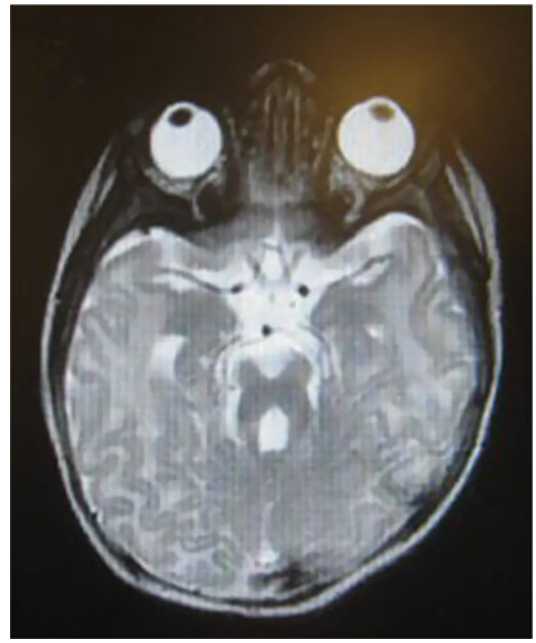

Fig. 3 MRI of the brain showed hypoplasia of cerebellum with "molar tooth sign" leading to diagnosis of Joubert syndrome

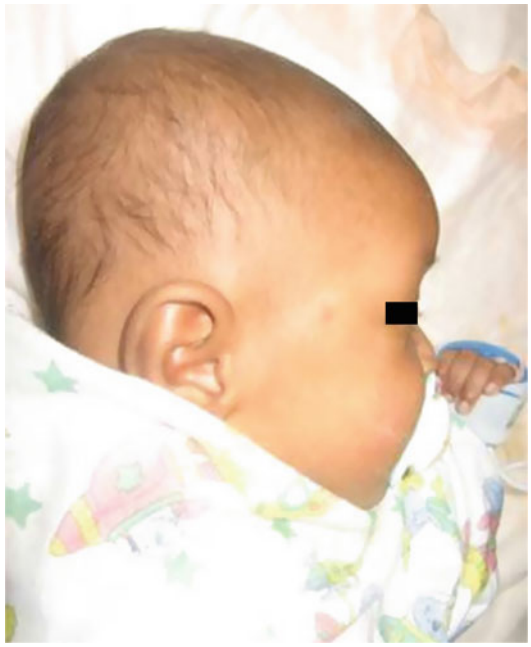

Fig. 2 Lateral view of the patient

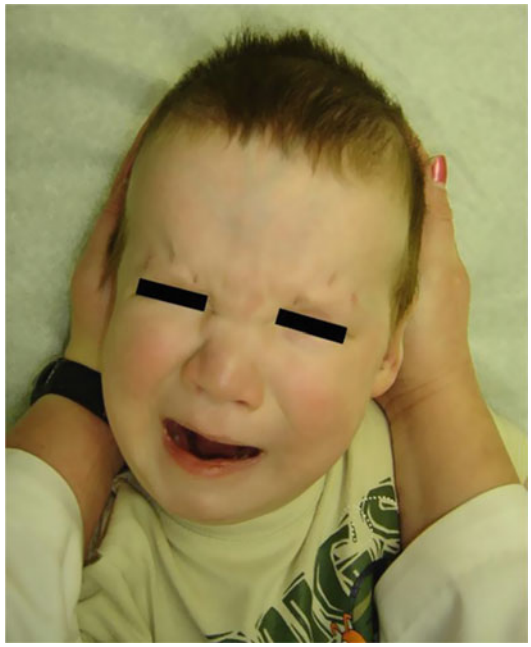

Fig. 4 This 22-month-old boy was evaluated for Joubert syndrome. He was delivered at 41 weeks of gestation via cesarean section with cord wrapping around the neck twice. Birth weight was 4,035 g and birth length 55 cm. Fetal ultrasound examination showed possible cerebellar hypoplasia. Follow-up MRI of the brain showed "molar tooth sign" consistent with Joubert syndrome. He had neonatal breathing dysregulation, delayed psychomotor development, hypotonia, and macrocephaly with a prominent forehead, high-round eyebrows, low set and "tilted" ears, abnormal jerky eye movement with right chorioretinal coloboma, epicanthal folds, and ptosis. FISH using a probe to the *NPHP1* locus showed no deletion of the *NPHP1* region. The result does not exclude the clinical diagnosis of Joubert syndrome and does not exclude a mutation in the *NPHP1* gene or other genes not detectable with this assay

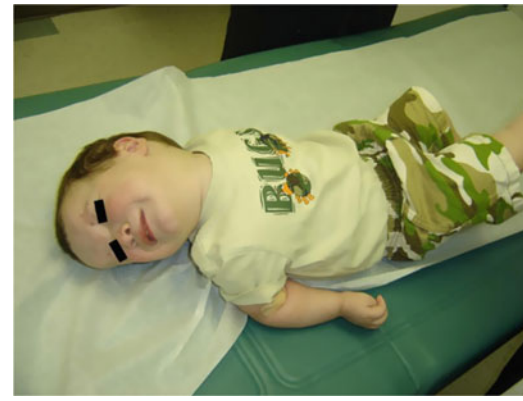

Fig. 5 Note psychomotor retardation

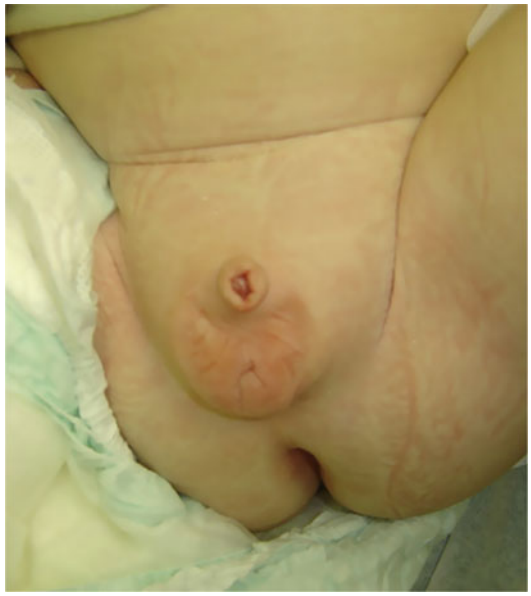

Fig. 6 Note the genital hypoplasia

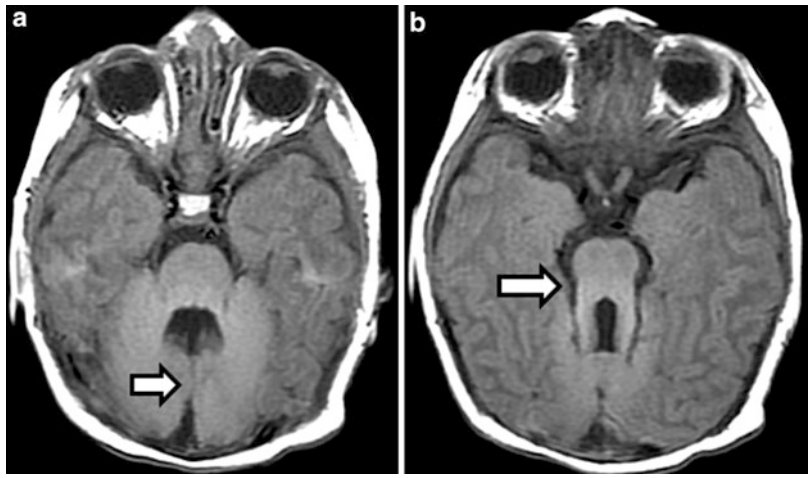

Fig. 7 (**a**, **b**) A 5-day-old boy was presented with exaggerated periodic breathing and developmental delay. The MRI of the brain demonstrated the absence of the vermis (**a**) (*arrow*) with enlarged superior cerebellar peduncles producing a molar tooth configuration of the midbrain (**b**) (*arrow*). The findings are compatible with Joubert syndrome. Genetic tests showed that this patient was heterozygous in the *AH11* and *CEP290* genes for the missense variants. While clinical significance of these missense variants is unknown, it is likely that both missense variants together are the cause of the recessive Joubert syndrome. The *NPHP1* gene mutation study was negative (Courtesy of Dr. Grace Guo)

Kabuki Syndrome

Contents

In 1981 and 1982, Niikawa (Niikawa et al. 1982) and Kuroki (Kuroki et al. 1981) independently described a previously unrecognized mental retardation-malformation syndrome, characterized by a unique combination of craniofacial anomalies, congenital heart defects, skeletal anomalies, persistent fetal fingertip pads, dermatoglyphic abnormalities, mental retardation, and short stature. Because the peculiar facial appearance resembles the makeup of Kabuki actors in a traditional Japanese theater, the Niikawa-Kuroki syndrome is also known as Kabuki or Kabuki makeup syndrome. The prevalence of the syndrome is estimated to be 1 in 32,000 live births in Japan (Niikawa et al. 1988). The syndrome is increasingly recognized in other parts of the world.

Synonyms and Related Disorders

Autosomal dominant type-1 Kabuki syndrome; Kabuki makeup syndrome; Niikawa-Kuroki syndrome; X-linked type-2 Kabuki syndrome

Genetics/Basic Defects

1. Sporadic in most cases (Schrander-Stumpel et al. 1994)
2. Autosomal dominant inheritance suggested in a few families (Halal et al. 1989; Kobayashi and Sakuragawa 1996; Tsukahara et al. 1997; Courtens et al. 2000)
3. Other hypotheses:
   1. Postzygotic mutation, suggested by discordance between the twins, although multifactorial causes, cannot be ruled out.
   2. Several instances of chromosomal abnormalities have been reported in the literature but without identical break points in those autosomal abnormalities.
   3. Microdeletion involving several contiguous genes, suggested by sporadic cases in the majority of patients and a wide spectrum of clinical manifestations. So far, no chromosomal deletion was detected at the sites of the DiGeorge/velocardiofacial chromosomal region within 22q11.2 or flanking the van der Woude syndrome region at 1q32-q41.
   4. 8p23.1-p33 duplication, detected by comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) in six unrelated patients with Kabuki syndrome (KS), was postulated to be a common etiology for the syndrome (Milunsky and Huang 2003). However, studies by Miyake et al. (2004) detected no

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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aberrations of the 8p region by either CGH or FISH on other patients and suggested that the patients studied by Milunsky and Huang had either atypical Kabuki syndrome or possibly an "8p23.1-p33 duplication syndrome."

5. It is possible that Kabuki syndrome is a heterogeneous disorder and abnormalities not only on chromosome 8 but also on other chromosomes, such as the X chromosome, which could lead to similar Kabuki syndrome features (Adam and Hudgins 2004).
6. Molecular karyotyping in 17 patients and mutation screening in 41 patients with Kabuki syndrome revealed no causative gene, but the locus of 9q21.11-q21.12, including *TRPM3*, *KLF9*, *SMC5*, and *MAMDC2*, may contribute to the cleft palate of Kabuki syndrome (Kuniba et al. 2009).

4. *KMT2D* (histone-lysine *N*-methyltransferase 2D) (12q12-q14) (*MLL2*) mutations in patients with autosomal dominant type 1 Kabuki syndrome (KS1) (Banka et al. 2012):
   1. *MLL2* mutations are detected in 55–80% of patients with Kabuki syndrome (KS).
   2. In 20–45% patients with KS, the genetic basis remains unknown, suggesting possible genetic heterogeneity.
   3. The majority of mutations are truncating and the pathogenic missense mutations are commonly located in exon 48.
   4. KS can be phenotypically variable, and therefore *MLL2* testing should be considered even in atypical KS patients.
5. Mutations in *KDM6A* (lysine-specific demethylase 6A) (Xp11.3) (*UTX*): a less frequent, recently discovered genetic abnormality causing X-linked type-2 Kabuki syndrome (KS2) (Lederer et al. 2012; Banka et al. 2015).

Clinical Features

1. Craniofacial abnormalities (Wessels et al. 2002; Matsumoto and Niikawa 2003):
   1. Peculiar facial appearance (100%). The most striking feature of the syndrome:
      1. Peculiar face that consists of eversion of the low lateral eyelid that is reminiscent of a Kabuki actor's makeup and arched eyebrows with sparseness of their lateral one third
      2. Long palpebral fissures
      3. Depressed nasal tip
      4. Prominent, large ears
   2. Microcephaly (26%)
   3. Eye abnormalities:
      1. Long palpebral fissure (99%)
      2. Lower palpebral eversion (92%)
      3. Arched eyebrow (85%)
      4. Ptosis (50%)
      5. Epicanthus (46%)
      6. Strabismus (36%)
      7. Blue sclerae (31%)
   4. Nasal abnormalities:
      1. Short nasal septum (92%)
      2. Depressed nasal tip (83%)
   5. Ear abnormalities:
      1. Prominent ears (84%)
      2. Malformed ears (87%)
      3. Preauricular dimple/fistula (22%)
   6. Oral abnormalities:
      1. High-arched palate (72%)
      2. Abnormal dentition (68%)
      3. Micrognathia (40%)
      4. Cleft palate/lip (35%) (Handa et al. 1991)
      5. Lower lip pit (27%)
   7. Low posterior hairline (57%)
2. Skeletal abnormalities (88%):
   1. A novel sign, namely, the attenuation and/or congenital absence of the distal interphalangeal (IPD) crease of the third and fourth fingers associated with limitation of flexion of the corresponding joints, which seem to be specific of KS and could help the clinician to diagnose KS (Michot et al. 2013)
   2. Pilonidal sinus (83%)
   3. Short fifth phalanxes (80%)
   4. Short fifth fingers (79%)
   5. Joint laxity (74%)
   6. Clinodactyly of fifth fingers (50%)

7. Sagittal cleft of the vertebral body (36%)
8. Scoliosis (35%)
9. Short metacarpals (35%)
10. Deformed vertebra/rib (32%)
11. Foot deformity (24%)
12. Spina bifida occulta (19%)
13. Hip dislocation (18%)
14. Rib anomaly (18%)
15. Coarse carpal bone (17%)
16. Cone-shaped epiphyses (13%)
17. Patellar dislocation
18. Craniosynostosis: rare (6%) (Armstrong et al. 2005; Martinez-Lage et al. 2010)

3. Dermatoglyphic abnormalities:
   1. Abnormal dermatoglyphics (96%):
      1. Frequent fingertip ulnar loop patterns
      2. Absence of digital triradius "c" or "d"
      3. An interdigital triradius "bc" or "cd"
      4. Fourth interdigital area patterns:
         1. Hypothenar loop patterns
         2. Ulnar loop patterns
   2. Presence of fingertip pads (89%): possible remnants of fetal pads
4. Neurologic abnormalities:
   1. Mild to moderate mental retardation (IQ <80) (84%)
   2. Hypotonia (68%)
   3. Neonatal hypotonicity (28%)
   4. Seizures (17%)
   5. Brain atrophy (4%)
   6. Retinal pigmentation (3%)
5. Short stature (55%)
6. Visceral abnormalities:
   1. Cutaneous abnormalities:
      1. Hyperpigmented nevus (22%)
      2. Generalized hirsutism (11%)
   2. Cardiovascular anomalies (42%) (Digilio et al. 2001):
      1. Ventricular septal defect
      2. Atrial septal defect
      3. Coarctation of the aorta
      4. Transposition of great vessels
   3. Gastrointestinal abnormalities:
      1. Umbilical hernia (9%)
      2. Inguinal hernia (7%)
      3. Malrotation of the colon (6%)
      4. Anal atresia/rectovaginal fistula (5%)
   4. Genitourinary abnormalities:
      1. Kidney/urinary tract malformations (28%) (Courcet et al. 2013)
         1. Horseshoe kidney (27%)
         2. Renal dysplasia (15%)
         3. Hydronephrosis (23%)
      2. Undescended testes (24%)
      3. Small penis (10%)
7. Other features:
   1. Susceptibility to infections:
      1. Recurrent otitis media (63%)
      2. Repeat upper respiratory tract infections and pneumonias
   2. Most KS patients show increased susceptibility to infections and have reduced serum immunoglobulin levels, while some suffer also from autoimmune manifestations, such as idiopathic thrombocytopenic purpura, hemolytic anemia, autoimmune thyroiditis, and vitiligo (Stagi et al. 2016).
   3. Precocious puberty: early breast development (28%) (Kuroki et al. 1987).
   4. Hearing loss (27%).
   5. Neonatal hyperbilirubinemia (20%).
   6. Obesity (19%).
   7. Anemia (9%).
   8. Polycythemia (4%).
   9. Cystic fibrosis (2%).
   10. Primary ovarian dysfunction (2%).
8. Genotype-phenotype correlation (Makrythanasis et al. 2013):
   1. Patients with likely pathogenic nonsense or missense *MLL2* mutations were usually more severely affected.
   2. Several typical facial features such as large dysplastic ears, arched eyebrows with sparse lateral third, blue sclerae, a flat nasal tip with a broad nasal root, and a thin upper and a full lower lip were observed more often in mutation positive patients.

Diagnostic Investigations

1. Blood sugar during infancy for neonatal hypoglycemia (7%).
2. Humoral immunodeficiency in patients with type-1 Kabuki syndrome (KS1) caused by

autosomal dominant KMT2D mutations is well described and resembles common variable immunodeficiency (CVID) (Lin et al. 2015; Lindsley et al. 2015):
    1. More than 80% of KS1 patients display hypogammaglobulinemia and diminished memory B-cell populations.
    2. Impaired somatic hypermutation in IgG transcripts and disrupted terminal differentiation can also be demonstrated in primary B cells (Lindsley et al. 2015).
3. Mild humoral immunodeficiency observed in a patient with X-linked Kabuki syndrome (Frans et al. 2016).
4. Thyroid profile for rare thyroxine-binding globulin (TBG) deficiency (2%).
5. Growth hormone determination for rare growth hormone deficiency.
6. Workup for autoimmune hemolytic anemia, if present.
7. Audiologic screening for hearing loss.
8. Radiography for skeletal abnormalities (Niikawa et al. 1981):
    1. Frequent features:
        1. Abnormalities of the spinal column:
            1. Thoracic or lumbar scoliosis
            2. Sagittal cleft vertebra
            3. Narrow disk space
            4. Cervical ribs
            5. Schmorl's node
        2. Dislocation of the hip joints
        3. Abnormalities of the hands:
            1. Brachymesophalangy of the fifth fingers
            2. Short fifth metacarpals
            3. Cone-shaped epiphysis of proximal phalanges II–V
    2. Less frequent features:
        1. Defective dentition
        2. Underpneumatized mastoids
        3. Sacral spina bifida occulta
        4. Osteoporotic changes of the carpal bone and metacarpals
        5. Underdeveloped ulnar styloids
        6. Dysplastic acetabulum
        7. Horseshoe kidney
        8. Bifid renal pelvis
9. Renal ultrasonography and renal function screening for renal abnormalities (Courcet et al. 2013).
10. Echocardiography for congenital heart defects.
11. EEG for seizures: characteristic features are focal seizures more frequently origin in fronto-central area (Lodi et al. 2010).
12. MRI/CT scan for rare central nervous system (CNS) anomalies.
13. Dermatoglyphic analysis.
14. *KMT2D* (*MLL2*) mutations study (Banka et al. 2012; Bögershausen and Wollnik 2013):
    1. Sequence analysis of *KMT2D* as a standard molecular genetic test in patients with suspected KS (Banka et al. 2012; Bögershausen and Wollnik 2013).
    2. For mutation negative patients, array-CGH should be performed (Bögershausen and Wollnik 2013):
        1. Multiple ligand probe amplification (MLPA) for *KMT2D* and *KDM6A* as a third-line diagnostic tool after Sanger sequencing of *KMT2D* and array-CGH.
        2. As an alternative, high-resolution array-CGH might be a powerful diagnostic tool to detect structural chromosomal aberrations as well as specific deletions in *KMT2D* and *KDM6A*.
        3. The finding of low-level mosaic mutations in *KMT2D* might lead to the establishment of deep-sequencing strategies for *KMT2D* molecular diagnostics in the near future.
        4. These next generation sequencing (NGS)-based strategies will also facilitate the sequencing of *KDM6A* in parallel to *KMT2D*, in order to detect rare single nucleotide alterations.
15. FISH analyses (Yang et al. 2016):
    1. To determine whether the deleted copy of *KDM6A* was located on the active or inactive X chromosome, FISH analysis was performed simultaneously using a

KDM6A probe (RP11-531L8 labeled with SpectrumOrange) and Xqter probe (labeled with SpectrumOrange) on the X chromosomes that had been differentially labeled by the incorporation of 5-bromo-2-deoxyuridine (BrdU) following established protocols (Lederer et al. 2012). The inactive X chromosome appears brighter than the active X chromosome after the BrdU staining.

2. FISH, using a bacterial artificial chromosome (BAC) clone (RP11-531L8, Xp11.3, 154 kb) within the deletion region for each of the family members, validated the presence of the deletion in the patient and the absence of the deletion in her parents, suggesting that the deletion on chromosome Xp11.3 in the patient was de novo.

Genetic Counseling

1. Recurrence risk (Kawame et al. 1999):
   1. Patient's sib: low recurrence risk, unless a parent has an autosomal dominant form of the syndrome
   2. Patient's offspring: low recurrence risk, unless the patient has an autosomal dominant form of the syndrome
2. Prenatal diagnosis: none described to date
3. Management:
   1. Multidisciplinary approach to developmental delay and mental retardation.
   2. Hearing aids for hearing loss.
   3. Treat infections.
   4. Growth hormone replacement therapy for growth hormone deficiency.
   5. Orthopedic intervention for scoliosis, dislocations, and foot deformities.
   6. Cardiac surgery for severe congenital heart defects.
   7. Surgical repair of cleft lip/palate, gastrointestinal, anorectal, and craniosynostosis anomalies.
   8. Naturally occurring nonsense mutations in

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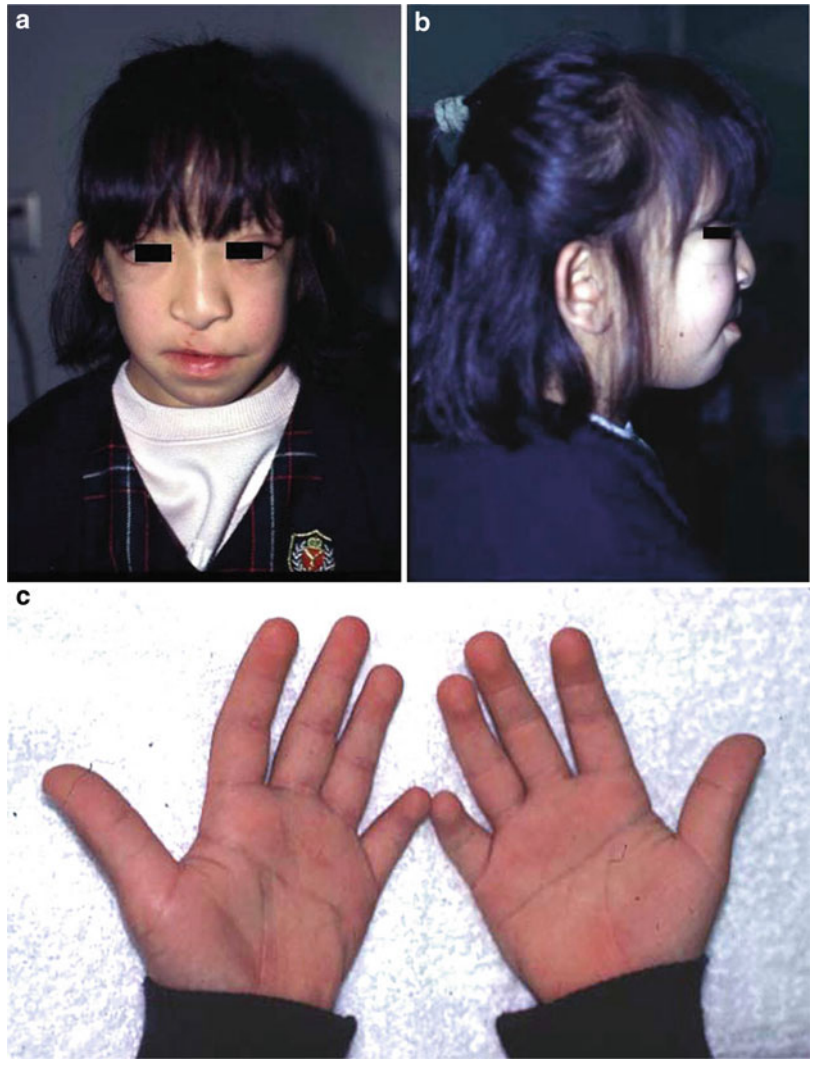

Fig. 1 (**a**–**c**) A 12-year-old girl with Kabuki syndrome (**a**, **b**) showing arched eyebrows, long palpebral fissures, everted lateral half of the lower eyelid, short nasal septum, post-cleft lip repair, prominent ears, and prominent finger pads (**c**)

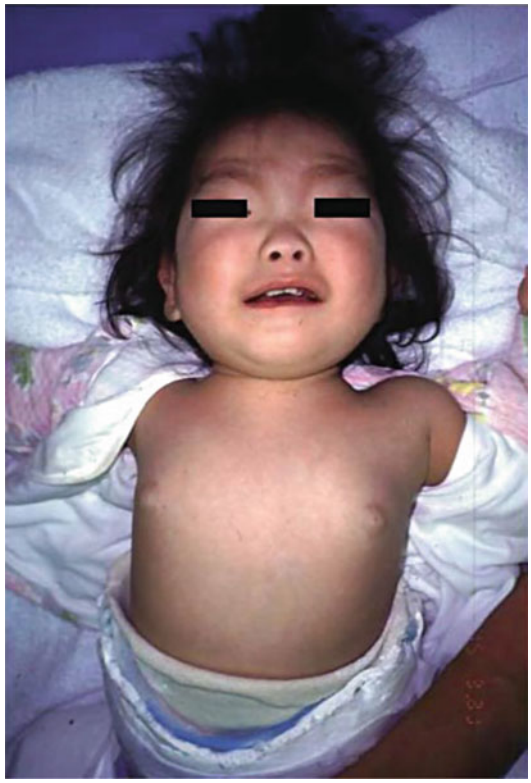

Fig. 2 A 1-year-old girl with Kabuki syndrome showing arched eyebrows, long palpebral fissures, short nasal septum, and hypertrophic breasts. The infant also has cleft palate, large ears, and congenital hip dislocations

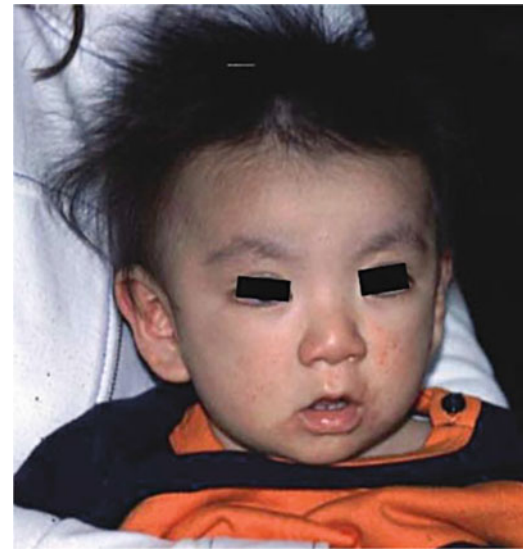

Fig. 3 A 1-year-old boy with Kabuki syndrome showing arched eyebrows, long palpebral fissures, everted lateral half of the lower eyelids, blue sclera, strabismus, short nasal septum, small chin, and large and prominent ears

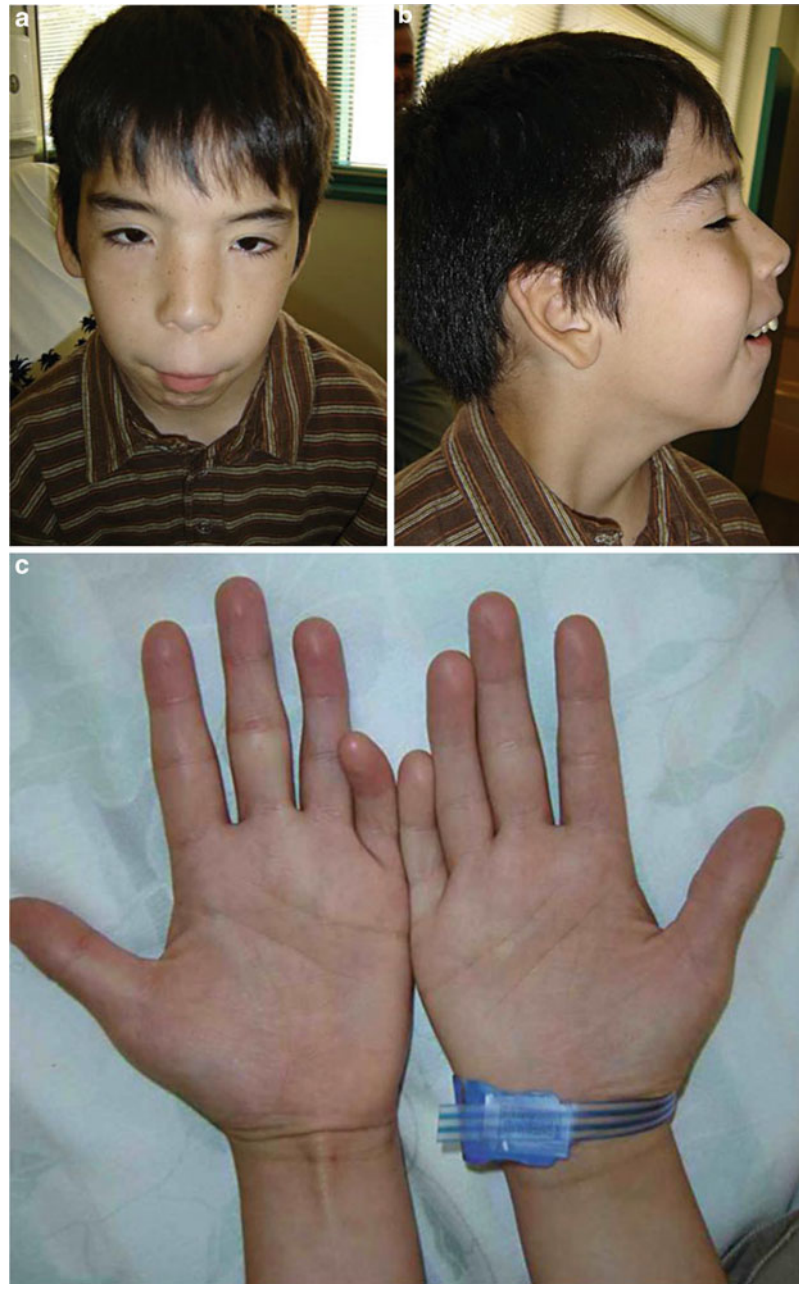

Fig. 4 (**a**–**c**) A 12-year-old boy with Kabuki syndrome (**a**, **b**) showing characteristic facial features consisting of long palpebral fissures, arched eyebrows, bilateral lower lateral palpebral eversion, short nasal septum, high-arched palate, low hairline, and prominent finger pads (**c**). Other anomalies include mild mental retardation, neonatal hypotonia, recurrent otitis media and upper respiratory infections, joint laxity, ventricular septal defect, hip dysplasia, and short and clinodactyly of the fifth fingers

Kasabach–Merritt Syndrome

Contents

Kasabach–Merritt syndrome (or phenomenon) is the association of a vascular tumor and thrombocytopenic coagulopathy (Enjolras et al. 2000). It is a life-threatening, acute, or chronic consumptive coagulopathy, characterized by profound thrombocytopenia and microangiopathic hemolytic anemia (Esterly 1983).

In *1940*, Kasabach and Merritt (1940) described the first case of Kasabach–Merritt syndrome with a case report of consumptive coagulopathy associated with a hemangioma. However, it is now recognized that Kasabach–Merritt syndrome is usually associated with Kaposiform hemangioendothelioma and tufted angioma, rather than the classic involuting hemangioma of infancy (Enjolras et al. 1997).

Synonyms and Related Disorders

Hemangioma–thrombocytopenia syndrome; Kaposiform hemangioendothelioma; Kasabach–Merritt phenomenon; Tufted hemangioma

Genetics/Basic Defects

1. Genetics
    1. Sporadic in majority of cases
    2. Autosomal dominant inheritance in rare reports
    3. Can be a part of recognized syndromes
2. Pathophysiology (Hall 2001)
    1. Platelet trapping by abnormally proliferating the endothelium within the hemangioma, resulting in the activation of platelets with a secondary consumption of clotting factors
    2. Continued consumption of both platelets and clotting factors along with the initiation of fibrinolysis eventually resulting in intralesional bleeding which manifests as rapid enlargement of the hemangioma

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Clinical Features

1. Diverse clinical presentation (Enjolras et al. 2000; Hall 2001)
    1. Type of hemangiomas
        1. Kaposiform hemangioendothelioma (O'Rafferty et al. 2015)
            1. A rare vascular tumor of infancy
            2. Often found in noncutaneous sites such as the retroperitoneum, mediastinum, and pelvis, as well as the skin (Gianotti et al. 1999)
            3. Platelet trapping within the lesion: associated with rapid enlargement
            4. Associated with Kasabach–Merritt syndrome: can be life-threatening
        2. Tufted angioma
        3. Mixture of Kaposiform hemangioendothelioma and tufted angioma
        4. Not "true" common hemangioma of infancy
    2. Reddish-brown skin lesion progressing to a violaceous bulging mass
        1. Often painful
        2. Aggressive infiltration with ulceration
        3. Bruising in other areas
        4. Possible infection
    3. Bleeding from thrombocytopenia and intravascular coagulopathy
    4. Increase in size and becoming tense, woody, and purplish of preexisting hemangiomas during pregnancy
2. Cutaneous involvement of Kaposiform hemangioendothelioma
    1. Smooth, shiny, dark purple, indurated, tender, and poorly delineated
    2. Nearly always single
3. Visceral involvement of hemangiomata
    1. Single
    2. Multiple
    3. Isolated within one organ as single or diffuse lesions
    4. Retroperitoneal hemangiomata
        1. Often giant in size
        2. Easily missed clinically: diagnosis suspected in patients presenting with an unexplained thrombocytopenia and coagulopathy
        3. Generally associated with high mortality
4. Diffuse and multiple nature
    1. Diffuse infantile (neonatal) hemangiomatosis
        1. Presence of multiple cutaneous and visceral hemangiomata
        2. High morbidity and mortality
    2. Intraosseous and soft tissue hemangiomata
5. Lifelong hemangioma in adults
    1. Hormone alterations and increase in blood volume in pregnancy may affect preexisting lesions, triggering episodes of acute disseminated intravascular coagulation (DIC).
    2. Development of acute consumptive coagulopathy after surgery of other unrelated tumor.
6. Primary angiosarcoma of the breast (Malolan et al. 2016) and metastatic angiosarcoma (Massarweh and Munis 2014) presenting as Kasabach–Merritt syndrome
7. Thrombocytopenic coagulopathy in patients with hemangiomata as a part of a recognized syndrome
    1. Klippel–Trenaunay syndrome
        1. A rare congenital generalized mesodermal abnormality
        2. Macular vascular nevus, skeletal/soft tissue hypertrophy
        3. Venous and lymphatic anomalies including viscera and facial hemangiomata
    2. Blue rubber bleb nevus syndrome
        1. Multiple cutaneous cavernous hemangiomata
        2. Cutaneous and occasional visceral hemangiomata
    3. Gorham-Stout disease ("vanishing bone disease")
        1. Massive osteolysis (Gorham sign)
        2. Followed by replacement of the bony matrix by proliferating thin-walled vascular and lymphatic channels
        3. Extension of these angiomatous masses into soft tissues
8. Differential diagnosis: Kaposiform hemangioendotheliomas and tufted angiomas should be part of the differential diagnosis in any infant presenting with purpura and an

unexplained profound thrombocytopenia (O'Rafferty et al. 2015).

9. Prognosis/complications (Cheerva 2016)
    1. Incomplete regression of the lesion after months or years
    2. Visceral involvement
        1. Mediastinum
        2. Neck
        3. Retroperitoneum
        4. Pelvis
    3. Hemorrhage by aggressive invasion
    4. Ulceration and bleeding into the vascular lesion
    5. Petechiae, ecchymoses, or purpura
    6. Profound thrombocytopenia (platelet count $<5 \times 10^{9}$/L ($<$5000/μL)
    7. Bleeding secondary to disseminated intravascular coagulation and unresponsive to platelet transfusions (potentially fatal)
    8. Anemia
    9. Congestive heart failure (potentially fatal)
    10. Severe infections
    11. Toxicity from the agents used to treat Kasabach–Merritt syndrome (e.g., secondary malignancy from radiation therapy)
    12. Pregnancy complicated by Kasabach–Merritt syndrome (Lee and Kirk 1967; Phillippe et al. 1980; Singh and Rajendran 1998)
    13. Residual lesions after "cure" of Kasabach–Merritt phenomenon (Enjolras et al. 2000)
        1. Common after the resolution of thrombocytopenia and coagulopathy
        2. Clinical patterns
            1. Cutaneous red stain with or without associated red papules
            2. Telangiectatic streaks and swelling
            3. A minor, firm, irregular subcutaneous mass assessed by palpation or deep infiltration evidenced by CT scan or MRI
            4. Sequelae in muscles and/or joints
    14. Overall mortality (estimated to be 20–30%) (El-Dessouky et al. 1988) due to complications such as (Enjoiras et al. 1990):
        1. Disseminated intravascular coagulation
        2. Respiratory failure due to a pressured airway
        3. High-output heart failure due to presence of a huge tumor

Diagnostic Investigations

1. Laboratory studies (Hall 2001; Cheerva 2016)
    1. A complete blood count (CBC) count with differential, reticulocyte count, platelet count, and peripheral smear is obtained to evaluate for microangiopathic hemolytic anemia and thrombocytopenia.
    2. Platelets may be larger than normal when they are released early from the bone marrow.
    3. Burr cells and schistocytes may be present in patients with microangiopathic hemolytic anemia.
    4. Generally severe thrombocytopenia occurs in 1–2 per 300–700 cases of hemangioma.
    5. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are prolonged in patients with significant DIC.
    6. Consumptive coagulopathy
        1. Prominent fibrinogenopenia
        2. Usually elevated fibrin split (degradation) products
        3. Usually elevated D-dimers (a measure of fibrin split products)
        4. Depressed clotting factors V and VII
    7. Radioisotopic study with Cr-51 tagged platelets: demonstration of platelet sequestration in giant hemangioma with thrombocytopenia (Brizel and Raccuglia 1965).
2. Ultrasound, MRI, or CT
    1. To assess extent of the lesions
    2. To identify the occult lesions
3. Histology to determine subtypes of vascular tumors found in Kasabach–Merritt syndrome (Alvarez-Mendoza et al. 2000)
    1. Kaposiform hemangioendothelioma of infancy and childhood (46%)
        1. The most frequently reported histological type
        2. A locally aggressive, low-grade malignant tumor

3. Lobules or sheets of tightly packed spindle cells or more rounded endothelial cells and pericytes
4. Infiltrative pattern of the cellular areas in the dermis and subcutaneous fat and muscles, generally containing few obvious vascular lumina
5. Aggregates of rounded dilated capillaries, lined by attenuated endothelial cells with small dark nuclei and filled with red blood cells
6. Containing lymphatic-like vessels

2. Tufted angioma (31%)
   1. A benign lesion
   2. Small tufts or lobules of rounded capillaries with small lumina
   3. Tufts: discrete and evenly distributed in a cannon ball pattern, characterized by peripheral crescentic slit-like vessels and fibrosis
   4. Aggregates of rounded dilated capillaries, lined by attenuated endothelial cells with small dark nuclei and filled with red blood cells
3. Infantile (juvenile) hemangioma (23%)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased unless a parent is affected
   2. Patient's offspring: 50% in case of autosomal dominant inheritance
2. Prenatal diagnosis
   1. Prenatal diagnosis of fetal facial hemangioma in a case of Kasabach–Merritt syndrome (Respondek-Liberska et al. 2002)
   2. Prenatal diagnosis of Klippel–Trenaunay–Weber syndrome with Kasabach–Merritt syndrome in utero (Tanaka et al. 2015)
3. Management (Larsen et al. 1987; Ryan et al. 2010; Cheerva 2016)
   1. General premise regarding treatment: Resolution of the lesion will lead to a correction of the consumptive coagulopathy, which is heralded by a recovery in the platelet count.
   2. Principle of management of thrombocytopenia in Kasabach–Merritt syndrome should be to "treat the patient and not the numbers."
   3. Prompt and vigorous management.
      1. Help to optimize the outcome
      2. No one treatment modality established as consistently efficacious
   4. Blood product support in the presence of sudden decompensation or enlargement of the lesion.
      1. Fresh frozen plasma.
      2. Cryoprecipitate (de Terlizzi et al. 1988) if fibrinogen is still less than 1.0 g/L.
      3. Platelet transfusion should be reserved for thrombocytopenic patient who is actively bleeding or in preparation for a surgical procedure.
      4. Tranexamic acid for profound fibrinolysis.
   5. Coagulation-directed treatment (O'Rafferty et al. 2015)
      1. Platelet transfusions
      2. Antiplatelet agents
      3. Antifibrinolytics, fibrinogen, and anticoagulants
   6. Simple or single lesion
      1. Vascular ligation
      2. Embolization of a giant liver hemangioma (Billio et al. 2001)
      3. Surgical excision
         1. Surgical removal of a giant hemangioma: usually hazardous in the presence of an uncontrolled consumptive coagulopathy.
         2. Supporting and stabilizing hemostasis while trying to remove or ablate the lesion.
         3. Partial resection of tumor, reduction of tumor blood, and vincristine chemotherapy (Shen et al. 2010): Since the huge tumor is the major cause of rapid platelet destruction, the partial removal of the tumor and U-shaped

suture to reduce tumor blood supply would reduce the platelet destruction and, therefore, improve the clinical condition, followed by skin graft or flaps of the wound, and vincristine chemotherapy necessary to prevent the enlargement of the remaining tumor.

4. Mechanical compression of Kaposiform hemangioendothelioma and tufted angioma lesions located on the extremities (O'Rafferty et al. 2015)
   1. Can decrease flow
   2. May assist in high-output cardiac failure
   3. Can be a useful temporizing method while other interventions are initiated

7. Diffuse or extensive lesions
   1. Prednisone (Dresse et al. 1991; Ozsoylu 2002)
   2. Alpha interferon (Hatley et al. 1993; Frevel et al. 2002; Biban 2003)
8. Adjuvant therapies
   1. Vincristine (Haisley-Royster et al. 2002)
   2. Localized radiotherapy (Ogino et al. 2001; Frevel et al. 2002; Hesselmann et al. 2002)
   3. Combination chemotherapy (vincristine, cyclophosphamide)
   4. Antifibrinolytic or antiplatelet agents (tranexamic acid, epsilon aminocaproic acid, pentoxifylline, ticlopidine)
   5. Vincristine and dual antiplatelet therapy durable responses in Kaposiform hemangioendothelioma (O'Rafferty et al. 2015)
   6. Interventions involving embolization, systemic interferon, cyclophosphamide, epsilon aminocaproic acid, and compression therapy (Blei 1998)
9. Potential future therapies
   1. Laser therapy
   2. Antiangiogenic agents
   3. Pegylated recombinant human megakaryocyte growth and development factor (peg-rHuMGDF)

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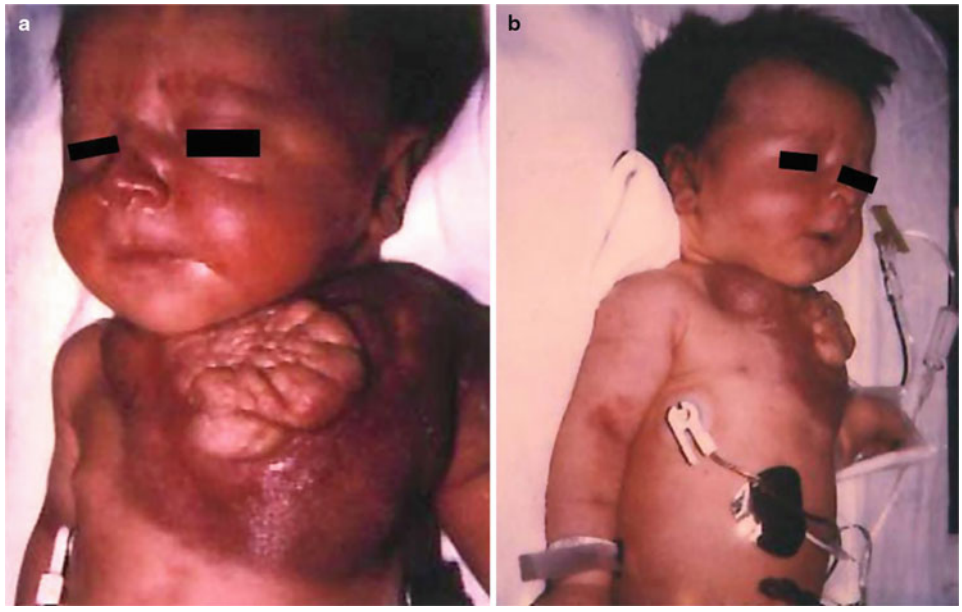

Fig. 1 (**a**–**b**) An infant with Kasabach–Merritt syndrome showing a giant cavernous hemangioma over most of the chest

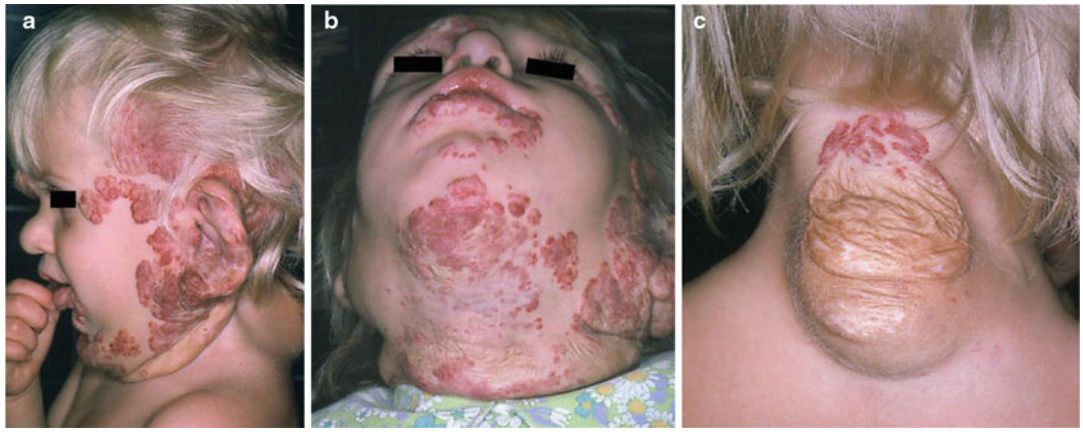

Fig. 2 (**a**–**c**) A patient with blue rubber bleb nevus syndrome

KID Syndrome

Contents

KID syndrome is an acronym for the syndrome characterized by *k*eratitis, *i*chthyosis, and *d*eafness, a term proposed by Skinner et al. in 1981 (Skinner et al. 1981).

Synonyms and Related Disorders

Hystrix-like ichthyosis-deafness (HID) syndrome; Keratitis-ichthyosis-deafness (KID) syndrome

Genetics/Basic Defects

1. Genetic heterogeneity
    1. Sporadic in most cases (Langer et al. 1990)
    2. Existence of familial cases suggesting a genetic etiology
        1. A vertical transmission suggesting an autosomal dominant disease (Kelly et al. 2008)
        2. The occurrence in two sisters born to consanguineous, unaffected parents suggesting an autosomal recessive inheritance (Kone-Paut et al. 1998)
2. Caused by germline mutations in the connexin-26 gene, *GJB2*, which is implied in the normal corneal function, hair growth, and carcinogenesis and in the *GJB3* (encoding connexin-31) (Richard 2000)
    1. Mutations in *GJB2* were identified de novo in 13 unrelated patients with KID and in a case of transmission of the disease from father to son (Richard et al. 2002; Van Steensel et al. 2002; Alvarez et al. 2003; Yotsumoto et al. 2003).
    2. Mutations in several other genes [*GJB3* (connexin-31), *GJB6* (connexin-30)], which encode members of the connexin family of gap junction proteins, are shown to be responsible for hearing impairment and skin disorders (Kelsell et al. 2001).
    3. *GJB6* mutation also causes hidrotic ectodermal dysplasia (Clouston syndrome) (Kutkowska-Kaźmierczak et al. 2015).
3. Occurrence of parental germline mosaicism in the lethal form of KID syndrome: suggested by three affected children (carry the same G45E mutation) born to healthy parents (mutation not detected) (Sbidian et al. 2010)
4. Fatal form of KID syndrome (Janecke et al. 2005)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. A fatal course of KID in the first year of life, due to severe infections of the skin lesions and septicemia, has been reported in at least nine patients (Gilliam and Williams 2002; Janecke et al. 2005).
2. Caused by G45E mutation of *GJB2* gene.
3. The phenotype bears similarities to cutaneous disorders associated with sensorineural hearing loss (HL) known to be caused by mutations in genes encoding gap junction proteins (connexins).
    1. Vohwinkel syndrome (Maestrini et al. 1999)
    2. Dominant HL associated with palmoplantar keratoderma (Heathcote et al. 2000)
    3. Keratoderma without HL
        1. Clouston syndrome (Lamartine et al. 2000)
        2. Erythrokeratodermia variabilis (Richard et al. 1998)
5. Pathogenesis: failure in development and differentiation of multiple stratifying epithelia
6. Hystrix-like ichthyosis deafness (HID) and KID syndromes are associated with the same connexin 26 mutation (Van Geel et al. 2002).
    1. These disorders are distinguished mainly on the basis of electron microscopic findings.
    2. KID and HID syndromes may be genetically related.

Clinical Features

1. Cutaneous features (McGrae 1990)
    1. The abnormal skin at birth: red, dry, thickened, and leathery
    2. Subsequent development of keratodermatous, nonscaly plaques
        1. Generally develop during the first year of life
        2. Described as verrucous, ichthyotic, doughy, rugal, or elephant skin-like
        3. Develop primarily on the face and extremities
        4. Plaques sharply demarcated and maplike in contour
        5. Plaques symmetrically located on the face
            1. Especially the cheeks
            2. With variable involvement of the forehead, ears, chin, and nose
            3. Furrows in the thickened skin of the chin and around the mouth
        6. Transverse ripples marking the surface of plaques over the knees
        7. Follicular keratoses, occasionally with spine like projections, on the extremities, eyebrows, scalp, earlobes, neck, and nose
    3. Distinct keratoderma of the palms and soles
        1. Pebbly excrescences and an intervening coarsely stippled pattern analogous to heavily grained leather
        2. Patulous stippling rendering a moth-eaten appearance
    4. Abnormal hair
        1. The sparse, fine, and sometimes absent scalp, eyebrow, and eyelash hair
        2. Pattern of patch scalp alopecia resembling pseudopelade
        3. Body hair may be absent
        4. Nails
            1. Thickened
            2. Hypoplastic
            3. Absent
            4. White
            5. Infrequently normal
2. Ophthalmologic features (Ghadially and Chong 1992)
    1. Invariably involving epibulbar structures with inflammation of the cornea
        1. Vascularized keratitis in majority of cases
        2. Secondary pannus formation
    2. Photophobia
    3. Varying degree of visual impairment
    4. Onset: usually before adolescence
3. Auditory features
    1. Sensorineural deafness
    2. Repeat otitis media and externa
4. Other ectodermal abnormalities
    1. Dental abnormalities
        1. Carious
        2. Brittle

3. Malformed
4. Delayed adult dentition

2. Hypohidrosis

5. Neuroectodermal abnormalities
   1. Short heel cord
   2. Cerebellar hypoplasia
6. Other associated features
   1. Normal intelligence
   2. Growth delay
   3. Increased risk of developing squamous cell carcinoma (Grob et al. 1987) and trichilemmal tumors (Coggshall et al. 2013)
   4. Increased susceptibility to viral, bacterial, and mycotic infections (Coggshall et al. 2013)
      1. The most commonly reported pathogens.
         1. *Staphylococcus aureus*
         2. *E. coli*
         3. *Pseudomonas aeruginosa*
         4. *Trichophyton rubrum*
         5. *Candida albicans*
      2. Invasive and overwhelming infection may be present in infancy and early childhood. Death secondary to overwhelming sepsis has been reported in infancy.
      3. Infections are typically persistent and recurrent but usually limited to the skin in older children and adults.
      4. No consistent pattern of immunologic dysfunction demonstrated in patients with KID syndrome.
7. Fatal form of KID syndrome
   1. A fatal course of KID has been reported in the first year of life due to severe infections of the skin lesions and septicemia.
   2. Characteristic severe neonatal phenotype (Sbidian et al. 2010).
      1. Facial dysmorphism
      2. Severe cornification with massive focal hyperkeratosis of the skin with erythroderma
      3. Dystrophic nails
      4. Complete atrichia (absence of hair)
      5. Absence of the foreskin

Diagnostic Investigations

1. Dental examinations for teeth abnormalities
2. Ophthalmological examination for corneal pathology and visual acuity
3. Audiologic examination to demonstrate sensorineural hearing loss
4. Histopathology of the skin (McGrae 1990)
   1. Findings not specific.
   2. Stratum corneum.
      1. Always hyperkeratotic, usually with a basket weave pattern
      2. Orthokeratotic and occasionally parakeratotic
   3. Stratum granulosum: generally intact.
   4. Eccrine sweat glands appearing normal, although a diminished number and aberrant morphology have been noted.
   5. Absent or atrophic hair follicles indicating the customary state of alopecia.
   6. Follicular plugging is the rule.
5. Histopathological, immunohistochemical, and molecular analysis of precancerous and cancerous skin lesions (Bergman et al. 2012)
6. Molecular genetic study to detect connexin-26 gene (*GJB2*) mutation: clinically available

Genetic Counseling

1. Recurrence risk.
   1. Patient's sib
      1. Autosomal dominant inheritance: not increased unless a parent is affected or parental germline mosaicism exists
      2. Autosomal recessive inheritance: 25%
   2. Patient's offspring
      1. Autosomal dominant inheritance: 50%
      2. Autosomal recessive inheritance: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis: Prenatal molecular genetic diagnosis of the lethal form of KID syndrome relating to a G45E mutation has been reported (Sbidian et al. 2010).
3. Management.
   1. No specific treatment for the skin lesions.
   2. Isotretinoin with inconsistent results.

1. May cause exacerbation of eye lesion
    1. Marked increase in pannus formation
    2. Marked increase in vascularization
2. Side effects of higher doses of isotretinoin
    1. Corneal opacities
    2. Punctate erosions
    3. Blepharoconjunctivitis
3. Excellent response to acitretin treatment of the hyperkeratosis of the scalp, trunk, and extremities (Patel et al. 2015) and alitretinoin treatment of dissecting cellulitis of the scalp (Prasad and Bygum 2013)

3. Ophthalmologic evaluations and follow-up. Corneal grafts revascularize rapidly with subsequent loss of vision.
4. Treat infections vigorously.
5. Surveillance for skin and mucosal malignancy.
6. Hearing aids.
7. Appropriate school placement.

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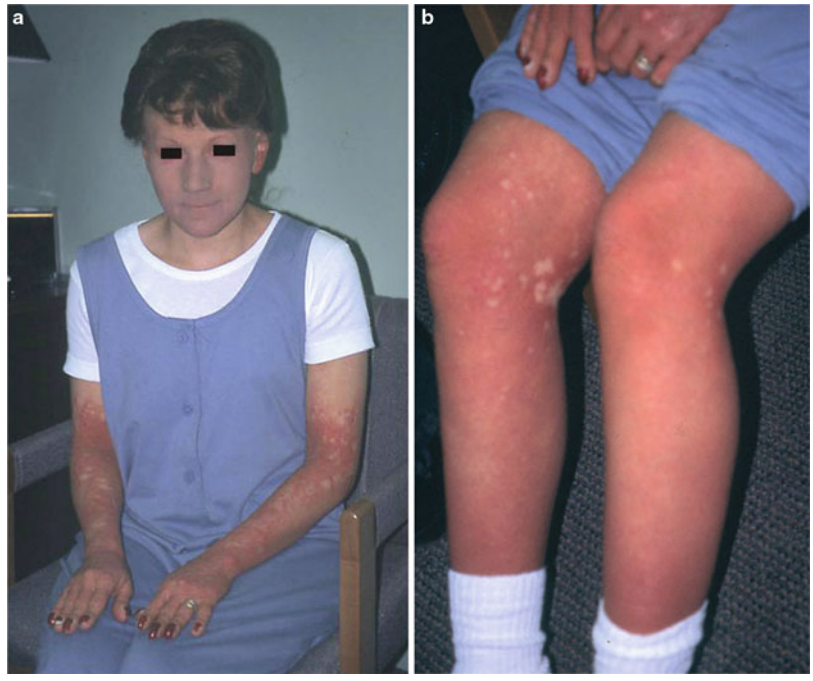

Fig. 1 (**a**–**b**) A 26-year-old woman with keratitis, ichthyosis, and deafness. Cutaneous manifestations show sharply demarcated red-brown hyperkeratotic plaques on the central face, around both eyes, and upper and lower extremities

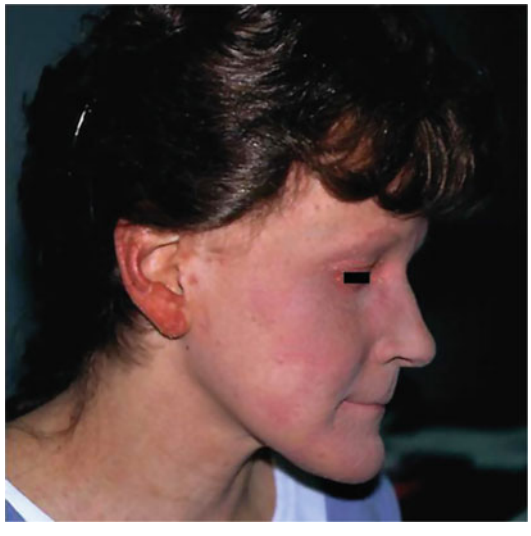

Fig. 2 Marked hyperkeratosis is visible around the eye and the outer rim of the ear

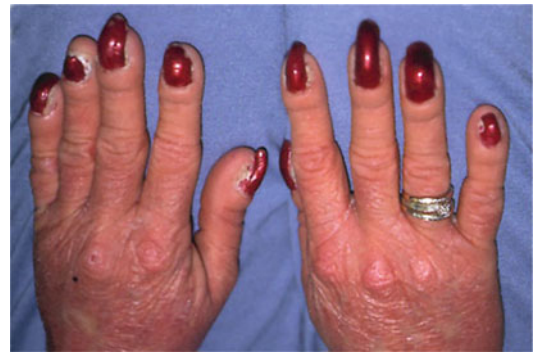

Fig. 3 Chronic *Candida albicans* onychia and paronychia with hypertrophy of the distal digits and hyperkeratosis of the skin are apparent on both hands

Klinefelter Syndrome

Contents

In 1942, Klinefelter et al. (1942) published a report on nine men who had enlarged breasts, sparse facial and body hair, small testes, and an inability to produce sperm. In 1959, these men with Klinefelter syndrome were discovered to have an extra sex chromosome (genotype XXY) instead of the usual male sex complement (genotype XY).

Klinefelter syndrome is the most common sex chromosomal disorder associated with male hypogonadism and infertility. Approximately 1 in 500–1,000 males is born with an extra X chromosome. Over 3,000 affected males are born yearly in the USA.

Synonyms and Related Disorders

47,XXY syndrome; Klinefelter syndrome mosaicism (46,XY/47,XXY, 46,XY/48,XXXY, 47,XXY/48,XXXY); Klinefelter syndrome variants (48,XXYY, 48,XXXY, 49,XXXYY, 49,XXXXY); Klinefelter syndrome with structurally abnormal X chromosome [47,X,i(Xq)Y, 47,X,del(X)Y]

Genetics/Basic Defects

1. Caused by at least an additional X chromosome in a male
2. The XXY form of Klinefelter syndrome:
    1. Due to meiotic nondisjunction of the sex chromosomes during gametogenesis in either parent
    2. Responsible meiotic nondisjunction (Carothers and Filippi 1988; Harvey et al. 1990):
        1. About 40% occur in the father.
        2. About 60% occur in the mother:
            1. Meiosis I errors (75%) when origin is maternal
            2. The presence of maternal age effect in the maternally derived cases
3. The mosaic forms of Klinefelter syndrome:
    1. Due to mitotic nondisjunction after fertilization of the zygote
    2. Can arise from a 46,XY zygote or a 47,XXY zygote
4. The variant forms:
    1. 48,XXXY: nondisjunction occurring either at the first or second meiotic divisions of oogenesis, resulting in an XXX ovum which is then fertilized by a Y-bearing sperm.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. 49,XXXXY: Please refer to 49,XXXXY chapter.
3. 48,XXYY and 49,XXXYY: occurrence of nondisjunction in paternal meiosis to have two Y chromosomes:
    1. An X ovum fertilized by an XYY sperm arising from successive nondisjunction in the first and second meiotic divisions
    2. An XX ovum from 47,XXX mother fertilized by a YY sperm

5. Pathophysiology (Chen 2015):
    1. The X chromosome carries genes that play roles in many body systems, including testis function, brain development, and growth (Giedd et al. 2007).
    2. The addition of more than one extra X or Y chromosome to a male karyotype results in variable physical and cognitive abnormalities.
    3. In general, the extent of phenotypic abnormalities, including mental retardation, is directly related to the number of supernumerary X chromosomes.
    4. As the number of X chromosomes increases, somatic and cognitive development are more likely to be affected.

Clinical Features

1. Growth (Chen 2015):
    1. Infants and children: normal heights, weights, and head circumferences
    2. Adolescents and adults:
        1. Eunuchoid body habitus
        2. Usually taller than average
        3. Disproportionately long arms and legs (Ratcliffe et al. 1982)
2. Mild developmental, learning, and behavioral difficulties (70% of patients) (Geschwind et al. 2000):
    1. Delayed speech and language acquisition
    2. Academic and reading difficulties
    3. Attention deficit disorder
    4. Poor self-esteem
    5. Insecurity
    6. Shyness
    7. Poor judgment
    8. Inappropriate assertive activity
    9. Decreased ability to deal with stress
    10. Fatigue
    11. Weakness
    12. Impeded psychosocial adaptation (Bender et al 1995)
3. CNS:
    1. Normal intelligence in most cases
    2. Subnormal intelligence or mental retardation associated with a higher number of X chromosomes
    3. Diminished short-term memory
    4. Prone to epilepsy and essential tremor (Boltshauser et al. 1978)
    5. Psychiatric disorders involving anxiety, depression, neurosis, and psychosis: more common than general population
4. Taurodontism (enlargement of the molar teeth by an extension of the pulp): present in about 40% of patients (vs. 1% in normal XY individuals)
5. Cardiac and circulatory problems:
    1. Mitral valve prolapse (55% of patients)
    2. Varicose veins (20–40% of patients):
        1. Venous ulcers
        2. Deep vein thrombosis
        3. Pulmonary embolism
6. A slightly increased risk of autoimmune disorder:
    1. Rheumatic diseases (Rovensky et al. 2010):
        1. Inflammatory rheumatic diseases
        2. Rheumatoid arthritis
        3. Juvenile idiopathic arthritis
        4. Psoriatic arthritis
        5. Polymyositis/dermatomyositis
        6. Systemic lupus erythematosus
        7. Systemic sclerosis
        8. Mixed connective tissue disease
        9. Antiphospholipid syndrome
        10. Ankylosing spondylitis
    2. Thyroid disease (Campbell and Price 1979)
    3. Sjogren syndrome
    4. Diabetes mellitus
7. Sexual characteristics:
    1. Gynecomastia secondary to elevated estradiol levels and increased estradiol/testosterone ratio:

1. Develop by late puberty in 30–50% of boys with Klinefelter syndrome
2. Risk of developing breast cancer: at least 20 times higher than normal

2. Lack of secondary sexual characteristics secondary to decrease in androgen production:
   1. Sparse facial, body, and sexual hair
   2. High-pitched voice
   3. Female type of fat distribution
3. Male psychosexual orientation in most patients
4. Subnormal libido
5. Erectile dysfunction
6. Oligospermia or azoospermia
7. Testicular dysgenesis in postpubertal patients (Schwartz and Root 1991):
   1. Small, firm testes
   2. Testis size <10 mL
8. Infertility and azoospermia resulting from atrophy of the seminiferous tubules:
   1. Seen practically in all patients with a 47, XXY karyotype.
   2. Klinefelter syndrome mosaics (46,XY/47,XXY) can be fertile.

8. Other characteristics:
   1. Some KS males present with no severe clinical features and lead normal lives, while others exhibit developmental, physical, behavioral, and learning disabilities and disorders (Bird and Hurren 2016).
   2. An increased prevalence of extragonadal germ cell tumors in the mediastinum (Völki et al. 2006) and brain.
   3. More common varicose veins, venous stasis ulcers (Verp et al. 1983; Veraart et al. 1995), and thromboembolic disease.
   4. The syndrome may go undiagnosed in the majority of affected men.
9. Klinefelter syndrome mosaics and variants:
   1. Klinefelter syndrome mosaic (46,XY/47,XXY):
      1. Less severe manifestations
      2. May have normal-sized testes
      3. Less severe endocrine abnormalities
      4. Less common gynecomastia and azoospermia
      5. Occasional fertile men
   2. Klinefelter syndrome variants (Visootsak and Graham 2006):
      1. 48,XXYY variant (Tartaglia et al. 2008):
         1. Tall stature.
         2. Disproportionately long lower extremities.
         3. Clinodactyly.
         4. Pes planus.
         5. Hypertelorism.
         6. Dental problems.
         7. Gynecomastia.
         8. Intention tremor.
         9. Neurodevelopmental disorders, including developmental delays, ADHD, autism spectrum disorders, mood disorders, and tic disorders.
         10. Unusual dermatoglyphic patterns.
         11. Peripheral vascular disease, especially varicose veins and stasis dermatitis.
         12. Poorly developed secondary sexual characteristics.
         13. Hypogonadism.
         14. Testicular histology similar to that of 47,XXY patients.
         15. The sex chromatin pattern indistinguishable from that of the 47,XXY patients except two fluorescent Y bodies is present in a high proportion of somatic nuclei.
      2. 48,XXXY variant (Venkateshwari et al. 2010):
         1. Moderate to severe mental retardation
         2. Behavior: often immature and consistent with IQ level, typically described as passive, cooperative, and not particularly aggressive
         3. Normal to tall stature
         4. Dysmorphic facies
         5. Radioulnar synostosis
         6. Fifth finger clinodactyly
         7. Hypergonadotropic hypogonadism
         8. Small testes
         9. Signs of androgen deficiency
      3. 49,XXXYY variant:
         1. Mental retardation
         2. Somatic anomalies
         3. Small testes

4. 49,XXXXY variant (Zaleski et al. 1966; Peet et al. 1998): severity and frequency of somatic anomalies increase as the number of X chromosomes increases:
    1. Mental retardation
    2. Microcephaly
    3. Short stature
    4. Hypotonia with lax joints
    5. Facial dysmorphic features: ocular hypertelorism, flat nasal bridge, epicanthal folds, bifid uvula, or cleft palate
    6. Short neck
    7. Congenital heart defects
    8. Radioulnar synostosis
    9. Genu valgum
    10. Pes cavus
    11. Fifth finger clinodactyly
    12. Hypergonadotropic hypogonadism with small genitalia
    13. Behavioral disorders: shy, friendly, occasional irritability, temper tantrums, low frustration tolerance, and difficulty in changing routines

10. Natural history of Klinefelter syndrome: estimated prevalence of phenotypic features (Herlihy et al. 2011; Groth et al. 2013; Nahata et al. 2013; Herlihy and McLachlan 2015):
    1. Prepubertal:
        1. Decreased penile size (10–25%)
        2. Cryptorchidism (27–37%)
        3. Delayed speech and motor development (69–75%)
        4. Learning difficulties (>75%)
    2. Postpubertal:
        1. Infertility (99%).
        2. Small testes (>95%).
        3. Decreased testosterone (63–85%) may present as low mood, reduced libido, fatigue, poor muscle development, generalized weakness, or erectile dysfunction.
        4. Decreased facial and body hair (<80%): often perceived as pubertal delay or incomplete virilization.
        5. Gynecomastia (<56%).
        6. Metabolic syndrome (46%).
        7. Diabetes (10–39%).
        8. Osteopenia (40%) – osteoporosis in up to 10%.

Diagnostic Investigations

1. Cytogenetic studies (Kleczkowska et al. 1988):
    1. Commonest indications: hypogonadism and/or infertility (Abramsky and Chapple 1997).
    2. 47,XXY (80–90%).
    3. Mosaicism (10%): Insisting on an adequate number of cells (at least 50) to be examined during karyotyping is important so as not to miss diagnosing mosaicism (Nor and Jalaludin 2016):
        1. 46,XX/47,XXY
        2. 46,XY/47,XXY
        3. 46,XY/48,XXXY
        4. 47,XXY/48,XXXY
    4. Variants (Linden et al. 1995):
        1. 48,XXYY
        2. 48,XXXY
        3. 49,XXXYY
        4. 49,XXXXY
    5. Structural abnormal X in addition to a normal X and Y:
        1. 47,X,i(Xq)Y
        2. 47,X,del(X)Y
2. Endocrinologic studies:
    1. A variable degree of feminization and insufficient androgenization (Vorona et al. 2007):
        1. Elevated plasma FSH, luteinizing hormone, and estradiol levels
        2. Low plasma testosterone levels in patients age 12–14 years
    2. Subnormal increased testosterone in response to human chorionic gonadotropin administration
3. Imaging studies:
    1. Testis ultrasound (US) (Rocher et al. 2016): The testes of KS men are smaller, more nodular, and more vascularized, and they contain more microliths than those of non-KS infertile men. This combination of US results should lead physicians to request a karyotyping.

2. Echocardiography to demonstrate mitral valve prolapse.
3. Radiography:
    1. Lower bone mineral density
    2. Radioulnar synostosis
    3. Taurodontism
4. Histology:
    1. Small, firm testes
    2. Seminiferous tubular hyalinization, sclerosis, and atrophy with focal hyperplasia of mostly degenerated Leydig cells
    3. Deficient or absent germ cells
    4. Rare spermatogenesis (azoospermia)
    5. Progressive degeneration and hyalinization of seminiferous tubules after puberty in mosaic patients
5. Majority of cases of Klinefelter syndrome are detected via one of the following scenarios (Herlihy et al. 2011; Nahata et al. 2013; Herlihy and McLachlan 2015):
    1. Prenatal (21% of diagnoses):
        1. Klinefelter syndrome may be an incidental finding when a karyotype is conducted following chorionic villus sampling or amniocentesis due to increased risk in pregnancy (high risk of Down syndrome, increased maternal age).
        2. More recently, through chromosomal analysis in noninvasive prenatal testing, which women with both low-risk and high-risk pregnancies are choosing because of high accuracy, low risk to pregnancy, and the rapidly decreasing cost of this testing (Simpson and Samango-Sprouse 2013).
    2. Childhood (12% of diagnoses):
        1. Global developmental delay in infancy (delayed walking or speech development)
        2. Behavioral or learning difficulties in childhood [attention deficit hyperactivity disorder (ADHD), autism]
    3. Puberty (16% of diagnoses):
        1. Incomplete (or perceived delayed) puberty in adolescence
        2. Hypogonadism, gynecomastia, or poor virilization noted by the astute physician
    4. Adulthood (51% of diagnoses):
        1. Fertility investigations
        2. Androgen deficiency in different contexts (e.g., sexual dysfunction, depression, osteoporosis)
    5. Incidental at any age: Karyotyping is carried out where Klinefelter syndrome is not the suspected diagnosis (e.g., investigation of an alternate genetic syndrome or hematological malignancy).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sibs: recurrence risk not increased for nonmosaic patients
    2. Patient's offspring:
        1. Recurrence risk not increased since all 47,XXY individuals are infertile
        2. Report of paternity in nonmosaic 47, XXY males (no other tissues were examined for possible mosaicism with a 46, XY cell line)
    3. A risk of having a 47,XXY offspring in a few 46,XY/47,XXY mosaic patients who fathered a child
2. Prenatal diagnosis:
    1. Cytogenetic analysis of fetal cells obtained from amniocentesis and CVS.
    2. Dilemma for parents since prognosis for the fetus with XXY is good but the possibility of phenotypic abnormalities does exist.
    3. Explanation to each couple about the genetic risks resulting from intracytoplasmic sperm injection (ICSI) (increased risk of sex chromosome and autosome abnormalities).
    4. Sperm fluorescence in situ hybridization analysis in a patient with mosaic Klinefelter's syndrome can provide a rough estimate of the risk of transmission of sex chromosomal aberrations to his offspring. This estimate can be of help to the patient and his female partner in deciding on ICSI and prenatal diagnosis (or preimplantation diagnosis) (Kruse et al. 1998).

5. Preimplantation genetic diagnosis by embryo biopsy offers an efficient tool for embryo selection (Friedler et al. 2001).
6. Preimplantation genetic diagnosis (PGD) is generally offered to couples with KS who undergo successful testicular sperm extraction and intracytoplasmic sperm injection. This technique allows for selecting chromosomally abnormal embryos in order to avoid transferring abnormal embryos (Aksglaede and Juul 2013).
7. Low rates of pregnancy termination for prenatally diagnosed Klinefelter syndrome and other sex chromosome polysomies (Meschede et al. 1998).

3. Management (Mandoki and Sumner 1991):
   1. Speech therapy.
   2. Physical therapy.
   3. Occupational therapy.
   4. Educational services.
   5. Stable and supportive family environment (Bender et al. 1995)
   6. Reassurance of patients that most of the clinical features can be explained by the diminished ability of the testes to produce testosterone.
   7. Testosterone replacement (Nielsen et al. 1988; Winter 1990; Smyth and Bremner 1998): Optimal time to initiate therapy is at age 11–12 years of age to allow for the maximum effect and permit boys to experience pubertal changes with their peers:
      1. Corrects hormone imbalance (symptoms of androgen deficiency)
      2. Improves self-image
      3. Positive effect on mood and behavior (Myhre et al. 1970)
      4. Increase in masculinity
      5. Increase in strength
      6. Increase in libido
      7. Increase in facial and pubic hair
      8. Diminish fatigue and irritability
      9. No positive effect on infertility
   8. Management of gynecomastia:
      1. Androgen replacement therapy effective in achieving regression of less severe gynecomastia in some patients
      2. Reduction mammoplasty or liposuction for severe or psychologically disturbing gynecomastia
   9. Management of infertility (Lanfranco et al. 2004):
      1. Nowadays patients with Klinefelter syndrome, including the nonmosaic type, need no longer be considered irrevocably infertile because intracytoplasmic sperm injection offers an opportunity for procreation even when there are no spermatozoa in the ejaculate.
      2. In a substantial number of azoospermic patients, spermatozoa can be extracted from testicular biopsy samples, and pregnancies and live births have been achieved.
      3. The frequency of sex chromosomal hyperploidy and autosomal aneuploidies is higher in spermatozoa from patients with Klinefelter syndrome than in those from normal men. Thus, chromosomal errors might in some cases be transmitted to the offspring of men with this syndrome.
      4. The genetic implications of the fertilization procedures, including pretransfer or prenatal genetic assessment, must be explained to patients and their partners.
      5. Banking testicular tissue from prepubertal KS boys should be performed only in a research framework (Gies et al. 2016).

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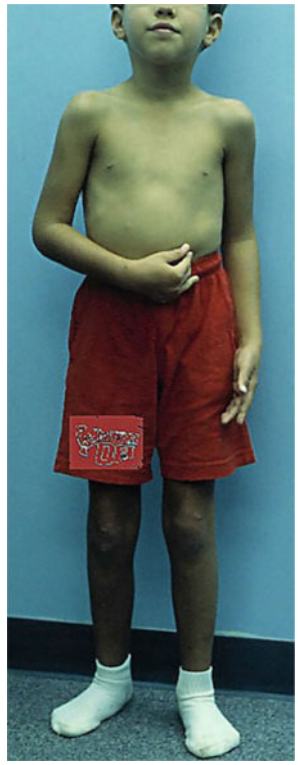

Fig. 1 A child with Klinefelter syndrome (47,XXY) showing normal phenotype

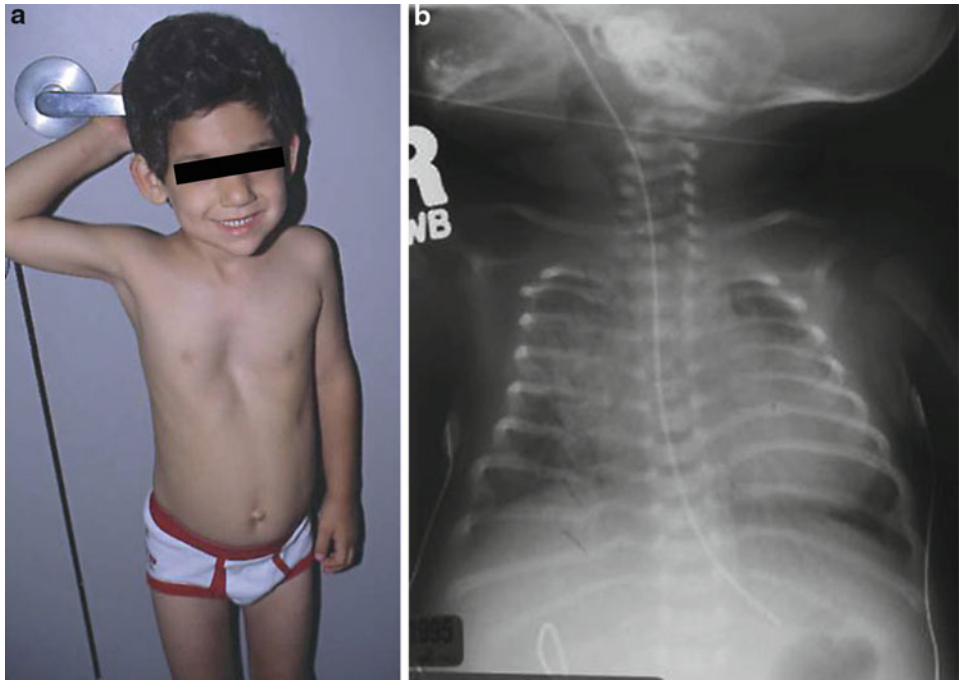

Fig. 2 (**a**, **b**) A child with Klinefelter syndrome (47,XXY) (**a**) showing pectus excavatum and multiple fractures of ribs (**b**) in the neonatal period during hospital stay

Fig. 3 The previous child at 14 years of age

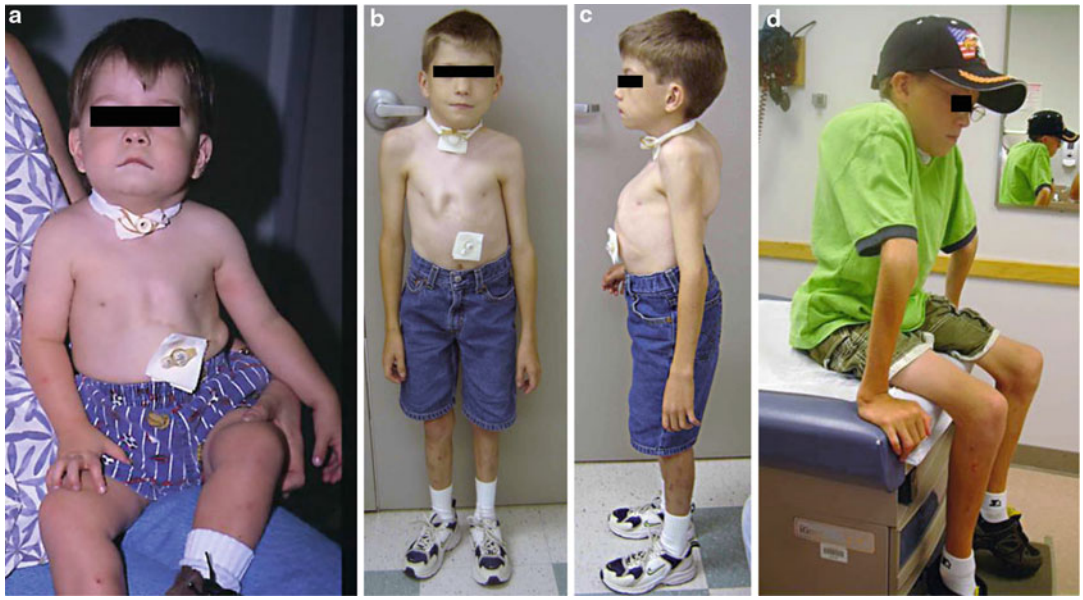

Fig. 4 (**a**–**d**) A child with Klinefelter syndrome (47,XXY) associated with paralyzed diaphragm requiring intubation. The photos were taken at early childhood (**a**), 9 (**b**, **c**), and 12 years of age (**d**) showing pectus excavatum, long extremities with hyperextended elbow, and kyphoscoliosis

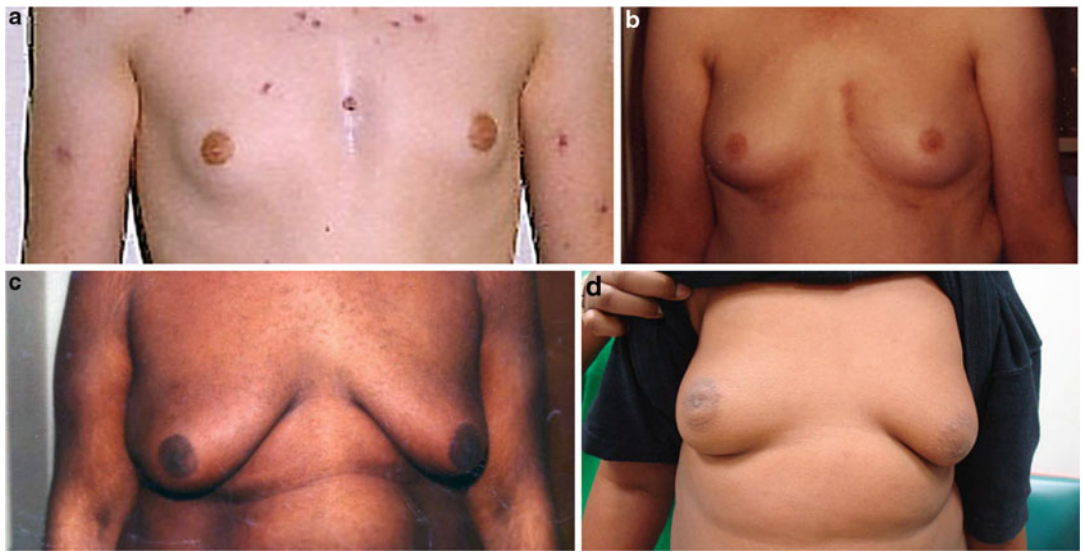

Fig. 5 (**a**–**d**) Two adolescent boys (**a**, **b**) and two adults (**c**, **d**) with Klinefelter syndrome (47,XXY) showing gynecomastia

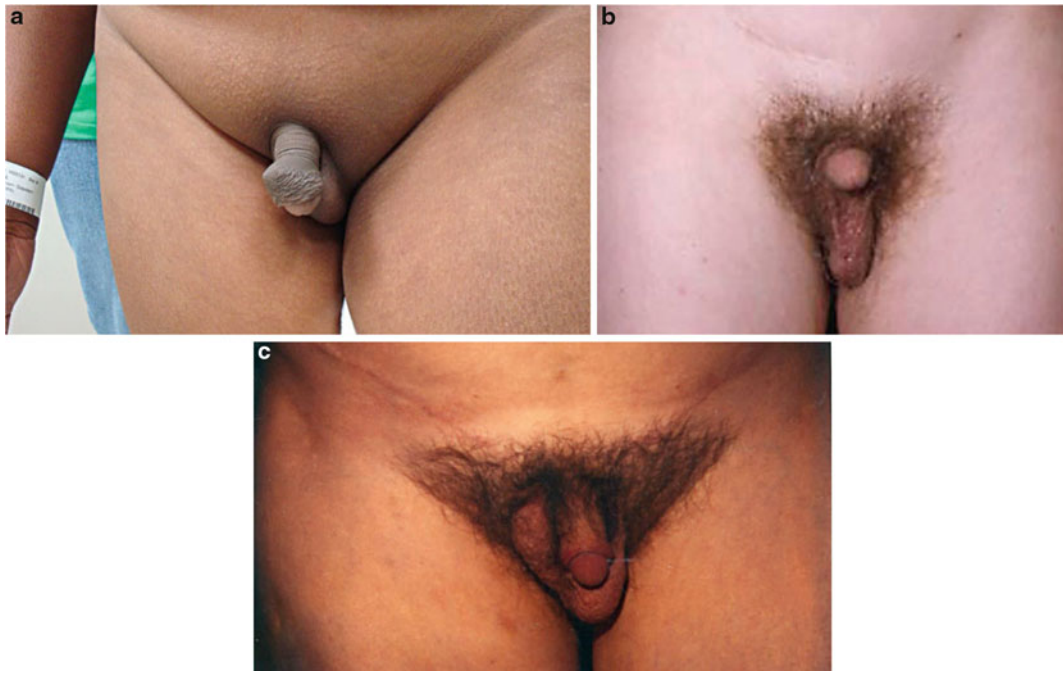

Fig. 6 (**a**–**c**) A 13-year-old boy (**a**), an adolescent boy (**b**), and an adult male (**c**) with Klinefelter syndrome (47,XXY) showing female distribution of pubic hair (last two patients) and small scrotum containing atrophic testicles

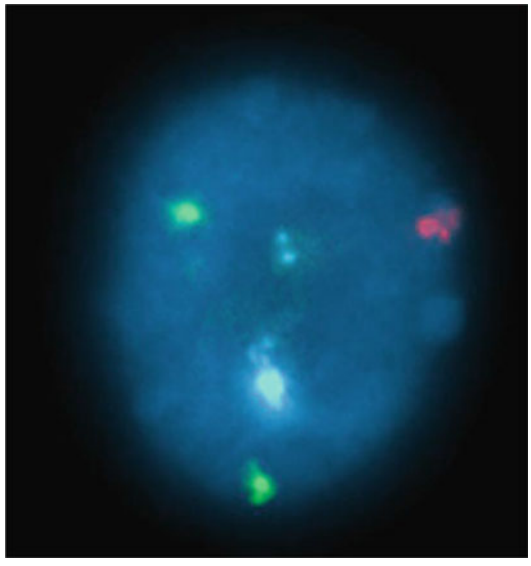

Fig. 7 Interphase FISH showing two copies of CEPX (*green*), one copy of CEPY (*orange*), and two copies of CEP18 (*aqua*), which was confirmed by chromosome karyotype of 47,XXY

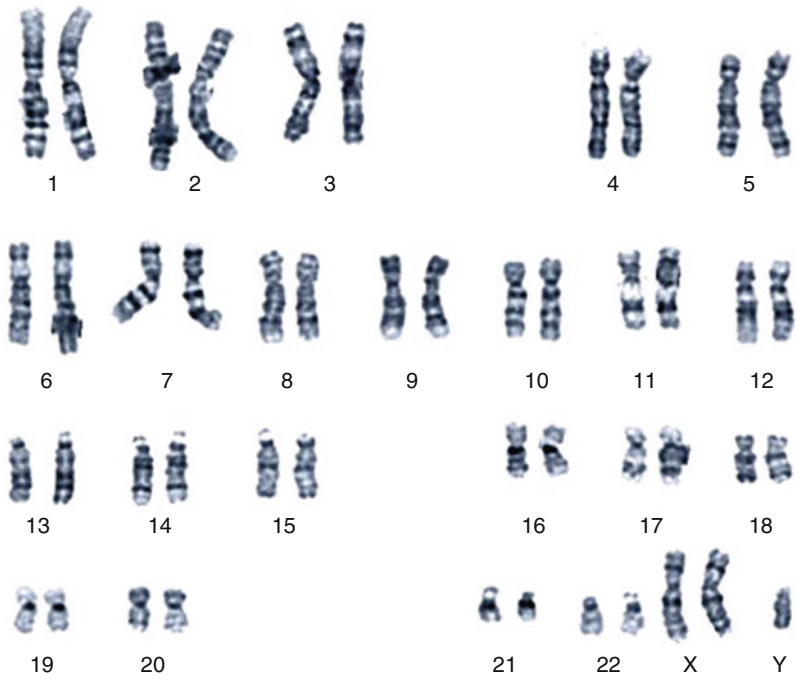

Fig. 8 A G-banded karyotype showing 47, XXY chromosome constitution

Klippel-Feil Syndrome

Contents

In *1912*, Klippel and Feil (1912) described a patient with a short neck, a low posterior hairline, and a severe restriction of motion of the neck due to complete fusion of the cervical vertebrae. These features now constitute a clinical triad of the Klippel-Feil syndrome (KFS) (Hensinger et al. 1974).

Synonyms and Related Disorders

Cervical vertebral fusion; Cervico-oculo-auditory (Wildervanck) syndrome

Genetics/Basic Defects

1. Genetic etiology unknown;
    1. Sporadic in majority of cases
    2. Rare autosomal dominant transmission: identification of a familial KFS gene locus on 8q [inv(8)(q22.2q23.3)] segregated with congenital vertebral fusion (Clarke et al. 1995)
2. Mechanism: failure in the process of segmentation of the vertebra.
3. Possible causes of phenotypic variation (Pourquie and Kusumi 2001):
    1. Variable expression of single genes
    2. Associated phenotypes due to deletions or large-scale rearrangements that disrupt several genes
    3. Secondary phenotypes resulting from disruption of normal cervical vertebral patterning
4. Familial Klippel-Feil syndrome (Clarke et al. 1995, 1996):
    1. Characterized by congenital fusion of spinal vertebrae in addition to other congenital anomalies:
        1. Otolaryngological abnormalities
        2. Craniofacial abnormalities
    2. The first KFS gene (*SGM1*) locus identified on chromosome 8q [inv(8)(q22.2q23.3)] segregating with vertebral fusions and associated vocal impairment within the family
5. Suggestion of a possible role of *PAX1* haploinsufficiency in Klippel-Feil syndrome (McGaughran et al. 2003):
    1. Observation that the mouse *PAX1* mutant phenotype *undulated* is characterized by vertebral segmentation defects reminiscent of the human disorder Klippel-Feil syndrome

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Observation of differences in the *PAX1* sequence (missense, silent, or intronic changes not represented in the control panel tested) in 6 out of 63 patients
6. Mutations in growth/differentiation factor 6 (*GDF6*, on chromosome 8q22.1) are associated with vertebral segmentation defects in Klippel-Feil syndrome (Tassabehji et al. 2008):
   1. Mutations at the *GDF6* gene locus in familial and sporadic cases of KFS including the recurrent missense mutation of an extremely conserved residue c.866 T > C (p.Leu289Pro) in association with mirror movements and an inversion breakpoint downstream of the gene in association with carpal, tarsal, and vertebral fusions.
   2. *GDF6* is expressed at the boundaries of the developing carpals, tarsals, and vertebrae and within the adult vertebral disc.
   3. *GDF6* knockout mice are best distinguished by fusion of carpals and tarsals, and *GDF6* knockdown in *Xenopus* results in a high incidence of anterior axial defects consistent with a role for *GDF6* in the etiology.
7. Mutations in *MEOX1*, encoding mesenchyme homeobox 1, cause Klippel-Feil anomaly (Mohamed et al. 2013).

Clinical Features

1. Triad seen in <50% of patients indicating almost complete cervical involvement and may be clinically evident at birth (McBride 1992; Herman and Pizzutillo 1999):
   1. Short, webbed neck
   2. Low posterior hairline
   3. Limitations of cervical motion (lateral bend and rotation) with associated congenital cervical fusions
2. Facial asymmetry
3. Torticollis
4. Associated anomalies:
   1. Congenital scoliosis (60%) (Winter et al. 1984)
   2. Sprengel deformity (30%):
      1. Congenital elevation of the scapula resulting from interruption of the normal caudal migration of the scapula
      2. Hypoplastic scapula
      3. Scapula fixation
      4. Associated anomalies including absent or fused ribs, chest wall asymmetry, Klippel-Feil syndrome, cervical ribs, congenital scoliosis, cervical spina bifida, and presence of omovertebral bone
   3. Cervical ribs (Hazra et al. 2016):
      1. Although mostly asymptomatic, these are the most common cause of compression of the subclavian vessels producing an arterial thoracic outlet syndrome (Roos 1979). Neurogenic (brachial plexus compression) and venous (subclavian or axillary vein compression) can also occur.
      2. Associated with 30% of the patients with Klippel-Feil syndrome (Sudhakar et al. 2008).
      3. Reports of thoracic outlet syndrome: rare (Konstantinou et al. 2004).
   4. Hearing impairment (audiologic testing) (30%)
   5. Synkinesia (mirror movements) (20%)
   6. Renal anomalies (35%) (renal ultrasound)
      1. Unilateral renal agenesis (most common renal anomaly) (Moore et al. 1975)
      2. Renal malrotation
      3. Horseshoe kidney
      4. Ectopic kidney
      5. Renal pelvic and ureteral duplication
      6. Renal dysgenesis
   7. Congenital heart disease (14%): most common being ventricular septal defect
   8. Hemifacial microsomia
   9. Neural tube defects
   10. Ptosis
   11. Cervico-oculo-auditory (Wildervanck) syndrome (Danilidis et al. 1980; Cremers et al. 1984)
      1. Mixed hearing loss
      2. Fused cervical vertebra
      3. Bilateral abducens palsy with retracted bulb (Duane syndrome)

12. Lateral rectus palsy
13. Facial nerve palsy
14. Association with malformed larynx (Clarke et al. 1994)
15. Upper extremity anomalies

5. Complaints
    1. Issues of appearance
    2. Torticollis (head tilt)
    3. Neck pain
    4. Changes in exercise tolerance
    5. Excessive instability of the upper cervical spine
    6. Problems related to associated anomalies
    7. Neurological problems from direct irritation of or impingement on a nerve root or from compression of the spinal cord
        1. Cranial nerve abnormalities
        2. Cervical radiculopathy from involvement of the nerve root
        3. Symptoms from spinal cord compression
            1. Spasticity
            2. Hyperreflexia
            3. Muscle weakness
            4. Complete paralysis
        4. At risk of sustaining a neurologic deficit including quadriplegia after minor trauma (Elster 1984)
6. Three clinical subtypes (Gunderson et al. 1967):
    1. Type I characterized by massive cervical and thoracic vertebral fusions into bony blocks
    2. Type II with fusion at one or two vertebral junctures, occipitoatlantal fusion, lower thoracic abnormalities, and more severe cervicothoracic fusions
    3. Type III with both cervical and lower thoracic or lumbar fusions
7. Risk factors
    1. Types I and III fusions
        1. Various neurologic, cutaneous, cardiac, skeletal, and oral anomalies
        2. Difficulty in the birth process
        3. Marked abnormal facial appearance with Sprengel deformity, accessory ear lobes, and pterygium colli
        4. Serious neurologic anomalies with early death or long-term neurologic deficits
    2. Type II fusion
        1. Normal appearance
        2. Normal lives
        3. Incidental symptoms from osteoarthritis, basilar impression, or occipito-atlas fusion
    3. Hypermobility of the upper cervical spine at increased risk of neurologic injury with presentation of neurologic sequelae in the teens or 20s (Pizzutillo et al. 1994)
    4. Lower cervical involvement at risk of developing cervical spondylosis at more advanced ages

Diagnostic Investigations

1. Audiologic evaluation for hearing loss
2. Renal ultrasonography
3. Radiography (Hensinger et al. 1974)
    1. Cervical spine fusion on flexion and extension views: roentgenographic hallmark of the Klippel-Feil syndrome
        1. Type I cervical fusion (C2–C3 fusion with occipitalization of the atlas)
        2. Type II cervical fusion (long cervical fusion with an abnormal occipitocervical junction)
        3. Type III cervical fusion (two blocked vertebral segments with a single open interspace)
    2. Other associated skeletal anomalies
        1. Flattening and widening of involved vertebral bodies
        2. Absent disc spaces
4. CT scan helpful in diagnosing nerve root and spinal cord impingement by osteophyte
5. MRI to evaluate instability and the risk of neurological compromise
    1. Spinal stenosis
    2. Cord compression
    3. Syringomyelia
6. CT and MRI for workup of cervicothoracic spinal dysraphism with diastematomyelia (Hudson and Makis 2016)
    1. An 18F-NaF bone positron emission tomography scan done as part of the

metastatic workup showing the characteristic sagittal bone spur
2. MRI demonstrated a complete split of the cervical and upper thoracic spinal cord.

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased unless a parent has an autosomal dominant disorder
   2. Patient's offspring: not increased unless the patient has an autosomal dominant type of the disorder
2. Prenatal diagnosis
   1. Ultrasonography: difficult to diagnose cervical vertebral anomalies and torticollis by ultrasonography
   2. Molecular genetic analysis on fetal DNA obtained from amniocentesis or CVS for *GDF6* mutation, provided the disease-causing allele of an affected family member has been identified prior to prenatal diagnosis
3. Management
   1. Treat renal, cardiovascular, and auditory anomalies accordingly
   2. Mechanical symptoms caused by degenerative joint disease
      1. Traction
      2. Wearing a cervical collar
      3. Analgesics
   3. Neurological symptoms
      1. Surgical stabilization with or without decompression
      2. Surgical correction of Sprengel deformity to improve appearance
   4. Surgery for congenital conductive deafness (Van Rijn and Cremers 1988)

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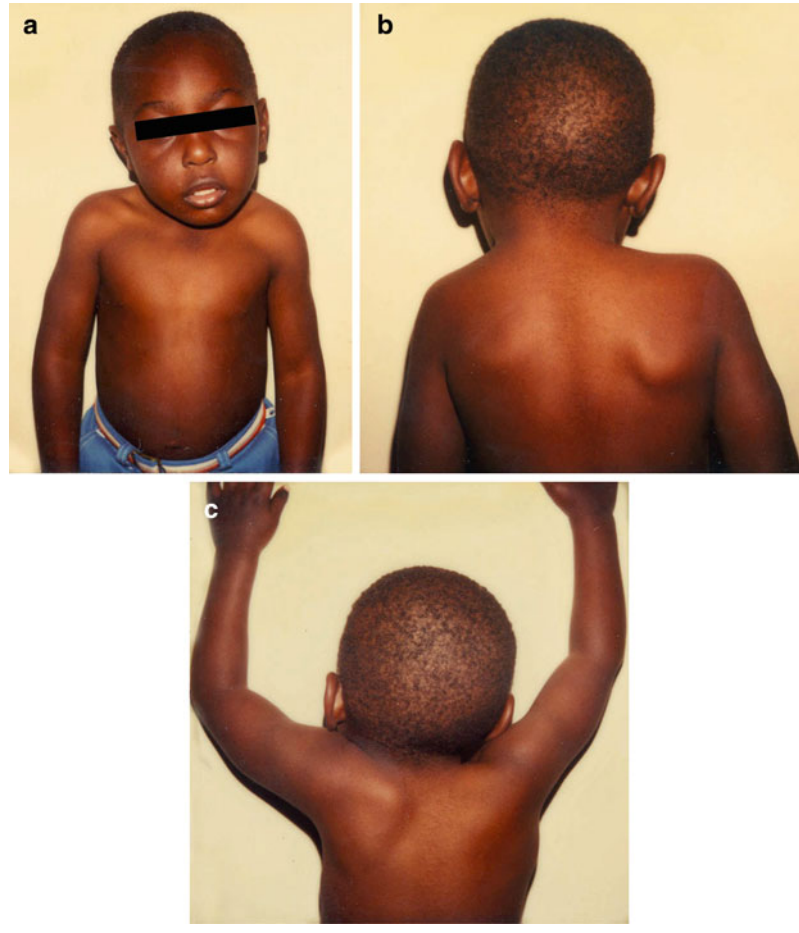

Fig. 1 (**a**–**c**) A child with Klippel-Feil syndrome and Sprengel deformity showing torticollis, short/webbed neck (**a**, **b**), and inability to raise left arm due to congenital elevation of left scapula (**c**)

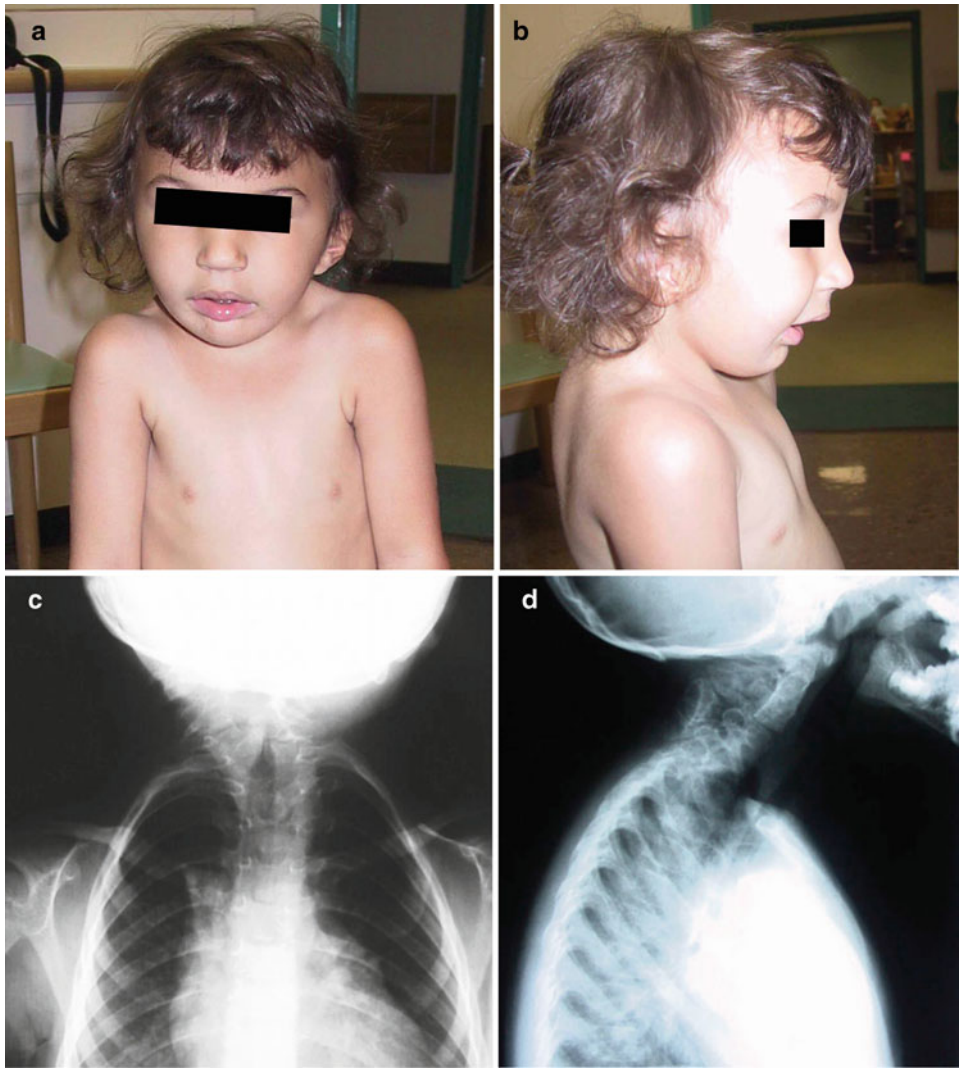

Fig. 2 (**a**–**d**) A girl with Klippel-Feil syndrome showing torticollis; short, webbed, and stiff neck (**a**, **b**); and cervical fusion (failure of segmentation) demonstrated by radiographs (**c**, **d**)

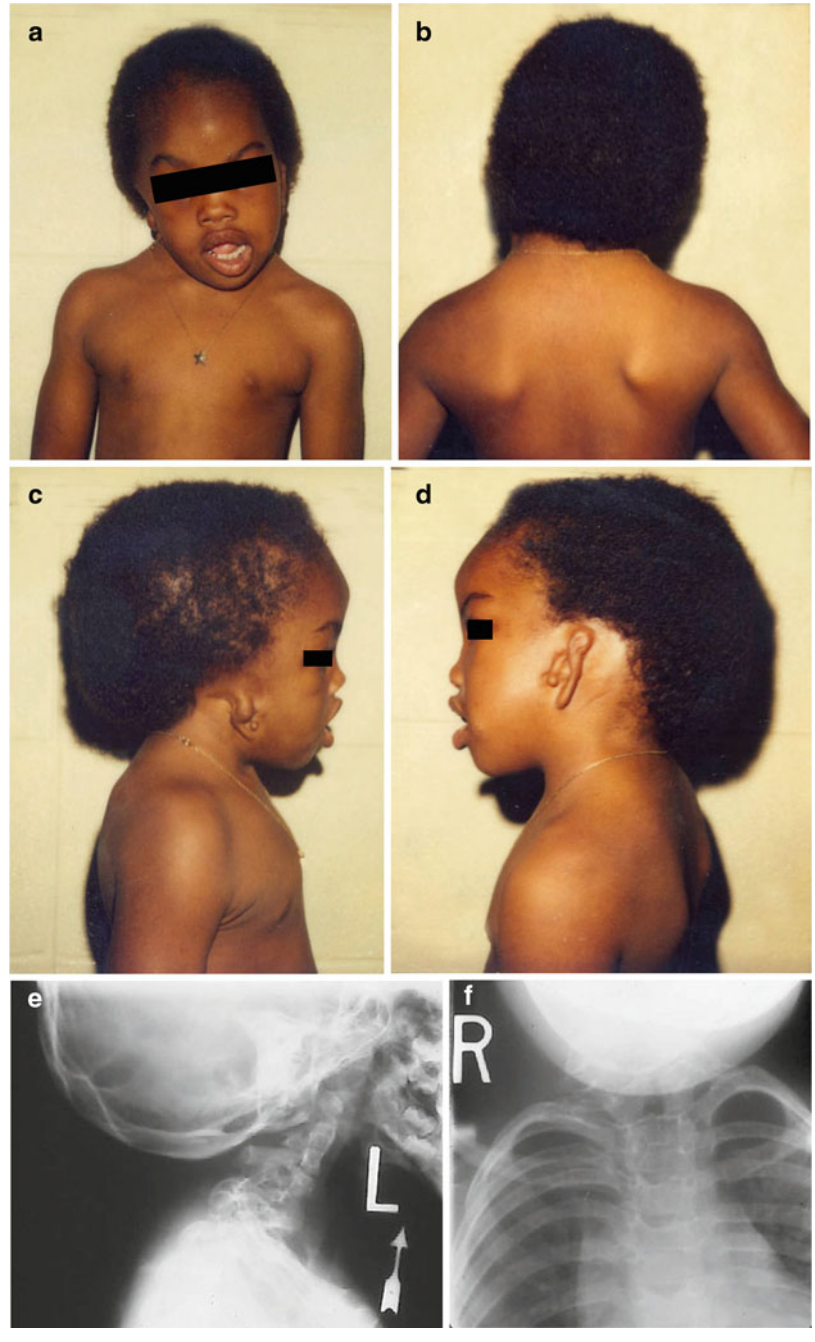

Fig. 3 (**a**–**f**) A child with Klippel-Feil syndrome showing hemifacial microsomia and torticollis (**a**); short, webbed, and stiff neck (**b**); microtia (**c**, **d**); and cervical fusion demonstrated by radiographs (**e**, **f**)

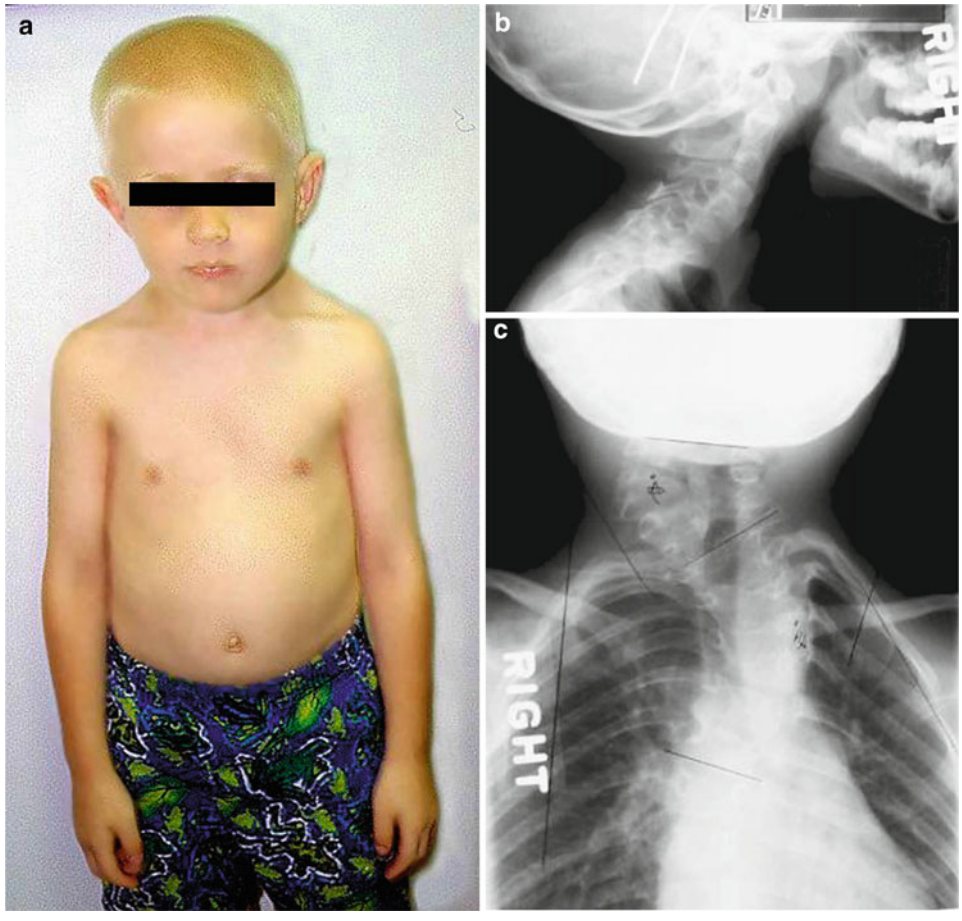

Fig. 4 (**a**–**c**) A 10-year-old boy with Klippel-Feil syndrome (**a**) showing torticollis; short, webbed, and stiff neck; low posterior hairline; elevated left scapula; failure of segmentation (fusion) of the cervical vertebrae; and cervicothoracic scoliosis demonstrated by radiographs (**b**, **c**). He has no neurologic defects or cervical discomfort

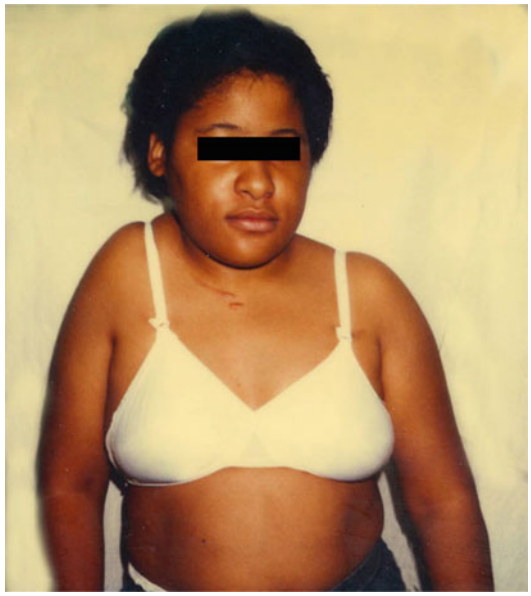

Fig. 5 A 15-year-old girl with Klippel-Feil syndrome, Sprengel deformity, and deafness

Klippel-Trenaunay Syndrome

Contents

Klippel-Trenaunay syndrome (KTS) is primarily a rare congenital capillary-venous vascular malformation associated with altered limb bulk and/or length. In 1900, Klippel and Trenaunay first reviewed systematically a condition consisting of capillary nevus, early onset of varicosities, and hypertrophy of tissues and bones of the affected limb. These three features constitute the primary diagnostic criteria of the syndrome today. The additional name Weber is sometimes added to describe those individuals who also have clinically significant arteriovenous malformations as a component of the syndrome, an association noted by Weber in 1918. More than 1,000 cases of Klippel-Trenaunay syndrome have now been reported in the literature (Berry et al. 1998).

Synonyms and Related Disorders

Angioosteohypertrophy syndrome; Klippel-Trenaunay-Weber syndrome; Parkes-Web syndrome; *PIK3CA*-related overgrowth spectrum

Genetics/Basic Defects

1. Etiology
    1. Sporadic occurrence
    2. Somatic mutation of an as-yet-unknown gene
    3. Multifactorial inheritance
    4. Autosomal dominant inheritance with variable expression
2. Genetics of KTS (Wang 2005): three chromosomal abnormalities reported in three different KTS patients
    1. Two balanced translocations t(5;11)(q13.3;p15.1) (Tian et al. 2004)
        1. Chromosomal breakpoints involved in translocation t(5;11)(q13.3;p15.1) have been fully characterized, which has led to the identification of a susceptibility gene, *AGGF1* (previously known as *VG5Q*), for KTS

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   2. *AGGF1* is located on chromosome 5q13.3 and encodes an angiogenic factor
   3. *AGGF1* as the first susceptibility gene that confers a risk to the development of KTS and suggests that that the molecular mechanism for the pathogenesis of KTS is the "increased" angiogenesis. These results are consistent with histological studies that showed an increase in both the number and diameter of the venules in the dermis and subdermal fat of KTS tissues (Baskerville et al. 1985)
2. Translocation t(8;14)(q22.3;q13) (Wang et al. 2001) and an extra supernumerary ring chromosome 18 (Timur et al. 2004) were reported in patients with KTS
   1. Shown to arise de novo, which strongly suggests that genetic factors contribute to the pathogenesis of KTS
   2. The specific vascular gene disrupted by either 8q22.3 or 14q13 breakpoint remains to be identified
   3. The ring chromosome 18, r(18), was mostly derived from the short arm of chromosome 18, and further analyses of the genes on the r(18) may lead to the identification of a vascular gene
3. Terminal deletion 2q37.3 (by comparative genomic hybridization) reported in a patient with Klippel-Trenaunay-Weber syndrome (Puiu et al. 2013)
4. Sporadic occurrence of KTS and a mosaic pattern of KTS features may be explained by the two-hit hypothesis and the concept of paradominant inheritance proposed by Happle (1986, 1987, 1993)
   1. Germline mutations in a KTS gene (e.g., *AGGF1*) are important for development of KTS but not sufficient
   2. A "second hit," somatic mutation in the same KTS gene or in a different gene is required for the development of KTS features
5. Klippel-Trenaunay syndrome belongs to the *PIK3CA*-related overgrowth spectrum (Vahidnezhad et al. 2015)
3. Possible mechanisms/pathogenesis leading to overgrowth of the affected limb: poorly defined
   1. Two phases of manifestations
      1. Increased bulk or girth
      2. Increased length accompanied by bone enlargement
   2. Increased girth and size of bone due to venous hypertension, based on observations following hind leg deep vein ligation in dogs
   3. Atresia of the venous system leading to stasis, edema, varicosities, and ultimately to limb elongation and hypertrophy
   4. Limb enlargement seen in children following thrombosis or ligation of a deep vein postnatally
   5. Overgrowth in fetal life promoted by increased blood flow through the abnormal capillary network and cutaneous venous channels
   6. A mesodermal defect acting on angiogenesis leading to the formation of hemangiomas and varicose veins (Martin et al. 2001)
   7. A defect in the process of vessel remodeling during embryogenesis

Clinical Features

1. Triad (Berry et al. 1998; Cohen 2000)
   1. Combined vascular malformations of the capillary, venous, and lymphatic types
   2. Varicosities of unusual distribution, in particular the lateral venous anomaly observed during infancy or childhood
   3. Limb enlargement
2. Cutaneous manifestations
   1. Primarily a diffuse capillary malformation
   2. Typically present on an affected limb
   3. May be present on any body part
   4. Often presenting as an irregular but relatively linear border
   5. Rarely crossing the midline when present on the trunk, sometimes exhibiting a sharp demarcation

3. Vascular malformations
    1. Typically combined with cutaneous capillary malformation
    2. Persistence of abnormal superficial veins associated with deep venous hypoplasia/duplications and abnormal venous valve formation
    3. Presence of mixed vascular malformations including capillary, venous, arterial, and lymphatic systems
    4. Classification of vascular malformations by Mulliken and Glowacki (1982)
        1. Capillary-venous malformation (CVM): typical finding
        2. CVLM (CVM + lymphatic malformation): common finding
        3. CLAVM (including arterial malformation): uncommon
    5. Congenital in nature
    6. Not responding to agents used in the treatment of hemangiomas such as prednisone or interferon-α
4. Limb hypertrophy
    1. Due to an increase in bulk of the subcutaneous tissues
    2. Bony hypertrophy
5. Sites of involvement (Mueller-Lessmann et al. 2001)
    1. Lower limb most common (about 95%)
    2. Upper limb (about 5%)
    3. Trunk only: uncommon
    4. Orofacial involvement
        1. Jaw enlargement
        2. Facial asymmetry
        3. Malocclusions
        4. Premature tooth eruption
        5. Hemangioma of the lips, tongue, and oral mucosa
6. Sex ratio: males and females affected equally
7. Complications
    1. Abnormal vasculature
        1. Thrombosis
        2. Coagulopathy
        3. Pulmonary embolism
        4. Heart failure (in the presence of significant AVM)
        5. Bleeding from abnormal vessels in gut, kidney, or genitalia
    2. Gastrointestinal varicoses
        1. Bleeding: uncommon but can be fatal (Samo et al. 2013)
        2. Pain
        3. Diarrhea
    3. Protein-losing enteropathy secondary to intestinal lymphangiectasia
    4. Infection is a particular risk for patients with abnormal lymphatic drainage. Antibiotics indicated in:
        1. Cellulitis
        2. Surgery
        3. Injury in an affected limb
    5. Pain due to venous insufficiency or lymphedema in some older children and adults
    6. Venous thromboembolism
        1. Chronic thromboembolic pulmonary hypertension
        2. Subsequent right ventricular failure
    7. Occurrence of ulceration on affected leg
    8. Rare occurrence of skin tumors on the affected limb
        1. Squamous cell carcinoma possibly secondary to a long-standing venous ulcer (De Simone et al. 2002)
        2. Basal cell carcinoma
    9. Pregnancy and KTS: known perinatal risks to both the mother and fetus (Fait et al. 1996; González-Mesa et al. 2012; Stein et al. 2006)
        1. Hemorrhage secondary to increased hemangiomas and varices
        2. Coagulopathy including deep and superficial thrombosis
        3. Acute and chronic disseminated intravascular coagulation
        4. Kasabach-Merritt syndrome (Neubert et al. 1995)
        5. Placental abnormalities
8. Four levels of severity of Klippel-Trenaunay syndrome (You et al. 1983)
    1. Venous dysplasias: phlebectasic dysplasias (Klippel-Trenaunay syndrome)
    2. Arterial dysplasias
    3. Arterial and associated venous dysplasias:
        1. Phlebarterectasia (no arteriovenous shunt)
        2. Angiodysplasias with shunt (Klippel-Trenaunay-Weber syndrome)

4. Mixed angiodysplasias: a typical Klippel-Trenaunay syndrome
9. Diagnostic criteria: Presence of two of the three following cardinal features is sufficient to make a diagnosis (Jacob et al. 1998)
   1. Capillary malformations (98%)
   2. Venous malformations or varicose veins (72%)
   3. Hypertrophy of the affected tissues (67%)
10. Diagnostic criteria and proposed definition: two major features at least one from congenital vascular malformations, which should always include either capillary malformations or venous malformations and at least one from disturbed growth (bi or bii) (Oduber et al. 2008)
    1. Congenital vascular malformations
       1. Capillary malformations (CMs). This includes port-wine stains
       2. Venous malformations (VMs): This includes hypoplasia or aplasia of veins, persistence of fetal veins, varicosities, hypertrophy, tortuosity, and valvular malformations
       3. Arteriovenous malformations (AVMs): This includes only very small AVMs or arteriovenous fistulas (AVF)
       4. Lymphatic malformations (LM): This includes any LM
       5. Localization
          1. CM can be located anywhere on the body, although location in the face is exceedingly rare
          2. AVM, VM, and LM are mainly located on the extremities and adjacent parts of the trunk (pelvis, shoulder) but in expressed forms of KTS also elsewhere (bladder, rectum, lower GI tract, penis, uterine, vulva, vagina, liver, kidneys, lung, spine)
          3. AVM, VM, and LM are not located in the face or brain
    2. Disturbed growth
       1. Disturbed growth of bone in the length or girth
       2. Disturbed growth of soft tissue in the length or girth
       3. The disturbed growth includes:
          1. Hypertrophy (frequent) of a small body part (isolated finger, macrodactyly) or larger body part (total limb, half of the total body)
          2. Hypotrophy (infrequent) of a small or larger body part
       4. Can be present both on the same site as the vascular malformation(s) (frequent) and at another site (infrequent)
11. Four commonly held conceptions about Klippel-Trenaunay syndrome challenged
    1. Renaming Klippel-Trenaunay-Weber syndrome by addition of arteriovenous fistulas (Meier 2009)
       1. Significant arteriovenous communications not observed in Klippel-Trenaunay syndrome in large surgical series
       2. Parkes Weber syndrome
       3. Parkes Weber syndrome (PWS)
          1. Characterized by enlarged arteries and veins, capillary or venous malformations and enlargement of a limb
          2. Closely associated with and similar to Klippel-Trenaunay syndrome, except that high-flow arteriovenous malformation (AVM) (resulting in high-output heart failure) occurs in association with a cutaneous capillary malformation (increased chance of skin ulcerations) and skeletal or soft tissue hypertrophy with increased limb-length discrepancies (Ziyeh et al. 2004; Sunderkrishman 2015)
          3. Lymphatic malformations found in Klippel-Trenaunay syndrome not observed in Parkes Weber syndrome
    2. Overlap with Sturge-Weber syndrome
       1. Characteristics of Sturge-Weber syndrome: craniofacial angiomatosis, port-wine nevus, and cerebral calcification
       2. Overgrowth in Sturge-Weber syndrome tends to be minor and is always secondary to the vascular anomaly. In contrast,

overgrowth in Klippel-Trenaunay syndrome is striking
3. Presence of a bleeding diathesis of the Kasabach-Merritt type
    1. Kasabach-Merritt syndrome erroneously applied to patients with extensive venous or lymphaticovenous malformations who develop a localized intravascular coagulopathy in which the platelet count is minimally depressed (varying from 50,000 to 150,000/mm^3)
    2. Profound thrombocytopenia in true Kasabach-Merritt phenomenon (varying from 3,000 to 60,000/mm^3)
    3. Klippel-Trenaunay-Weber syndrome with Kasabach-Merritt coagulopathy and hydronephrosis (Bhat et al. 2015)
        1. Rare
        2. Mortality: high with development of Kasabach-Merritt syndrome
4. Familial aggregation with various genetic interpretations
    1. Inadequate documentation of cases
    2. Over interpretation of minor manifestations in relatives, including "nevus flammeus," hemangiomas, and varicosities (common manifestations in general populations)
    3. Klippel-Trenaunay syndrome defined as a capillary malformation with or without "hemihypertrophy" without mentioning of lymphatic malformations, lateral venous anomaly, lymphatic vesicles, or venous flares within the capillary malformation, or macrodactyly
5. Klippel-Trenaunay syndrome, Parkes Weber syndrome, and Sturge-Weber syndrome
    1. Each occurring sporadically
    2. Each considered separate entity because clinical manifestations and types of complications are different

12. Cutaneous vascular anomalies in the neonatal period (Hook 2013)
    1. Nevus simplex
    2. Port-wine stain
    3. Vascular malformation syndromes with overgrowth
        1. Sturge-Weber syndrome
        2. Klippel-Trenaunay syndrome
        3. Parkes Weber syndrome
        4. Capillary malformation-macrocephaly syndrome
        5. Proteus syndrome
        6. Beckwith-Wiedemann syndrome
    4. Cutis marmorata telangiectatica congenita
    5. Capillary malformation-arteriovenous malformation syndrome
    6. Blue-rubber-bleb nevus syndrome
    7. Vascular tumors
    8. Infantile hemangioma
    9. Congenital hemangioma
    10. Tufted angioma
    11. Kaposiform hemangioendothelioma

Diagnostic Investigations

1. Color duplex ultrasonography (Berry et al. 1998)
    1. AV malformation
    2. Deep venous hypoplasia (a decrease in caliber of at least 50% of a vein along its length)
    3. Venous duplication
    4. Variable varicosities
2. Radiography
    1. Enlargement of the limb bones
    2. Yearly to monitor evidence of leg length discrepancy
3. Noninvasive imaging and endoscopy for severe gastrointestinal bleeding
4. Lymphoscintigraphy using radionuclide tracers
    1. Indication: edema or a girth discrepancy more than 4 cm
    2. No uptake of tracer along major lymphatics of the affected limb during repeated scans over at least a 1-h period
5. MRI
    1. Pelvis: to look for vascular malformations involving the kidneys, bladder, or intestines
    2. MRI with gadolinium to distinguish lymphatic from venous malformations
    3. Magnetic resonance venogram or phlebography/venography to document the

lateral venous anomaly and any abnormalities that may be present in the deep veins of the leg
4. Able to demonstrate arteriovenous fistulas in Parkes Weber syndrome
5. Diffuse venous malformation of the uterus in a pregnant woman with Klippel-Trénaunay syndrome diagnosed by DCE-MRI (dynamic contrast-enhanced MRI) (Yara et al. 2016)

6. Angiography (Sunderkrishman 2015)
   1. Arteriography: primarily indicated when spinal cord or brain involvement is suspected
   2. Venography: rarely indicated

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased
   2. Patient's offspring: not increased (doubtful that autosomal dominant inheritance exists)
2. Prenatal diagnosis
   1. 2D/3D ultrasonography (Paladini et al. 1998; Roberts et al. 1999; Cakiroglu et al. 2013)
      1. Asymmetric limb hypertrophy associated with cutaneous or subcutaneous multiloculated cystic or multicystic lesions. Color Doppler examination reveals the presence of persistent embryonic lateral marginal veins
      2. Limb edema
      3. Cardiac failure ranging from isolated cardiomegaly to severe hydrops
      4. Prenatal sonographic diagnosis of Klippel-Trenaunay-Weber syndrome with cardiac failure (Zoppi et al. 2001)
      5. Prenatal ultrasound diagnosis of Klippel-Trenaunay-Weber syndrome with Kasabach-Merritt syndrome which caused acute hemolytic anemia, leading to high-output cardiac failure and fetal hydrops, in utero (Tanaka et al. 2015)
   2. MRI
      1. Limb hypertrophy
      2. Multiple subcutaneous and internal hemangiomas
      3. Good definition of soft tissue lesions
      4. Identify vascular malformations and their extent
      5. Presence of low signal indicating flow voids, hemosiderin deposits, or calcification indicative of vascular malformations
3. Management (James et al. 1999; Gloviczki and Driscoll 2007; Sharma et al. 2015; Sunderkrishman 2015)
   1. Normally conservative
   2. Elastic garment or compression bandage: beneficial in managing both lymphedema and chronic venous insufficiency
   3. Physical therapy using massage treatment and intermittent pneumatic compression therapy
   4. Local wound care, compression dressings, special orthopedic footwear, and lifestyle modification
   5. Prednisolone
      1. Used to treat coagulopathy
      2. Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reducing capillary permeability
   6. Psychological support: participate in the activities of a support group
   7. Stripping of superficial varicose veins
   8. Successful pulmonary thromboendarterectomy in a patient with Klippel-Trenaunay syndrome (Walder et al. 2000)
   9. Pulsed dye laser treatment for superficial hemangioma component (Jih 2003)
   10. Sclerotherapy and embolotherapy
   11. Reduction of significant arteriovenous malformations
   12. Rare reconstructive surgery at sites of deep venous obstruction
   13. Orthopedic procedures for overgrowth
      1. Epiphysiodesis: to prevent (stop) overgrowing of limb and correction of bone deformity
      2. Excision of soft tissue hypertrophy
   14. Use of thromboembolic prophylaxis with low-molecular-weight heparin is generally recommended, mainly in the postpartum (Güngor Gündoğan and Jacquemyn 2010; González-Mesa et al. 2012)

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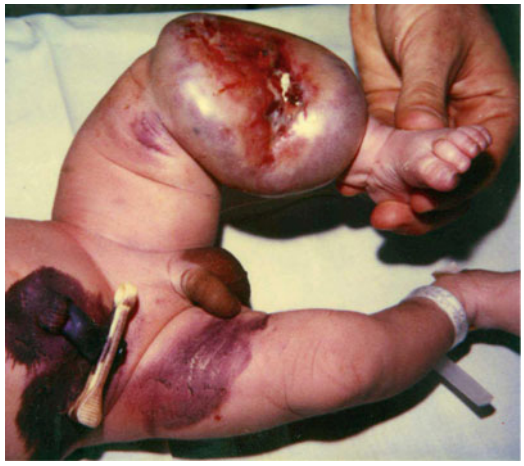

Fig. 1 A newborn with Klippel-Trenaunay syndrome showing overgrowth of left leg with vascular malformation

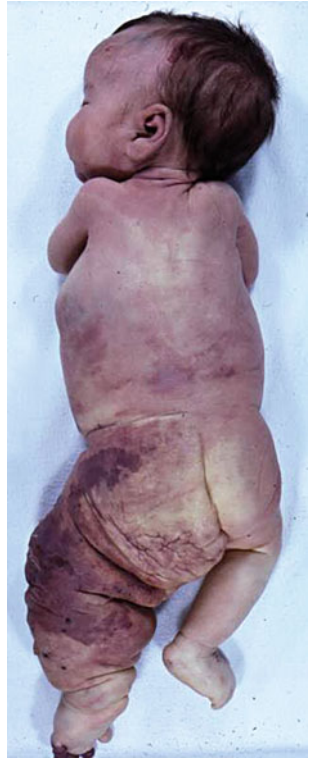

Fig. 2 A neonate with Klippel-Trenaunay syndrome showing left leg overgrowth with vascular malformation

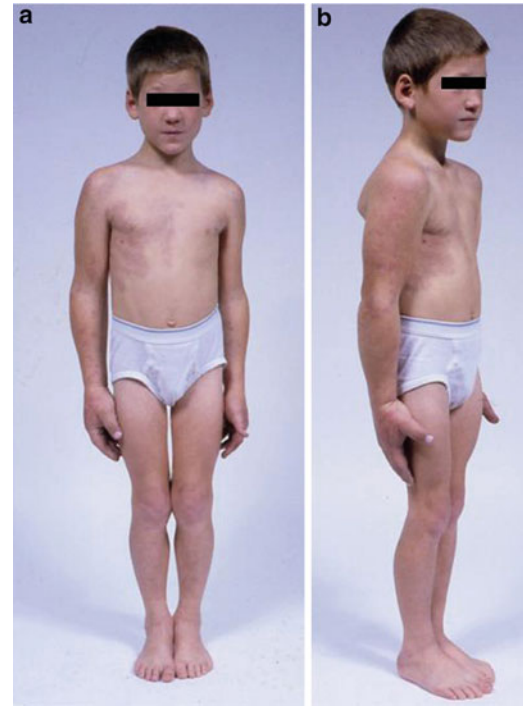

Fig. 3 (**a**, **b**) A boy with Klippel-Trenaunay syndrome showing overgrowth of the right arm and leg with vascular malformation (**a**, **b**)

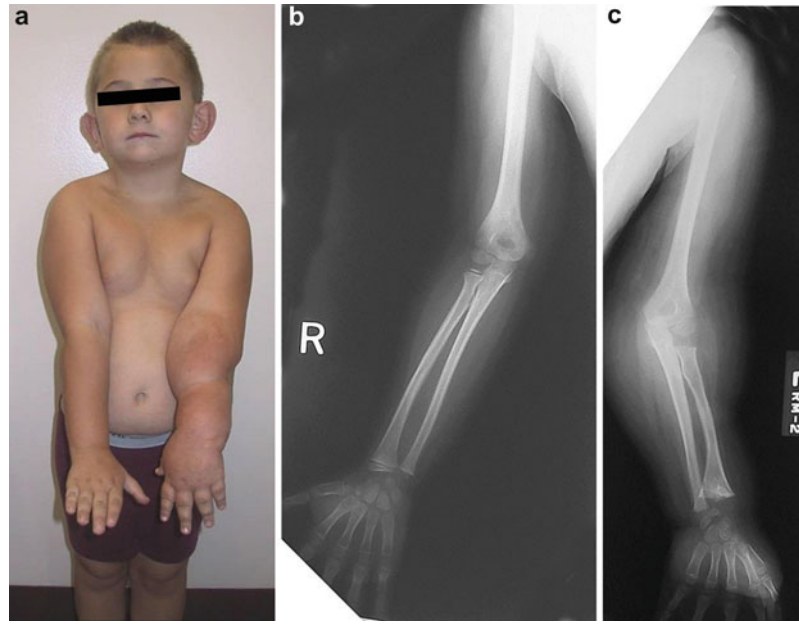

Fig. 4 (**a**–**c**) A 6-year-old boy with Klippel-Trenaunay syndrome showing overgrowth of left arm associated with vascular malformation (**a**), illustrated by radiographs (**b**, **c**)

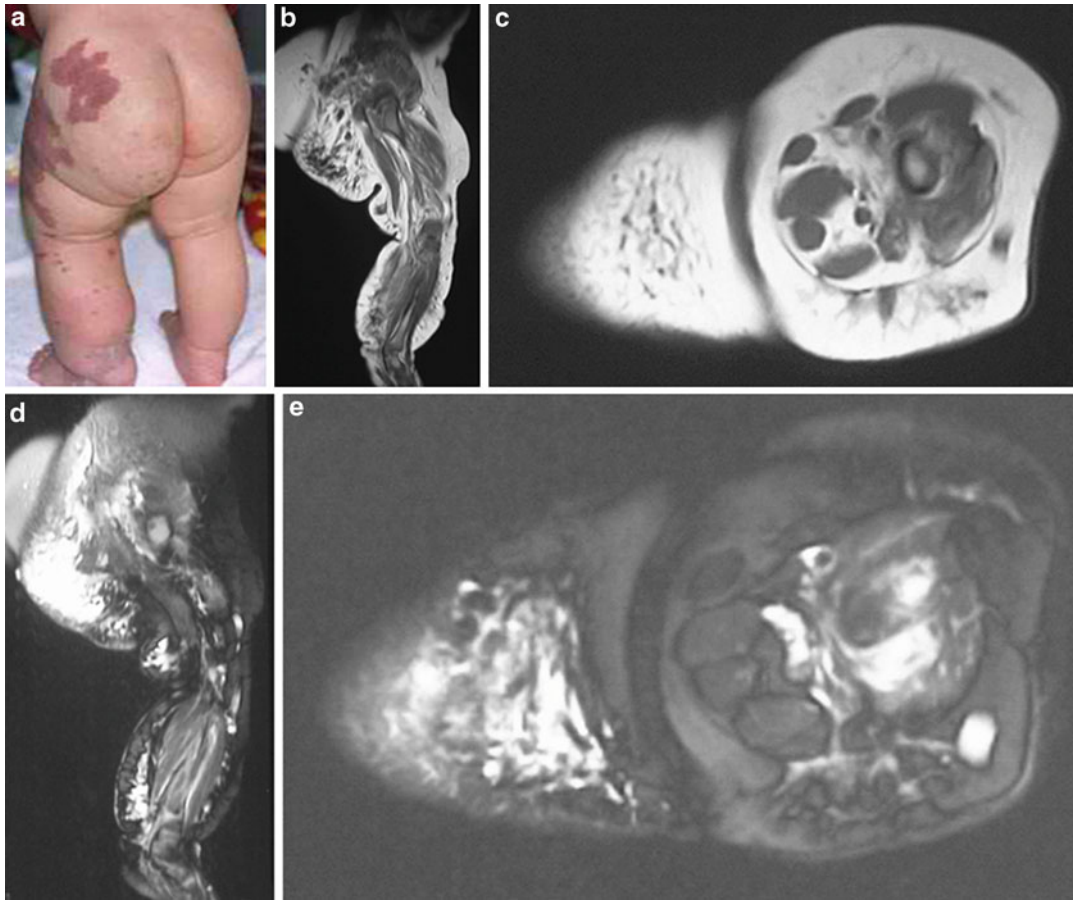

Fig. 5 A 1-year-old infant with Klippel-Trenaunay syndrome showing asymmetric lower extremities with hypertrophic left lower extremity associated with vascular malformation (**a**). T1-enhanced MRI (**b**, **c**) and T2-enhanced MRI (**d**, **e**) images at thigh level show cystic and vascular lesions, indicated by high signals suggesting lymphangiomas and hemangiomas

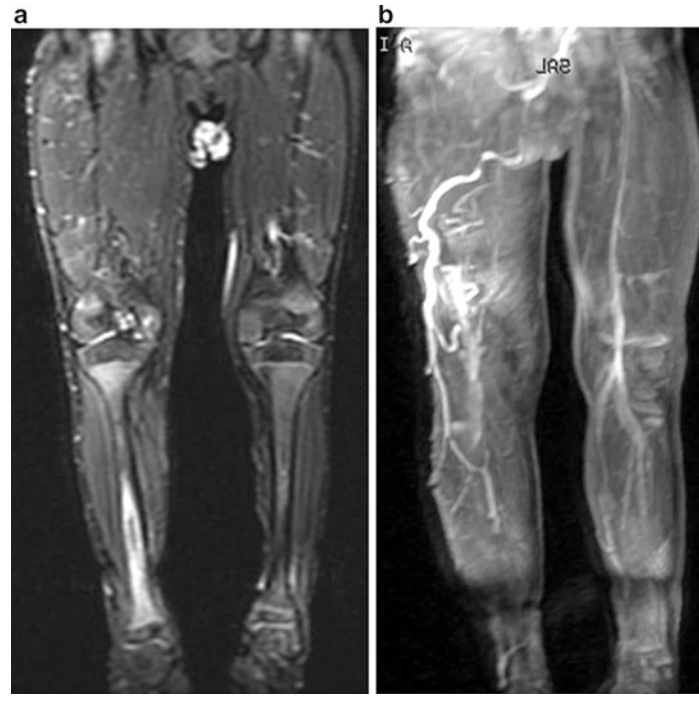

Fig. 6 (**a**, **b**) A 2-year-old boy with a history of Klippel-Trenaunay syndrome. MR image of the bilateral lower extremities demonstrates that the right lower extremity is larger than the left, with greater muscle mass in both legs and larger circumference (**a**). There is a length discrepancy in legs. A tortuous abnormal venous system is identified within the superficial fat along the posterior lateral aspect of the leg, which is seen draining through the gluteal and perineal regions into the pelvis (**b**). The deep venous system on the right is smaller than that on the left, although it is seen in its entirety (Courtesy of Dr. Grace Guo)

Kniest Dysplasia

Contents

In 1952, Kniest (1952) described an unusual form of disproportional dwarfism, called "atypical chondrodystrophy." Kniest dysplasia is a type II collagenopathy with characteristic clinical, radiographic, and histological findings. Kniest dysplasia is distinguished by platyspondyly and delay in ossification of the proximal epiphyses. After ossification, the epiphyses are enlarged resulting in dumbbell-shaped long bones.

Genetics/Basic Defects

1. Inheritance
    1. Autosomal dominant (Wilkin et al. 1999)
    2. New dominant mutations in most cases (Gilbert-Barnes et al. 1996)
2. Molecular basis (Wilkin et al. 1994; Cole 1997; Spranger et al. 1997)
    1. Caused by mutations in the gene (*COL2A1*) that encodes type II collagen, the predominant protein of cartilage
    2. A specific type of mutation and/or position of mutation within the collagen chain may explain the unique features of Kniest dysplasia among the type II collagenopathies
3. Kniest dysplasia in the middle of the following phenotypic spectrum of disease (type II collagenopathy caused by *COL2A1*) (Spranger et al. 1994a, b; Nagendran et al. 2012; Barat-Houari et al. 2015)
    1. Achondrogenesis type II/hypochondrogenesis at the severe end.
    2. Spondyloepiphyseal dysplasia/spondyloepimetaphyseal dysplasia Strudwick type in the middle.
    3. Genetically heterogeneous: Stickler syndrome type I, nonsyndromic predominantly ocular (Winterpacht et al. 1993) and familial adult early-onset osteoarthritis at the milder end.
    4. Characterized by abnormalities of variable severity in the ocular, skeletal, orofacial, and audiological systems. Clinical variability is common, and phenotypic overlap between *COL2A1*-associated disorders may be seen within the same family (Winterpacht et al. 1993).
    5. Phenotypic variability can be explained in some families by somatic mosaicism.

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Clinical Features

1. Skeletal anomalies (Wilkin et al. 1999; Siggers et al. 1974; Spranger and Maroteaux 1974; Lachman et al. 1975)
    1. Disproportionate dwarfism
    2. A short trunk
    3. Short, slightly bowed limbs
    4. More severe rhizomelic shortness in the lower limbs
    5. Prominent joints
    6. Delayed motor milestones secondary to joint deformities
    7. Progressive and painful joint enlargement accompanied by joint contractures
    8. Muscle atrophy resulting from disuse
    9. Short and broad thorax with sternal protrusion
    10. Kyphoscoliosis
        1. Dorsal kyphosis
        2. Accentuated lumbar lordosis
        3. Thoracic scoliosis
    11. Odontoid hypoplasia resulting in atlantoaxial instability
    12. Clubfoot
    13. Small pelvis
    14. Premature osteoarthritis that restrict movement
    15. Waddling gait
2. Craniofacial characteristics
    1. Relatively large head
    2. Flat face
    3. Shallow supraorbital ridges
    4. Prominent eyes
    5. Flat nasal bridge
    6. Short nose
    7. Micrognathia
    8. Cleft palate
3. Ocular manifestations: very similar to those in other disorders of type II collagen such as Stickler syndrome (Douglas 1985; Maumenee and Traboulsi 1985; Sergouniotis et al. 2015)
    1. Abnormal long axial length causing high early-onset myopia
    2. Vitreoretinal degeneration
    3. Retinal detachment
    4. Cortical and posterior subcapsular opacity of the lens
    5. Veil-like vitreous opacity in the periphery
    6. Congenital glaucoma
    7. Blindness
4. Hearing loss
5. Prognosis: phenotype varying significantly
    1. Frequently potentially life-threatening complications
        1. Early postnatal tracheomalacia resulting in respiratory insufficiency and feeding difficulties (Hicks et al. 2001)
        2. Secondary failure to thrive
    2. Can lead a relatively normal life with mild disproportionate short stature, kyphoscoliosis, and/or craniofacial manifestations

Diagnostic Investigations

1. Radiography (Lachman et al. 1975; Kozlowski et al. 1977; Gilbert-Barnes et al. 1996; Wilkin et al. 1999)
    1. Distinguishing radiographic features from other type II collagenopathies identifiable at birth
        1. Coronal clefts of the vertebrae
        2. Dumbbell-shaped femora
    2. Other radiographic features
        1. Narrowed joint spaces
        2. Platyspondyly
        3. Kyphoscoliosis
        4. Short tubular bones
        5. Dysplastic epiphyses and metaphyses
            1. Broad metaphyses
            2. Enlarged and deformed epiphyses
2. MR imaging of both unossified and ossified epiphyses reveals a similar pattern of lakes of bright T2 signal against a relatively normal background, representing an interesting analogue to the histologic and radiographic features (Dwek 2005)
3. Histopathology (Gilbert-Barnes et al. 1996)
    1. Pathologic changes of cartilage
        1. "Swiss cheese" appearance of the cartilage matrix (a bizarre pattern of

chondrocytes lying amid a highly vacuolated matrix) (Horton and Rimoin 1979; Dwek 2005)
    2. Ossified epiphyses: unusual in showing clouds of dense punctuate calcifications randomly distributed throughout
    3. Soft crumbly cartilage
  2. Microscopic changes
    1. Disorganization of the growth plate.
    2. Deficiency of collagen matrix.
    3. Poorly staining cartilage with myxoid degeneration.
    4. PAS positive cytoplasmic inclusions in many chondrocytes. Ultrastructurally, the inclusions correspond to pools of proteinaceous material within dilated rough endoplasmic reticulum (Horton and Rimoin 1979).
4. Hearing test
5. Visual evaluation
6. Molecular genetic analysis of *COL2A1* gene mutation
  1. Targeted mutation analysis
  2. Mutation scanning
  3. Sequencing of entire coding region

Genetic Counseling

1. Recurrence risk
  1. Patient's sib: low recurrence risk unless a parent is affected or has gonadal mosaicism
  2. Patient's offspring: 50%
2. Prenatal diagnosis
  1. Difficult to diagnose Kniest dysplasia by early sonography since the biometry does not become notably abnormal until the third trimester (Bromley et al. 1991).
  2. Combined use of 3D-CT with ultrasonography (Wada et al. 2011).
  3. Fetal MRI findings: By delineating the cartilaginous abnormalities, fetal MRI can contribute to the prenatal diagnosis of chondrodysplasias (Yazici et al. 2010).
    1. Enlarged hyaline cartilaginous structures with abnormally high T2 signal intensity
    2. Delayed ossification of the pubic and ischial bones
    3. Platyspondyly
  4. Molecular genetic analysis of *COL2A1* mutation on fetal DNA obtained from amniocentesis or CVS for previously characterized disease-causing gene mutation in the proband
3. Management
  1. Cleft palate repair
  2. Hearing aid for hearing loss
  3. Vitrectomy and silicon oil injection for reattaching the retina from retinal detachment (Yokoyama et al. 2003)
  4. Orthopedic care for clubfoot and kyphoscoliosis

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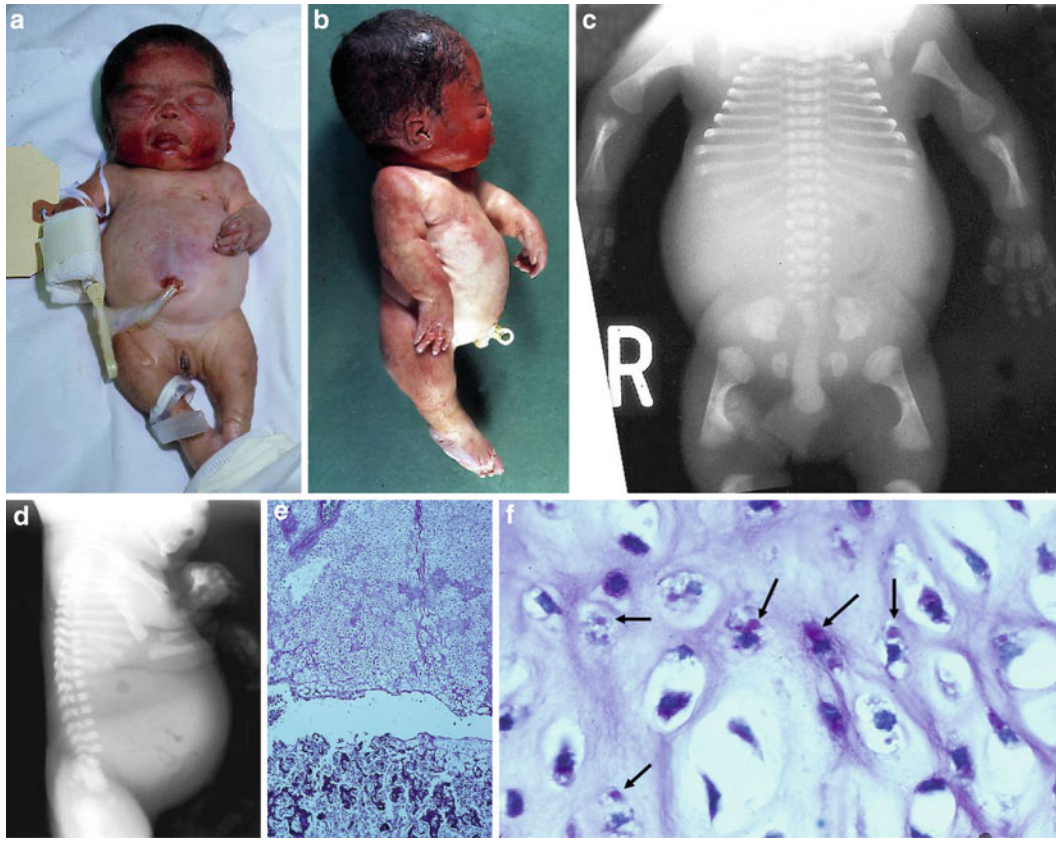

Fig. 1 (**a**–**f**) A neonate with Kniest dysplasia showing short trunk and large head, similar to SED congenita. However, the moderately shortened limbs show prominent joints (**a**, **b**). Radiographs show enlarged metaphyses of limb bones (dumbbell-shaped femora) and coronal clefts of the vertebrae (**c**, **d**). The remaining findings are similar to those of SED congenita. The physeal growth zone of femur is hypercellular and disorganized (**e**). The transverse cleft beneath the physis is an artifact. Many chondrocytes contain cytoplasmic inclusions (**d**) (*arrows*); they are seen in the resting cartilage and the zone of proliferation, similar to those of SED congenita (Chen et al. 1980)

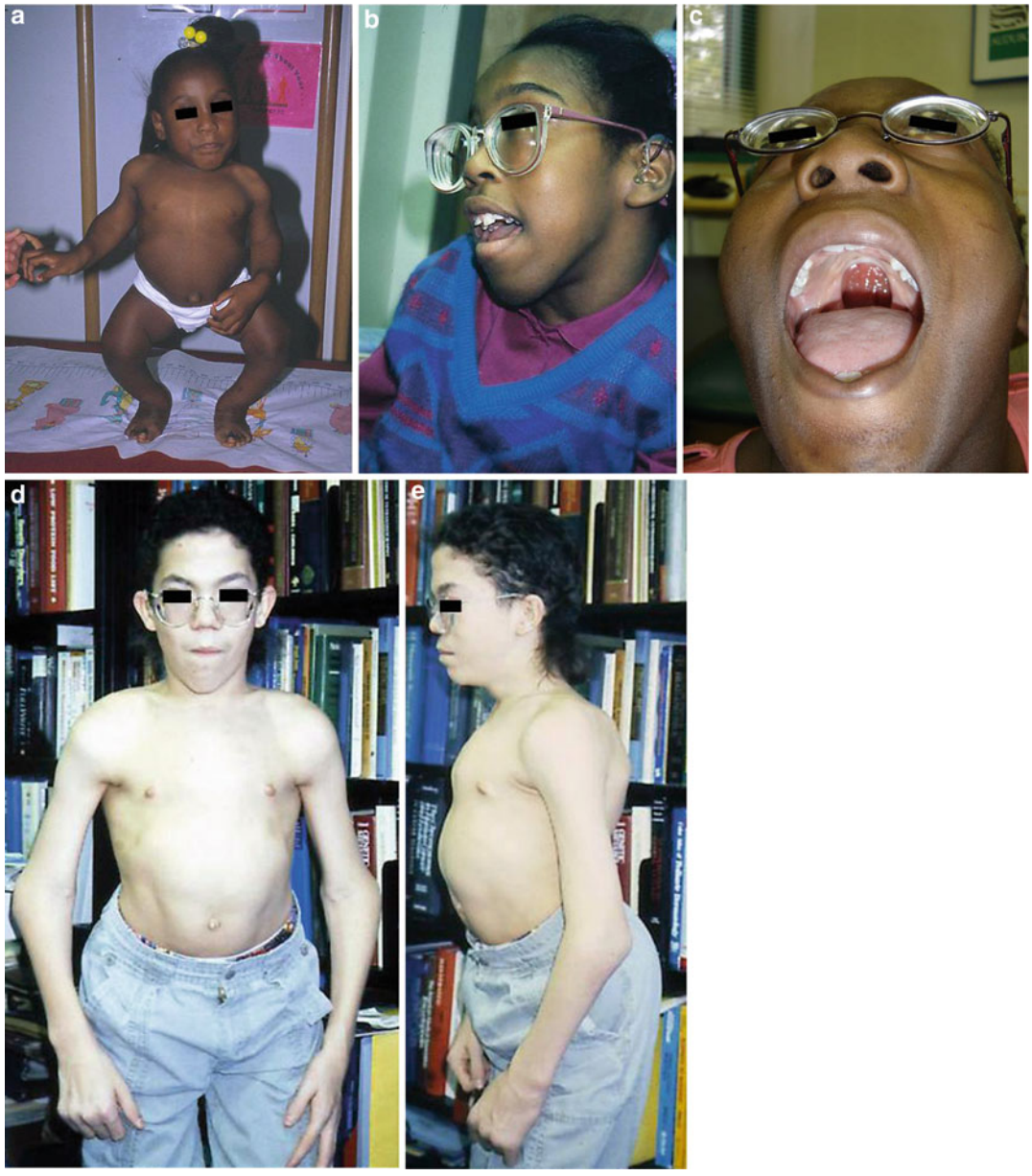

Fig. 2 (**a**–**e**) Three children (**a**, **b**, **c**, **d**, **e**) with Kniest dysplasia showing varying features of the dysplasia: short trunk dwarfism, flat facies, myopia, cleft palate, deafness requiring hearing aids, dorsal kyphosis, accentuated lumbar lordosis, short and broad thorax with sternal protrusion, and prominent joints with restricted joint mobility

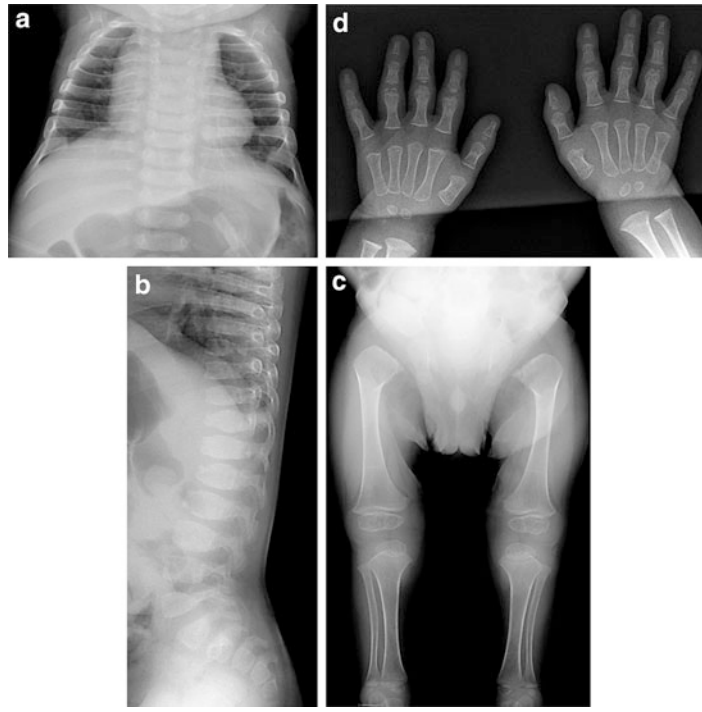

Fig. 3 (**a**–**d**) A 15-month-old white male with diagnosis of Kniest dysplasia. He is the second child in the family and was born at 38-1/2 weeks by cesarean section. His mother was diagnosed to have polyhydramnios during pregnancy. An antenatal ultrasound demonstrated short limbs and genetic tests confirmed that he positively had Kniest dysplasia. DNA testing showed a gene change within the *COL2A1* gene, consistent with the diagnosis of a Type II collagenopathy. The exact gene change identified was Alal02Val. This change is predicted to cause a small deletion within the amino acid sequence of the protein. He has had a number of medical issues during his early infantile course. He was born with a cleft palate, bilateral hearing impairment, myopia, esophageal reflux, respiratory issues (apneic episodes), and swallowing difficulty. Radiographies demonstrate foreshortening of the ribs which appear slightly flared (**a**). There is irregularity of the vertebral bodies of the lower thoracic and upper lumbar spine anteriorly (**b**). There is flaring of the ilia with dysplasia of the acetabulum. There is widening of the metaphyses and irregularity of the epiphyses of foreshortening long bones (**c**). Bilateral hands imaging demonstrates osteoporosis, large carpals, and bulbous phalangeal joints with narrow spacing (**d**) (Courtesy of Dr. Grace Guo)

Larsen Syndrome

Contents

In 1950, Larsen et al. described a condition characterized by multiple large joint dislocations and flat face (Larsen et al. 1950). The condition occurs in approximately 1 in 100,000 births.

Synonyms and Related Disorders

FLNB-related disorders (boomerang dysplasia; atelosteogenesis type I; atelosteogenesis type III; spondylocarpotarsal synostosis syndrome; Larsen syndrome); Lethal Larsen-like syndrome; Multiple joint dislocations, short stature, craniofacial dysmorphism, and congenital heart defects

Genetics/Basic Defects

1. Subtypes:
    1. Sporadic form
    2. Autosomal dominant form (Harris and Cullen 1971; Habermann et al. 1976; Stanley and Seymour 1985; Fryns et al. 1993; Al-Kaissi et al. 2003)
    3. Autosomal recessive form (Steel and Kohl 1972; Strisciuglio et al. 1983; Topley et al. 1994; Knoblauch et al. 1999): clinical phenotype more debilitating with higher mortality than the autosomal dominant form
    4. Craniosynostosis: a previously unreported association with *CHST3*-related skeletal dysplasia (autosomal recessive Larsen syndrome) (Searle et al. 2014)
    5. Possible parental germ-line mosaicism (Petrella et al. 1993)
    6. Possible lethal form (Chen et al. 1982)
2. The first known gene mutated in Larsen syndrome, *LAR1*, for autosomal dominant form: mapped to 3p21.1-14.1 in the proximity of, but distinct from, the *COL7A1* locus (Vujic et al. 1995).
3. Clinical similarities between Larsen syndrome and a group of lethal osteochondrodysplasias including atelosteogenesis types I (AOI) and III (AOIII) and boomerang dysplasia suggested that they represent an allelic series of conditions (Hunter and Carpenter 1991; Sillence et al. 1997):
    1. These more severe dysplasias are characterized by underossification of skeletal elements, hypoplastic or absent limb bones, joint dislocations, and craniofacial abnormalities.

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2. These observations, with the phenotypic similarities between Larsen syndrome and otopalatodigital syndrome type 1 (OPD1), an X-linked skeletal disorder caused by mutations in *FLNA* (Robertson et al. 2003), the gene encoding filamin A, led to the description of mutations in the paralogous gene filamin B (*FLNB*) gene underlying Larsen syndrome, AOI, AOIII, and boomerang dysplasia (Bicknell et al. 2005; Krakow et al. 2004).
3. Mutations leading to AOI and AOIII were clustered in calponin homology domain 2 (CH2) and repeats 13–17 (Farrington-Rock et al. 2006).

4. Molecular and clinical study of Larsen syndrome caused by mutations in *FLNB* (Bicknell et al. 2007):
   1. The clinical signs most frequently associated with an *FLNB* mutation are the presence of supernumerary carpal and tarsal bones and short, broad, spatulate distal phalanges, particularly of the thumb.
   2. All individuals with Larsen syndrome-associated *FLNB* mutations are heterozygous for either missense or small inframe deletions:
      1. Three mutations are recurrent, with one mutation, 5071GRA, observed in 6 of 20 subjects.
      2. The distribution of mutations within the *FLNB* gene is nonrandom, with clusters of mutations leading to substitutions in the actin-binding domain and filamin repeats 13–17 being the most common cause of Larsen syndrome.
   3. These findings collectively define autosomal dominant Larsen syndrome and demonstrate clustering of causative mutations in *FLNB*.
   4. The *FLNB*-related disorders include a spectrum of phenotypes ranging from mild (spondylocarpotarsal synostosis syndrome and Larsen syndrome) to severe (atelosteogenesis types I and III, boomerang dysplasia) (Robertson 2013).

5. Molecular basis of recessive Larsen syndrome (Hermanns et al. 2008; Unger et al. 2010):
   1. Eight *CHST3* (carbohydrate sulfotransferase 3, also known as chondroitin 6-sulfotransferase) mutations, causing CHST3 deficiency, were identified in unrelated individuals who presented at birth with congenital joint dislocations:
      1. These patients had been given a diagnosis of either Larsen syndrome (three individuals) or humero-spinal dysostosis (three individuals), and their clinical features included congenital dislocation of the knees, elbow joint dysplasia with subluxation and limited extension, hip dysplasia or dislocation, clubfoot, short stature, and kyphoscoliosis developing in late childhood.
      2. Analysis of chondroitin sulfate proteoglycans in dermal fibroblasts showed markedly decreased 6-*O*-sulfation but enhanced 4-*O*-sulfation, confirming functional impairment of CHST3 and distinguishing them from diastrophic dysplasia sulfate transporter (DTDST)-deficient cells.
   2. These observations provide a molecular basis for recessive Larsen syndrome and indicate that recessive Larsen syndrome, humero-spinal dysostosis, and spondyloepiphyseal dysplasia Omani type form a phenotypic spectrum.
6. Unilateral manifestation of typical skeletal defects in some patients indicates that this condition might represent unilateral somatic cell-line mosaicism (Debeer et al. 2003).

Clinical Features

1. Broad inter- and intrafamilial clinical variability (Becker et al. 2000; Al-Kaissi et al. 2003)
2. Characteristic flat facial appearance ("dish face"):
   1. Prominent forehead (frontal bossing)
   2. Hypertelorism
   3. Hypoplastic midface
   4. Depressed nasal bridge

5. Micrognathia
6. Occasional cleft palate, lip, or uvula

3. Bilateral multiple joint dislocations (Latta et al. 1971; Silverman 1972; Robertson et al. 1975):
   1. Shoulders
   2. Elbows
   3. Wrists
   4. Hips
   5. Patella
   6. Ankles
   7. Knees
4. Variable handicap due to joint luxations
5. Hand abnormalities:
   1. Long, cylindrical, and tapering fingers (pseudoclubbing)
   2. Spatulate/bifid thumbs
   3. Dislocation of distal radioulnar joint
   4. Delayed carpal ossification
   5. Supernumerary ossification centers
   6. Brachymetacarpia
   7. Brachytelephalangia
   8. Hyperextension of distal interphalangeal joints
6. Feet abnormalities:
   1. Spatulate hallux
   2. Equinovarus or valgus deformities of the feet
7. Respiratory distress due to tracheolaryngomalacia (Rock et al. 1988):
   1. Stridor:
      1. Inspiratory reflecting laryngomalacia or extrathoracic cervical tracheomalacia
      2. Expiratory reflecting intrathoracic tracheomalacia
   2. Cyanosis
   3. Obstructive apnea
   4. Possibly life threatening
8. Bronchomalacia:
   1. Lobar atelectasis
   2. Hyperinflation
   3. Pneumonias
9. Respiratory embarrassment in infancy due to soft tracheolaryngeal cartilage
10. Soft/collapsing thorax
11. Cardiovascular abnormalities (similar to Marfan syndrome) (Kiel et al. 1983):
    1. Congenital defects:
       1. Bicuspid aortic valve
       2. Subaortic stenosis
       3. Atrial septal defect
       4. Ventricular septal defect
       5. Patent ductus arteriosus
       6. Pulmonary stenosis
       7. Endocardial fibroelastosis
    2. Acquired lesions:
       1. Dilated aortic root
       2. Elongated aorta (Liang and Hang 2001)
       3. Mitral valve prolapse
       4. Aneurysm of ductus arteriosus
       5. Arterial tortuosity and dilatation
12. Associated spinal anomalies (Bowen et al. 1985; Banks et al. 2003):
    1. Cervical spine involvement:
       1. More often affected than thoracic or lumbar spine
       2. Results in:
          1. Midcervical kyphosis, usually at the C4–C5 region
          2. Cervicothoracic lordosis
          3. Spinal instability
       3. Flattened, hypoplastic, and often bifid cervical vertebrae
    2. Atlantoaxial instability/dislocation (Le Marec et al. 1994):
       1. A rare finding
       2. May be associated with other abnormalities of the upper cervical spine:
          1. Occipitalization of the atlas
          2. Basilar impression
    3. Subaxial kyphotic deformity itself may not be the cause of cord compression in all cases of adult Larsen syndrome. Adjacent-level degenerative changes may be responsible for cord compression (Sahoo et al. 2016).
    4. Lumbosacral dysraphism: may lead to neurological impairment.
    5. Dural ectasia (Jain et al. 2014): an abnormal expansion of the dural sac surrounding the spinal cord and may result in spinal morphologic changes, instability, and spontaneous dislocation.
    6. Thoracic scoliosis.
    7. Hypoplasia of the vertebral bodies or posterior elements.

8. Quadriplegia secondary to segmentation abnormalities of the vertebrae.
13. Mixed hearing loss due to ossicular abnormality
14. CNS anomalies:
    1. Hydrocephalus (rare)
    2. Glial proliferation in the brain
15. Short stature
16. Normal intelligence
17. Possible lethal form (Chen et al. 1982; Clayton-Smith and Donnai 1988; Mostello et al. 1991):
    1. Tracheomalacia
    2. Pulmonary hypoplasia
    3. Collagen fiber dysmaturity
18. Prognosis:
    1. Generally good after aggressive orthopedic management, except some lethal cases due to tracheolaryngomalacia and/or lung hypoplasia
    2. Compatible with successful pregnancy if the maternal and fetal safety issues are properly considered
19. Differential diagnosis (*FLNB*-related disorders) (Robertson 2013):
    1. Spondylocarpotarsal synostosis syndrome (Langer et al. 1994):
        1. Characteristic clinical features:
            1. Disproportionate short stature
            2. Vertebral anomalies with block vertebrae
            3. Scoliosis and lordosis
            4. Carpal and tarsal synostosis
            5. Clubfeet
            6. Mild facial dysmorphisms with round face, frontal bossing, and anteverted nares
        2. Other manifestations can include the following:
            1. Midline cleft palate
            2. Conductive hearing loss
            3. Joint laxity
            4. Dental enamel hypoplasia
        3. Diagnostic radiographic features:
            1. Fusion of adjacent vertebrae and posterior elements that can involve noncontiguous areas of the cervical, thoracic, and lumbar spine.
            2. Carpal and tarsal synostosis. Carpal synostosis is usually capitate-hamate and lunate-triquetrum (Langer et al. 1994).
            3. Delayed ossification of epiphyses (especially of carpal bones) and bilateral epiphyseal dysplasia of the femur: reported in two individuals (Honeywell et al. 2002; Mitter et al. 2008).
    2. Atelosteogenesis type I (AOI) and type III (AOIII) (Farrington-Rock et al. 2006):
        1. Once thought to represent distinct entities, they now appear to be part of a phenotypic continuum (Farrington-Rock et al. 2006).
        2. AOIII:
            1. Milder than AOI, commonly with survival beyond the neonatal period
            2. Clinical findings: dislocated hips, knees, and elbows and clubfeet
            3. Radiographic features: distal tapering of the humeri and femora, short and broad tubular bones of the hands and feet, and mild vertebral hypoplasia
        3. AOI:
            1. Characterized by perinatal lethality with severe short-limbed dwarfism; dislocated hips, knees, and elbows; and clubfeet
            2. Radiographic features: marked platyspondyly; hypoplastic pelvis; incomplete or absent, shortened, or distally tapered humeri and femora; absent, shortened, or bowed radii; shortened and bowed ulnae and tibiae; absent fibulae; and unossified or partially ossified metacarpals and middle and proximal phalanges
    3. Boomerang dysplasia (Bicknell et al. 2005):
        1. A perinatal lethal bone dysplasia with close similarities to AOI
        2. Distinguished primarily by characteristic bowing of the femora and, occasionally, extraskeletal manifestations

including encephalocele and omphalocele

20. Other differential diagnoses (Robertson 2013):
    1. Otopalatodigital syndrome type 1 (OPD1) differs chiefly from Larsen syndrome in the following ways:
        1. X-linked inheritance of OPD1
        2. Absence of dislocation of the large joints (except dislocation of the radial heads) and cervical spine dysplasia in OPD1
        3. Absence of radiologically supernumerary ossification centers within the carpus and/or tarsus in OPD1
    2. *CHST3*-related skeletal dysplasia (also known as spondyloepiphyseal dysplasia, Omani type) (Thiele et al. 2004):
        1. Characterized by short stature of prenatal onset, joint dislocations (knees, hips, radial heads), clubfeet, and limitation of range of motion that can involve all large joints.
        2. Kyphosis and occasionally scoliosis with slight shortening of the trunk develop in childhood.
        3. Minor heart valve dysplasia has been described in several persons.
        4. Intellect, vision, and hearing are normal.
        5. The chief differences are the presence of the following in *CHST3*-related skeletal dysplasia and not in Larsen syndrome:
            1. Epiphyseal dysplasia
            2. Progressive spondylodysplasia in early and mid-childhood
            3. Rhizomelic shortening of the limbs
    3. Desbuquois dysplasia is a chondrodysplasia in which affected individuals have severe prenatal and postnatal growth retardation, progressive scoliosis, joint laxity, joint dislocations, and short extremities. A majority of affected individuals have biallelic mutations in CANT1 (Huber et al. 2009; Nizon et al. 2012). Desbuquois dysplasia differs from Larsen syndrome in the following ways:
        1. Short stature (< -3 SD)
        2. Advanced carpal bone age
        3. Characteristic radiographic manifestations in the hips, pelvis, and hands
    4. B3GAT3 deficiency (Baasanjav et al. 2011) is characterized by dysmorphic facial features, short stature, bilateral dislocations of multiple joints (elbows, hips, and knees), clubfeet, and cardiovascular defects. Unlike Larsen syndrome, B3GAT3 deficiency may include the following features:
        1. Brachydactyly
        2. Cardiac defects, including bicuspid aortic valve and dilatation of the aorta
    5. Chondrodysplasia with joint dislocations, GPAAP type, is characterized by short stature, congenital joint dislocations, chondrodysplasia with brachydactyly, dysmorphic facial features, micrognathia, and cleft palate. This condition is caused by biallelic mutations in IMPAD1 (Vissers et al. 2011). Differences from Larsen syndrome include the following:
        1. Pronounced brachydactyly
        2. Asymmetry in the hands
        3. Short stature

Diagnostic Investigations

1. Radiography (Kozlowski et al. 1974; Al-Kaissi et al. 2003):
    1. Bilateral dislocations of the shoulders, elbows, wrists, hips, patella, ankles, and knees (anterior dislocation of the tibia on the femur, most characteristic)
    2. Genu recurvatum
    3. Talipes deformities (clubfeet)
    4. Spatulate thumbs
    5. Shortened metacarpals
    6. Multiple supernumerary carpal ossification centers (short, small, and increased in number)
    7. Poor ossification of phalanges
    8. Delayed coalescence (duplication) of calcaneal ossification centers

9. Occasional abnormal segmentation of vertebrae (+/− fusion defects of cervical spine)
10. Cervical kyphosis
11. Spina bifida occulta
12. Scoliosis
13. Multiple coronal cleft vertebrae (Wieisenbach and Melegh 1996)
14. Craniofacial disproportion

2. Audiometry to assess hearing.
3. Polysomnography for assessing the severity of airway obstruction.
4. Echocardiography for cardiovascular lesions.
5. MRI of the brain for cerebral malformations.
6. Diagnosis: based on clinical and radiographic findings and confirmed by *FLNB* molecular genetic testing (Girisha et al. 2016). A molecular diagnosis for Larsen syndrome can be achieved by testing selected exons of the *FLNB* gene, such as exons 2–5, exons 27–33, as well as exon 13.

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib:
        1. Sporadic form (consider germ-line mosaicism when neither parent appears to be affected)
        2. Autosomal dominant inheritance: risk not increased unless a parent is affected
        3. Autosomal recessive inheritance: 25% risk of having sibs affected
    2. Patient's offspring:
        1. Sporadic form: risk not increased unless the patient has germ-line mosaicism
        2. Autosomal dominant inheritance: 50% risk of having offspring affected
        3. Autosomal recessive inheritance: risk not increased unless the spouse is also a carrier
2. Prenatal diagnosis (Robertson 2013):
    1. Ultrasonography: prenatal diagnosis accomplished in rare cases by ultrasonography in pregnancies at risk (Mostello et al. 1991; Tongson et al. 2000; Ghazle 2012):
        1. Multiple joint dislocations:
            1. Elbow
            2. Knees
            3. Hips
        2. Flat facial profile (Becker et al. 2000):
            1. Prominent forehead
            2. Hypertelorism
            3. A depressed nasal bridge
            4. Micrognathia
            5. Cleft palate
        3. Genu recurvatum (Lewit et al. 1995)
        4. Clubfeet
    2. Molecular genetic testing:
        1. De novo case (Winer et al. 2009):
            1. Genomic DNA was extracted from cultured amniocytes using a standard protocol. FLNB polymerase chain amplification reactions and sequence analysis were performed using previously published conditions (Krakow et al. 2004).
            2. Heterozygosity for a missense mutation, c.502G > A (p.Gly168Ser), was identified.
        2. Possible for at-risk pregnancies provided that prior identification of the disease-causing mutation(s) in the family is done
    3. Preimplantation genetic diagnosis may be an option for some families in which the disease-causing mutation(s) has been identified.
3. Management:
    1. Supporting therapy for airway difficulty:
        1. Antibiotics as needed
        2. Supplemental oxygen
        3. Chest physiotherapy to augment mucus clearance
        4. Require intubation for severe respiratory distress with positive end-expiratory pressure (PEEP) to maintain a patent airway (Rock et al. 1988)
    2. Anesthetic considerations (Malik and Choudhry 2002):
        1. Optimize respiratory status prior to the anesthetic and careful postoperative management.
        2. Patients with subglottic stenosis may benefit from perioperative intravenous

steroids, and nebulized racemic epinephrine may be necessary in the postoperative period to treat postextubation stridor.
3. If a surgical procedure does not truly warrant tracheal intubation, administration of anesthetic with a face mask or a laryngeal mask airway may avert complications associated with tracheal intubation and minimize manipulation of the neck.
4. Skeletal deformities, contractures, and cervical instability necessitate gentle handling and careful positioning.
5. Cervical instability with cord myelopathy may be associated with distal muscle weakness. Hence, care should be taken during administration of depolarizing neuromuscular blocking agents (i.e., succinylcholine) due to the possibility of hyperkalemia.

3. Cleft palate repair
4. Closed or open reduction and stabilization of dislocated joints (Lutter 1990):
   1. Securing stability of the knee joints for weight-bearing: primary importance
   2. Correction of foot deformities through operative and nonoperative measures
5. Stabilization of the cervical spine (Banks et al. 2003):
   1. Early bracing and stabilization.
   2. Stabilization of the neck may be required before surgical correction of joint abnormalities to prevent possible complications associated with the induction of anesthesia.
6. Surgical decompression and stabilization of the spine for dural ectasia (Jain et al. 2014)
7. Care for possible poor wound healing
8. Obstetrical care of an affected mother and fetus (Rochelson et al. 1993):
   1. Regional anesthesia for possible difficulty in intubation and the cervical spine may be subluxated during extension of the neck for intubation.
   2. Cesarean section if the patient is unable to abduct the hips, making vaginal delivery potentially traumatic for both the mother and infant.
   3. Risk of fetal injury includes cervical spine instability.

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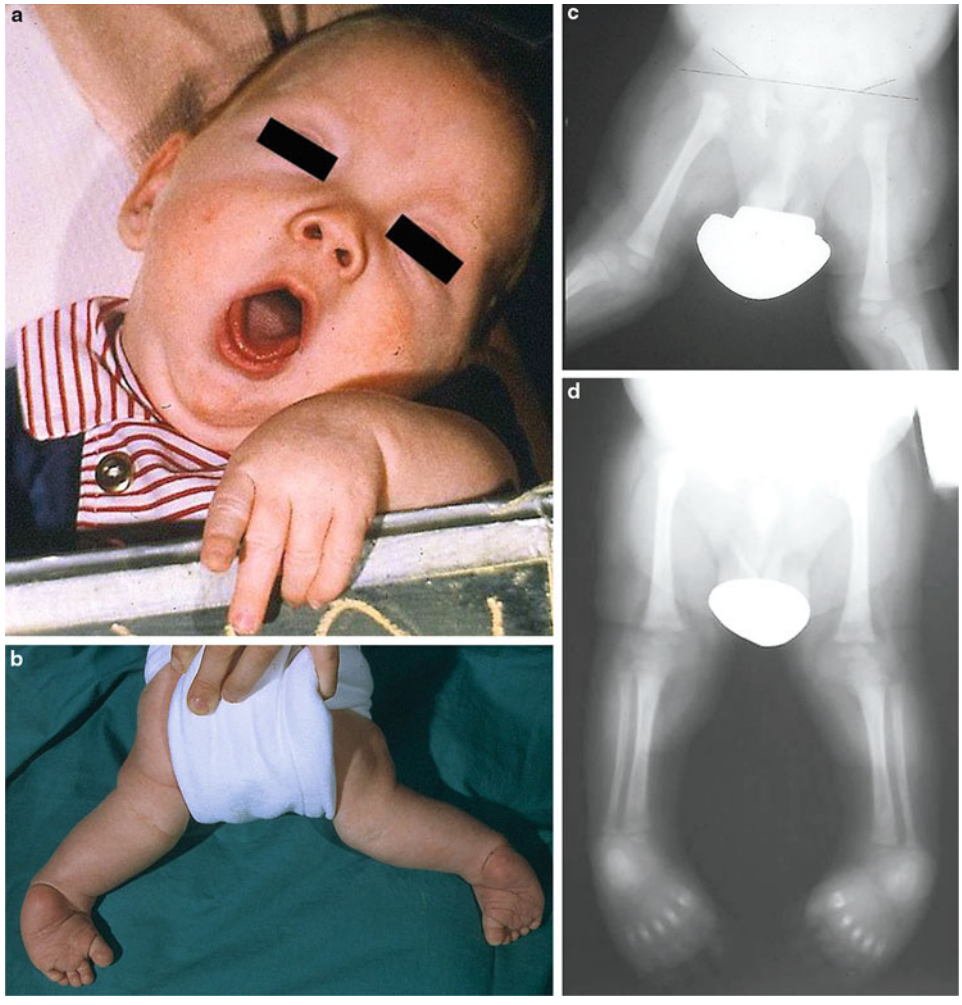

Fig. 1 (**a**–**d**) An infant with Larsen syndrome (**a**, **b**) showing characteristic flat facies with hypertelorism, depressed nasal bridge, cleft palate, dislocations of hips, knees, and talipes equinovarus, demonstrated by radiographs (**c**, **d**)

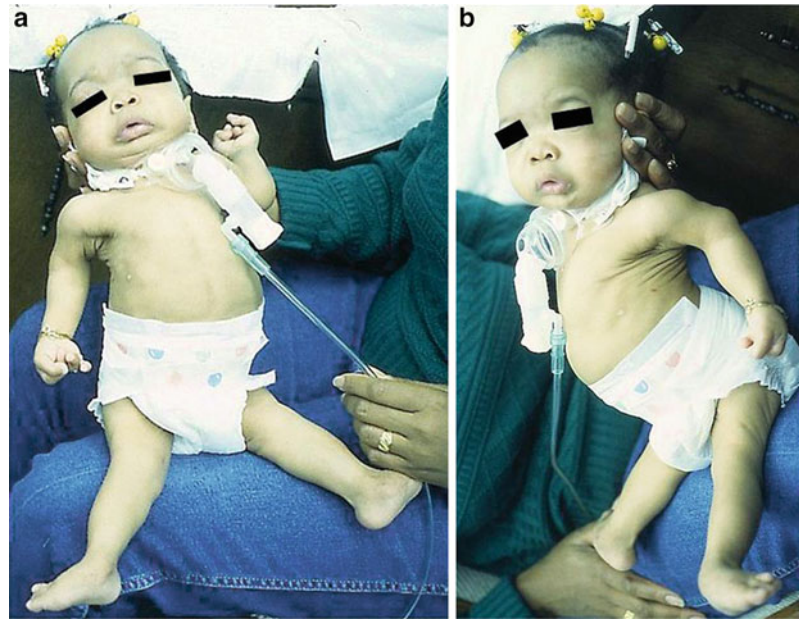

Fig. 2 (**a**, **b**) Another infant with Larsen syndrome (**a**, **b**) showing flat facies with prominent forehead, hypertelorism, depressed nasal bridge, micrognathia, tracheostomy for tracheomalacia, scoliosis, dislocation of knees, and clubfeet

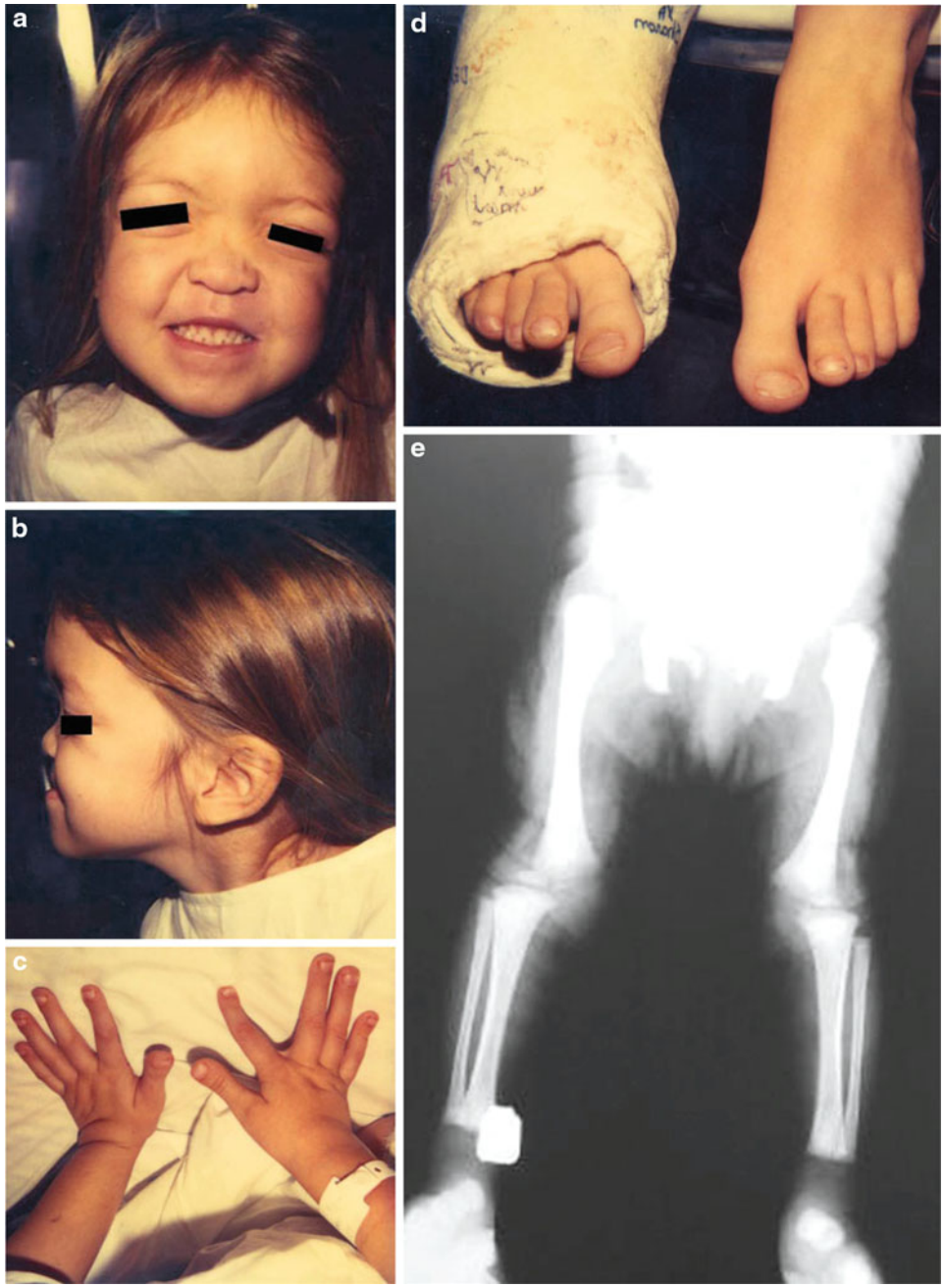

Fig. 3 (**a**–**e**) A girl with Larsen syndrome showing characteristic flat facies (**a**, **b**) with prominent forehead, depressed nasal bridge, bilateral knee dislocations, and long, cylindrical fingers with spatulate thumbs (**c**) and great toes (**d**). Radiograph shows lateral and anterior dislocation of both knees (**e**)

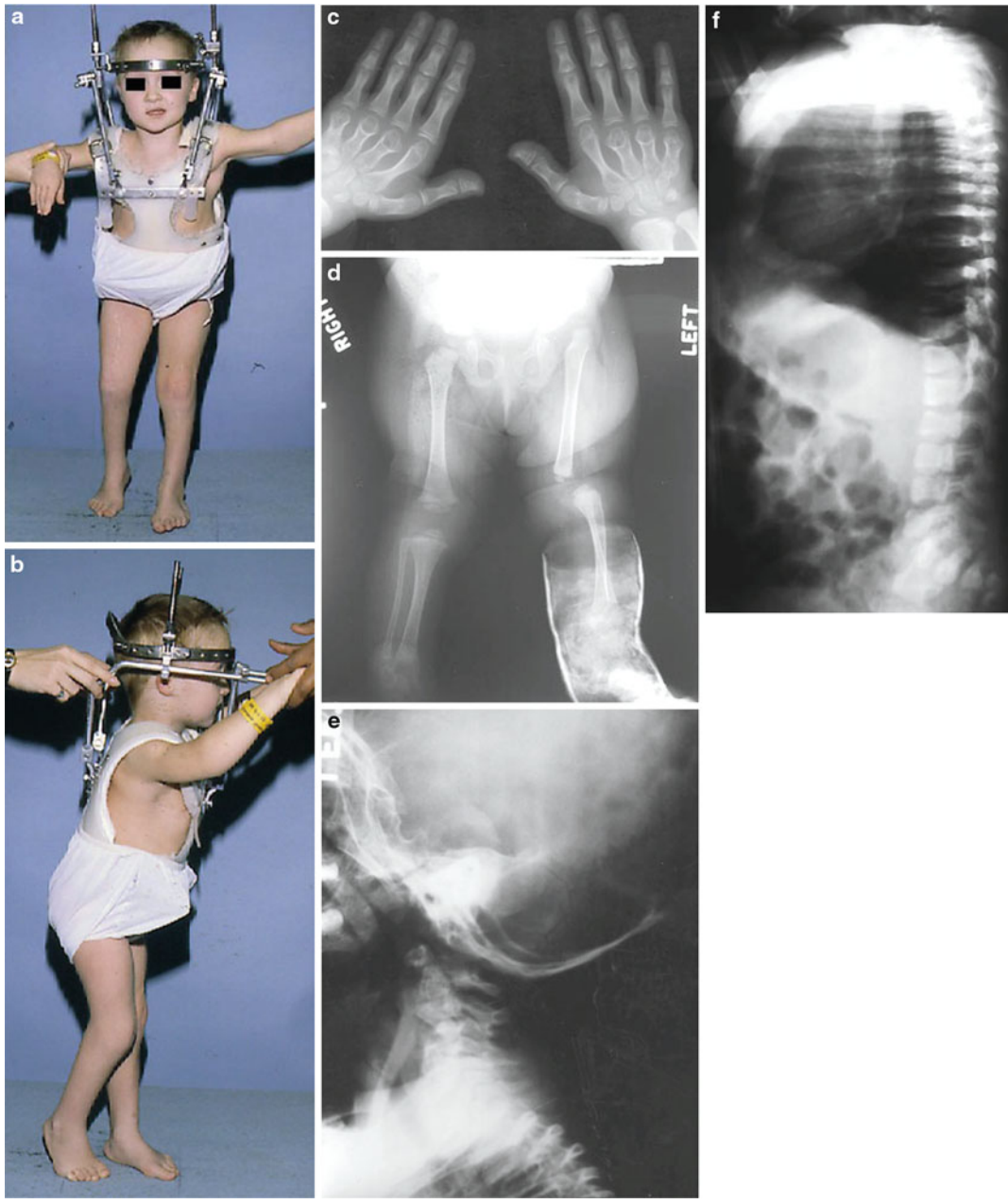

Fig. 4 (**a**–**f**) A girl with Larsen syndrome (**a**, **b**) wearing orthosis, showing flat facies. Radiographs show an increased number of carpal bones (**c**), anterior and lateral dislocation of tibiae (**d**), hyperextended cervical vertebrae (**e**), and coronal clefting of the lumbar vertebrae (**f**)

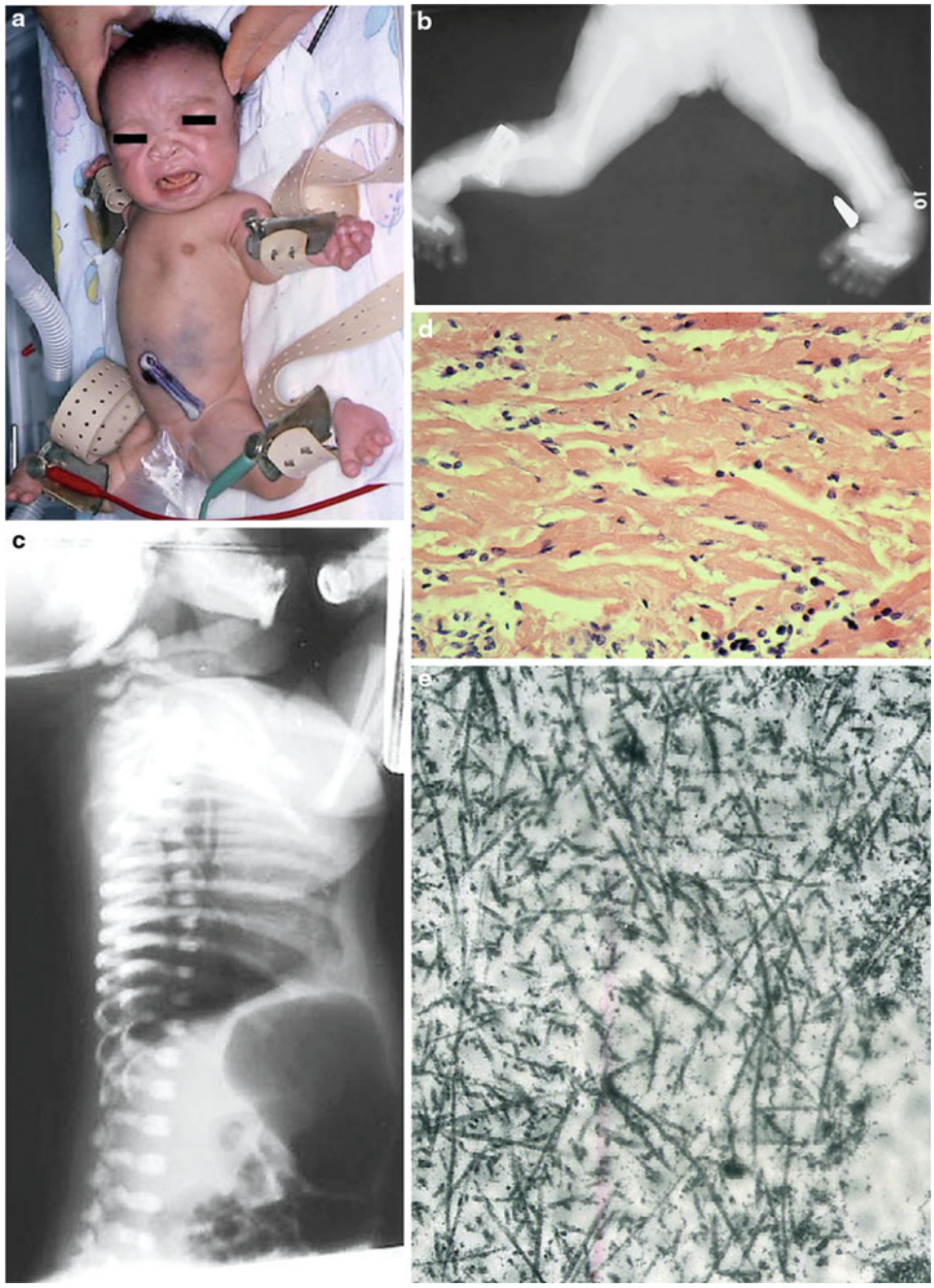

Fig. 5 (**a**–**e**) An infant with lethal, Larsen-like syndrome (**a**) showing characteristic flat facies (prominent forehead, hypertelorism, depressed nasal bridge, micrognathia, and cleft palate); multiple dislocations involving shoulders, elbows, wrists, knees, ankles, and hips; and talipes equinovarus. The radiographs showed anterior dislocation of the tibia, lateral dislocation of the hips, hypoplasia of fibulae and of distal ends of the fibulae (**b**), cervical kyphosis with the apex at C4, and coronal clefts of the lower lumbar vertebrae (**c**). Necropsy showed tracheomalacia. The dermal histology showed relatively broad and smudgy collagen bundles (**d**). The electron microscopic study (**e**) showed a relative increase in small short fibers with a reduction of mature collagen fibers in the hyaline cartilage of the trachea (Chen et al. 1982)

LEOPARD Syndrome

Contents

The acronym "LEOPARD syndrome," coined by Gorlin et al. (1969), is derived from clinical features which include *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, growth *r*etardation, and sensorineural *d*eafness. It is also known as multiple lentigines syndrome and Moynahan syndrome and classified as a cardiocutaneous syndrome of neural crest origin (Moynahan 1970).

Synonyms and Related Disorders

Cardiocutaneous lentiginosis syndrome (Jóźwiak et al. 1996); Cardiocutaneous syndrome of neural crest origin (Nordlund et al. 1973); Cardiomyopathic lentiginosis; Moynahan syndrome; Multiple lentigines syndrome; RASopathies

Genetics/Basic Defects

1. Inheritance:
   1. An autosomal dominant disorder with high penetrance and variable expressivity (Char 1971; Seuanez et al. 1976; Begić et al. 2014)
   2. Multiple siblings affected with the lack of features of LEOPARD syndrome in the parents may represent mosaicism of the germinal cells or, more probably, incomplete penetrance of the gene (Jóźwiak et al. 1998)
   3. Allelic to Noonan syndrome (Sarkozy et al. 2003)
2. Caused by mutations in the protein tyrosine phosphatase nonreceptor type 11 (*PTPN11*) gene (Legius et al. 2002), mapped on chromosome 12q22-qter, which is known to be mutated in the Noonan syndrome (Digilio et al. 2002):
   1. Worldwide recurrent missense mutation (c.836A/G; p.Tyr279Cys) in exon 7: associated with high phenotypic diversity (Nemes et al. 2015).
   2. Missense mutation (1403C → T; Thr468Met) in exon 12.
   3. Both mutations affect the PTPN11 phosphotyrosine phosphatase domain, which is involved in <30% of the Noonan syndrome *PTPN11* mutations.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. LEOPARD syndrome is caused in 85% of patients by a heterozygous missense mutation in the *PTPN11* gene leading to reduced SHP2 phosphatase activity. Given the implication of germline, RAS–mitogen-activated protein kinase mutations in RASopathies and tumorigenesis, the link between LEOPARD syndrome and multiple granular cell tumors could be explained by gene mutation within this signaling pathway (Aragüés et al. 2016).
4. Also can be caused by mutations in the V-RAF-1 murine leukemia viral oncogene homologue 1 (*RAF1*) gene (mapped on chromosome 3p25).
5. RASopathies or RAS/mitogen-activated protein kinase (MAPK) syndromes: a group of phenotypically overlapping syndromes caused by germline mutations that encode components of the RAS/MAPK signaling pathway. Recently, novel gene variants, including *RIT1*, *RRAS*, *RASA2*, *A2ML1*, *SOS2*, and *LZTR1*, have been shown to be associated with RASopathies, further expanding the disease entity. These disorders include (Aoki et al. 2008, 2016):
    1. Neurofibromatosis type I
    2. Legius syndrome
    3. Noonan syndrome
    4. Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome)
    5. Costello syndrome
    6. Cardiofaciocutaneous (CFC) syndrome
    7. Noonan-like syndrome
    8. Hereditary gingival fibromatosis
    9. Capillary malformation–arteriovenous malformation

Clinical Features

1. Cutaneous features (Sarkozy et al. 2008; Abdelmalek et al. 2002):
    1. Lentigines:
        1. Dark brown irregularly shaped macules ranging from pinpoint size to 5 cm in diameter
        2. Noted in infancy or childhood
        3. Continue to increase in number until puberty
        4. Primarily on the face, neck, and upper trunk with some involvement of the extremities
        5. Less commonly on the palms, soles, genitalia, iris, and sclera, but sparing oral mucosa
        6. Generalized symmetric distribution of lentigines
    2. Other cutaneous abnormalities (Jóźwiak et al. 1996):
        1. Café au lait spots (38% of patients)
        2. Café noir spots (a term proposed by Gorlin et al. (1971)): by analogy to café au lait spots to describe larger and more pigmented lentigines in patients with LEOPARD syndrome (Bujaldón 2008)
        3. Melanoma
        4. Localized hypopigmentation
        5. Interdigital webs
        6. Dermatoglyphic abnormalities
        7. Onychodystrophy
        8. Multiple granular cell myoblastomas
        9. Steatocystoma multiplex
        10. Hyperelastic skin
2. Noncutaneous features:
    1. Cardiac anomalies (Gorlin et al. 1971):
        1. Valvular pulmonary stenosis (40% of cases) and hypertrophic cardiomyopathy: the most frequent anomalies observed (Coppin and Temple 1997; Martinez-Quintana and Rodriguez-González 2012)
        2. Subaortic stenosis
        3. Subpulmonic stenosis
        4. Mitral valve involvement
        5. Left and right ventricular outflow tract obstructions
        6. Atrial septal defect
        7. Atrial myxomas
        8. Variable conduction abnormalities:
            1. Benign asymptomatic arrhythmia
            2. Malignant arrhythmias resulting in sudden cardiac death
        9. Cardiac symptoms:
            1. Dyspnea on exertion
            2. Congestive heart failure

3. Paroxysmal atrial tachycardia
4. Sudden death
5. Death at cardiac surgery

2. Noncardiac anomalies:
   1. Craniofacial features:
      1. Ocular hypertelorism (25%)
      2. Epicanthic folds
      3. Ptosis
      4. Mandibular prognathism
      5. High-arched palate
      6. Dental abnormalities
      7. Low-set posteriorly rotated ears
   2. Skeletal abnormalities:
      1. Joint hypermobility
      2. Short webbed neck
      3. Winging of the scapula
      4. Pectus excavatum and carinatum
      5. Rib anomalies
      6. Cervical spine fusion
      7. Syndactyly
      8. Scoliosis
   3. Genitourinary abnormalities (26% of cases):
      1. A small penis
      2. Cryptorchidism
      3. Hypospadias
      4. Ovarian disorders
   4. Neurologic abnormalities:
      1. Learning disability
      2. Mild mental retardation
      3. Sensorineural deafness
      4. Nystagmus
      5. Seizures
      6. Hyposmia
      7. Mild atrophy of the brain
      8. Neuropathic pain associated with hypertrophic roots and plexi (Spatola et al. 2015)
   5. Retardation of growth (short stature)
   6. Delayed puberty
3. Diagnostic criteria (Voron et al. 1976):
   1. Multiple lentigines plus two other features
   2. Immediate family member with LEOPARD syndrome plus at least three other features in the absence of lentigines
4. Although the diagnosis can be suspected clinically, confirmation requires the identification of a heterozygous germline mutation occurring in the first and third coding exons in the proto-oncogene *HRAS* (Aoki et al. 2005; Gelb and Tartaglia 2015).
5. Differential diagnosis with other neuro-cardio-facial-cutaneous syndromes (RASopathies) (Kalev et al. 2010; Santoro et al. 2014; Aoki et al. 2016):
   1. Noonan syndrome (Please see chapter on "▶ Noonan Syndrome")
   2. Noonan syndrome with multiple lentigines (NSML) (van den Berg et al. 2016):
      1. Rare association with multiple giant cell lesions (MGCL).
      2. A mutation p.Thr468Met in the *PTPN11* gene mutation.
      3. Despite a different molecular pathogenesis and effect on the RAS/MEK pathway, NSML shares the development of MGCL, with other RASopathies.
   3. Costello syndrome:
      1. Causative genes: *HRAS*, *KRAS*, *BRAF*, and *MEK1*
      2. Autosomal dominant
      3. Phenotype:
         1. Short stature
         2. Congenital heart defect
         3. Characteristic facies with more coarse features
         4. Mental retardation: more severe
         5. Distinctive skin involvement – curly, sparse hair, loose soft skin, and papillomata
   4. Cardio-facio-cutaneous syndrome:
      1. Causative genes: *KRAS*, *BRAF* (most frequent, 5–75% of cases), *MEK1*, and *MEK2*
      2. Autosomal dominant, de novo
      3. Phenotype:
         1. Short stature.
         2. Congenital heart defect.
         3. Cardiomyopathy.
         4. Characteristic facies.
         5. Mental retardation: more severe.
         6. Distinctive features: hyperkeratotic dry skin and sparse, curly hair.
         7. Phenotype overlaps most with Noonan syndrome, but facial appearance tends to be coarse.

8. Cardiac problems overlap mostly with LEOPARD syndrome.
5. Neurofibromatosis type 1-like syndrome
6. Costello syndrome (Martinez-Quintana and Rodriguez-González 2012):
    1. Clinical features:
        1. Neonatal atrial arrhythmias
        2. Ulnar deviation
        3. Excess skin which darkens with age
        4. Papillomata, usually after the age of 2 years
        5. Childhood cancers, particularly embryonic rhabdomyosarcoma and bladder carcinoma, the latter typically from teenage years onward (Kerr et al. 2006)
6. Although each one of the RASopathies exhibits typical phenotypic features, they share many clinical signs, including craniofacial anomalies, congenital heart defects, short stature, varying degrees of neurocognitive impairment, cutaneous and musculoskeletal abnormalities, and predisposition to malignancies (Santoro et al. 2014). Thus, differential diagnosis can represent a clinical dilemma, particularly among neurofibromatosis 1, Noonan syndrome, LEOPARD syndrome, and neurofibromatosis type 1-like syndrome.

Diagnostic Investigations

1. ECG abnormalities (Torres et al. 2004):
    1. Left axis deviation
    2. Bundle branch block
    3. Abnormal P wave
    4. Prolongation of the P-R interval
    5. Right or left ventricular hypertrophy
    6. Infarction patterns
    7. Ischemic patterns with nonspecific ST and T wave changes
    8. Isolated ventricular ectopic beats
    9. Ventricular fibrillation
    10. Bradycardia
    11. Paroxysmal atrial fibrillation
2. Careful cardiac assessment including echocardiography.
3. Hearing tests.
4. Histology of lentigines:
    1. Large membrane-bound accumulations of melanin granules within the Langerhans cells (Fryer and Pope 1992)
    2. Giant melanosomes rarely seen within keratinocytes and melanocytes
5. LEOPARD syndrome in the first months of age can be suspected in patients presenting with HCM, characteristic facial features, and café au lait spots, but the clinical diagnosis should be confirmed by molecular testing of *PTPN11* gene (Digilio et al. 2006).
6. Molecular testings (blood, chorionic villi, or amniotic fluid samples) can be used to confirm the diagnosis (Martinez-Quintana and Rodriguez-González 2012). The following order of testing is recommended:
    1. *PTPN11* sequence analysis of coding exons 7, 12, and 13 (these exons encompass all the codons of the *PTPN11* gene identified to be mutated in LEOPARD syndrome thus far)
    2. If no mutation is identified, sequence analysis of coding exons 6, 13, and 16 of *RAF1* and coding exons 6 and 11–17 of *BRAF*
    3. If no mutation is identified, sequence analysis of the remaining coding exons of *PTPN11*, *RAF1*, and *BRAF* (Gelb and Tartaglia 2015).
7. Diagnosis of Noonan syndrome and related disorders using target next-generation sequencing (Lepri et al. 2014), enabling a prompt diagnosis especially for those patients with mild, nonspecific, or atypical features, in whom the detection of the causative mutation usually requires prolonged diagnostic timings when using standard routine.

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: low unless a parent has the syndrome (possibility of germline mosaicism exists)
    2. Patient's offspring: 50%
2. Prenatal diagnosis (Gelb and Tartaglia 2015):
    1. Available clinically by mutation analysis of *PTPN11*, *RAF1*, *BRAF*, or *MAP2K1* genes

on fetal DNA obtained by amniocentesis or CVS, provided the disease-causing allele has been identified in an affected family member.
2. Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified.

3. Management:
1. Avoid strenuous physical exercise when outflow tract obstruction or significant cardiac dysrhythmias are present.
2. β-Adrenergic receptor or calcium channel blocking agents to reduce cardiac outflow tract obstruction and adrenergic responsiveness.
3. Amiodarone treatment in cases of life-threatening ventricular ectopy.
4. Severe arrhythmias: the most common perioperative complications (Yeoh et al. 2014).
5. Surgery may be needed to relieve severe cardiac outflow tract obstruction.
6. Surgery for cryptorchidism or severe skeletal deformity.
7. Hearing aids for sensorineural deafness.
8. Dermabrasion for cosmetic correction on the face.

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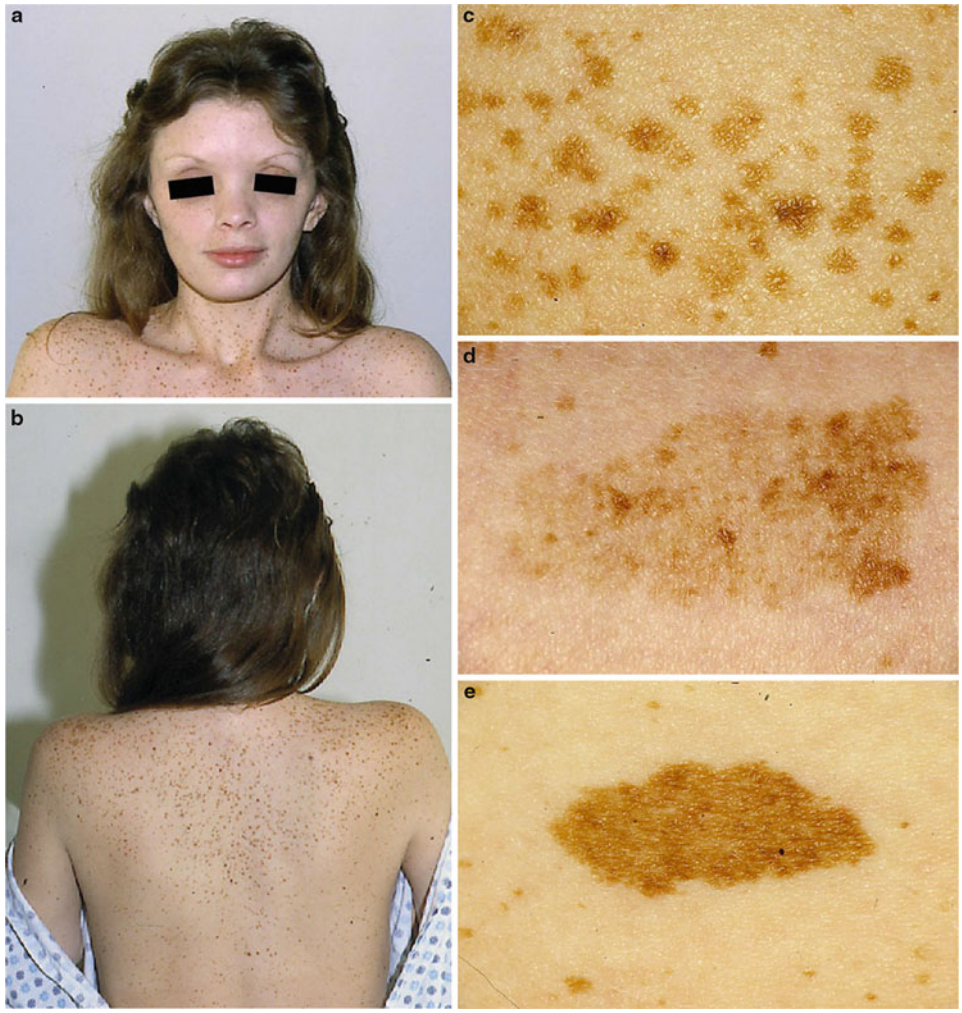

Fig. 1 A lady (**a**, **b**) with LEOPARD syndrome showing ocular hypertelorism and generalized symmetric distribution of lentigines. Close views of lentigines (**c**–**e**) show variation in size and color. There is striking mottling of pigment within any one lentigo

Lesch-Nyhan Syndrome

Contents

In 1964, Lesch and Nyhan provided the first detailed clinical description of Lesch-Nyhan syndrome with a report of two brothers with hyperuricemia and a characteristic neurobehavioral syndrome that included motor dysfunction and self-injurious behavior. The prevalence of the syndrome is estimated to be approximately 1:380,000.

Synonyms and Related Disorders

Hypoxanthine-guanine phosphoribosyltransferase 1 deficiency; Lesch-Nyhan disease

Genetics/Basic Defects

1. Inheritance: X-linked recessive
2. Enzymatic defect (Jinnah and Friedman 2001; Jinnah 2013)
    1. Caused by deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT), which catalyzes the conversion of hypoxanthine to inosine monophosphate and guanine to guanine monophosphate in the presence of phosphoribosyl pyrophosphate
    2. Three major clinical elements associated with Lesch-Nyhan syndrome
        1. Overproduction of uric acid
        2. Neurologic disability
        3. Behavioral problems
3. Hypoxanthine-guanine phosphoribosyltransferase gene (*HPRT1*) (Jinnah et al. 2000)
    1. Mapped to chromosome Xq26-q27.2
    2. The only gene known to be associated with Lesch-Nyhan syndrome
    3. Heterogeneous mutations
        1. Single base substitutions
        2. Deletions
        3. Insertions
        4. Substitutions
4. Heterogeneity of clinical phenotype (Sarafoglou et al. 2010)
    1. An approximately inverse relationship exists between HPRT enzyme activity measured in intact cells and clinical severity (Page et al. 1981; Puig et al. 2001).
    2. Affected patients with classic Lesch-Nyhan disease, the most severe and frequent form, have the lowest HPRT enzyme activity (<1.5% of normal) in intact cultured

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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fibroblasts, and the patients display the full spectrum of clinical abnormalities.
3. Patients with partial HPRT deficiency, designated as Lesch-Nyhan variants (LNVs), have HPRT enzyme activity ranging from 1.5% to 8.0% (Nyhan 2008).
4. Individuals with the intermediate form of LNV (also known as neurologic variants) have a variable clinical phenotype and, in most cases, are neurologically indistinguishable from patients with Lesch-Nyhan disease (Puig et al. 2001; Nyhan 2009).
5. However, they do not have self-injurious behaviors, and their intelligence is normal or near normal. The least-affected patients with LNV have residual HPRT enzyme activity exceeding 8%, and their only manifestations have been attributed to hyperuricemia and include gout, hematuria, and nephrolithiasis.
6. There is another LNV, HPRT Salamanca, that is characterized by spastic gait, mental retardation, and skeletal abnormalities (Nyhan 2008; Page et al. 1987).

5. Pathogenesis
   1. Metabolic basis of overproduction of uric acid: results from changes in the regulation of purine synthesis and degradation (Nyhan 1997).
   2. Pathogenesis of neurologic and behavioral features remains incompletely understood. Growing evidence suggests that these features result from dysfunction of the dopamine transmitter systems of the basal ganglia (Baumeister and Frye 1985).

Clinical Features

1. Normal prenatal and perinatal course.
2. Early developmental milestones (Nyhan 1973, 1976, 1978).
   1. Hypotonia and developmental delay: most common presenting features evident by 3–6 months of age
   2. Failure to reach normal motor milestones, such as delayed in crawling, sitting, and walking
3. Within the first few years (Watts et al. 1982)
   1. Extrapyramidal involvement
      1. Dystonia
      2. Choreoathetosis
      3. Opisthotonus
      4. Ballismus
   2. Pyramidal involvement
      1. Spasticity
      2. Hyperreflexia
      3. Extensor plantar reflexes
      4. Ankle clonus
      5. Scissoring of the legs
4. Between 2 and 3 years
   1. Impaired cognition
      1. Moderate to severe mental retardation in most patients
      2. Varying degree of impairment
      3. Difficult to obtain adequate assessments of cognitive abilities
   2. Compulsive behavioral disturbances
      1. Aggressiveness
      2. Vomiting
      3. Spitting
      4. Coprolalia
      5. Copropraxis
      6. Manipulative behavior
   3. Persistent self-injurious behavior: a hallmark of the disease
      1. Biting the fingers, hands, lips, and buccal mucosa
      2. Banging the head or limbs
5. Overproduction of uric acid: hyperuricemia-related renal and articular symptoms. These symptoms are present in all HPRT-deficient patients and are not related to the severity of the enzyme defect (Torres and Puig 2007; Torres et al. 2012b).
   1. Uric acid crystalluria noted as orange crystals in the diaper during the first weeks of life.
   2. Deposition of uric acid crystals or calculi in the kidneys, ureters, or bladder.
   3. Leading to nephrolithiasis, obstructive uropathy, and azotemia if untreated.

4. Gouty arthritis develops later in the course of the disease.
5. All characteristic findings associated with gout may be present (acute arthritis, tophi, nephrolithiasis or urolithiasis, and renal disease). However, nowadays, allopurinol treatment prevents the development of gouty manifestations.

6. Other features
   1. Delayed growth and puberty
   2. Testicular atrophy in most affected males
   3. Associated orthopedic problems
      1. Hip subluxation or dislocation
      2. Fractures
      3. Autoamputation
      4. Infections
      5. Minor scoliosis
      6. Contractures
   4. Nephrocalcinosis and renal failure reported in two familial cases (Vargiami et al. 2016)
7. Life expectancy
   1. Most surviving into the second or third decade of life if properly managed
   2. No evidence suggesting disease progression over time
   3. Complications
      1. Aspiration pneumonia
      2. Chronic nephrolithiasis
      3. Renal failure
      4. Sudden unexpected death
8. The classical phenotype of Lesch-Nyhan disease (Fu et al. 2014a, b)
   1. Overproduction of uric acid
      1. Resulting in elevated serum levels of uric acid and increased excretion of uric acid in the urine
      2. Because uric acid is near its limit of solubility in the body, it tends to precipitate in vulnerable body regions. Precipitation in the urogenital system, where it is concentrated by excretion, results in nephrolithiasis and associated problems such as urinary obstruction and renal failure.
      3. Precipitation in the subcutaneous tissues due to temperature gradients leads to solid masses known as tophi.
      4. Precipitation in the joints of the hands and feet with subsequent inflammation elicited by phagocytosis of the crystals by polymorphonuclear cells leads to gouty arthritis.
   2. Neurobehavioral phenotype
      1. Severe and recurrent self-injurious behaviors: self-biting, self-hitting, eye poking, and others.
      2. Severe motor handicap resembling dystonic cerebral palsy.
9. The milder Lesch-Nyhan variants (Fu et al. 2014a, b)
   1. Some clinical features are absent or sufficiently mild that they may escape clinical detection.
   2. The mildest clinical phenotype of hypoxanthine-guanine phosphoribosyltransferase (HGprt)-related hyperuricemia (HRH) includes only overproduction of uric acid and its associated problems. These patients do not have clinically overt neurological or behavioral abnormalities, although many have minor motor clumsiness or mild cognitive impairments that can be detected with appropriate neurological or psychometric testing.
   3. In between the severe Lesch-Nyhan disease phenotype and the mild HRH phenotype is a broad spectrum of phenotypes with varying degrees of neurological and behavioral abnormalities known as HGprt-related neurological dysfunction.
10. Lesch-Nyhan syndrome in females
    1. Extremely rare
    2. Female carriers
       1. Generally considered to be asymptomatic
       2. Have increased uric acid excretion
       3. Develop symptoms of hyperuricemia in later years
    3. Affected females
       1. Affected carrier females: considered to have nonrandom X chromosome inactivation or skewed inactivation of the normal *HPRT1* allele.

2. The first female case reported was caused by a microdeletion of the maternally derived *HPRT* gene and nonrandom inactivation of the paternally derived X chromosome.
3. Two additional cases were caused by a point mutation in one allele and markedly reduced mRNA expression from the other allele.

Diagnostic Investigations

1. EEG: nonspecific changes of slowing or disorganization (Nicklas et al. 2010).
2. CT and MRI of the brain: nonspecific changes of atrophy of the basal ganglia or cerebrum.
3. Positron emission tomography to demonstrate a selective decrease of 50–70% in dopamine transporters in the caudate and putamen.
4. Hyperuricuria or hyperuricemia (serum uric aids concentration >8 mg/dL): often present but not sensitive or specific enough for diagnosis.
5. 24-h uric acid excretion (>20 mg/kg): characteristic but not diagnostic.
6. Uric acid to creatinine ratio >2.0: characteristic for patients under 10 years of age.
7. In males: hypoxanthine-guanine phosphoribosyltransferase enzyme activity <1.5% of normal enzyme activity in cells from any tissue (blood, cultured fibroblasts, or lymphoblasts): establishes the diagnosis.
8. In females: measurement of HPRT enzyme activity for carrier detection is technically demanding and not widely used. Measurement of HPRT enzyme activity on hair bulbs from women at risk has had both false-positive and false-negative results.
9. Molecular genetic testing of the *HPRT1* gene (Nyhan et al. 2014; Torres and Puig 2007).
    1. Purposes
        1. To define the mutation in the affected males
        2. To determine carrier status in at-risk females: requires prior identification of the disease-causing mutation in the family (Alford et al. 1995)
    2. Sequence analysis or mutation scanning to detect *HPRT1* mutations in males affected with Lesch-Nyhan syndrome: available on clinical basis
    3. Deletion/duplication analysis
        1. To detect exonic or whole-gene deletions
        2. Between 21% and 24% of mutations in *HPRT1* are large deletions that cannot be detected in females by sequence analysis

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. When the mother is not a carrier: not increased unless the mother has germ line mosaicism in which case there is an undetermined, but real, risk of having future affected sons or carrier daughters
        2. When the mother is a carrier
            1. A 25% risk of having an affected male
            2. A 25% risk of having a carrier female
            3. A 50% risk of having an unaffected male or female
    2. Patient's offspring
        1. Severely affected males: not surviving to reproductive age
        2. Less severely affected males: all of his daughters are obligatory carriers and none of his sons affected
2. Prenatal diagnosis available to at-risk pregnancies (Torres and Puig 2007; Liu et al. 2015).
    1. Fetal sex determination by amniocentesis or CVS
    2. Confirmation of a previously known *HPRT1* disease-causing mutation in a male fetus
        1. Perform HPRT enzyme activity
        2. Perform molecular genetic testing
    3. Assay of HPRT enzyme activity in cultured amniocytes or chorionic villus cells (Graham et al. 1996): the method of choice if the *HPRT1* mutation has not been identified in the family
    4. Carrier and prenatal diagnosis of Lesch-Nyhan disease due to a defect in HPRT

gene expression regulation (Torres et al. 2012a)
5. Preimplantation genetic diagnosis possible for a previously characterized disease-causing mutation (Ray et al. 1999)

3. Management (Seegmiller 1968; Crawhall et al. 1972; Nicklas et al. 2010)
   1. Hyperuricemia
      1. Control hyperuricemia to reduce the risk of nephropathy, nephrolithiasis, and gouty arthritis.
      2. Allopurinol
         1. To block the conversion of oxypurines into uric acid
         2. To prevent uric acid accumulation and subsequent arthritic tophi, renal stones, and nephropathy
         3. Has no effect on behavioral and neurologic symptoms
   2. Renal stones
      1. Lithotripsy
      2. Surgery
   3. Neurologic dysfunction
      1. No medication known to be consistently effective in controlling the extrapyramidal motor features
      2. Baclofen or benzodiazepine for spasticity
   4. Neurobehavioral symptoms
      1. No effective intervention available
      2. Use behavioral modification techniques
      3. Control self-injurious behavior
         1. Requires physical restraints.
         2. Removal of teeth.
         3. A noninvasive approach with a special appliance fabricated for the prevention of damage to oral and perioral soft tissues (Fardi et al. 2003).
         4. Carbamazepine to attenuate the behavioral manifestations.
   5. Surgery for orthopedic problems (Sponseller et al. 1999).
   6. Bone marrow transplantation or red blood cell transfusions do not significantly ameliorate the neurologic disorder.
   7. Successful unrelated umbilical cord blood transplantation in Lesch-Nyhan syndrome (Kállay et al. 2012).

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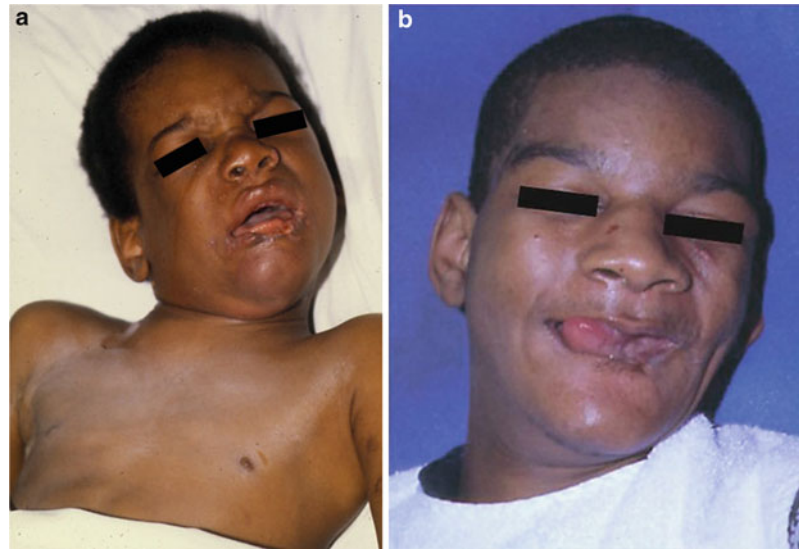

Fig. 1 (**a**, **b**) Two boys with Lesch-Nyhan syndrome showing severe mental retardation and self-mutilation of the lips and tongue

Lethal Multiple Pterygium Syndrome

Contents

Lethal multiple pterygium syndrome (LMPS) is a lethal hereditary disorder characterized by a distinct constellation of multiple anomalies, consisting of multiple pterygia, flexion contractures of multiple joints, characteristic facial appearance, cystic hygroma, hydrops, and pulmonary and cardiac hypoplasia.

Synonyms and Related Disorders

Chen syndrome; Gillin-Pryse-Davis syndrome; Herva syndrome; Lethal fetal akinesia deformation sequence syndrome (FADS); Multiple pterygium syndrome/Escobar syndrome (Chen et al. 1980); Van Regemorter syndrome

Genetics/Basic Defects

1. Inheritance: possible heterogeneity
    1. Autosomal recessive inheritance
    2. Possible X-linked recessive inheritance (Tolmie et al. 1987; Meyer-Cohen et al. 1999)
2. Mutations in genes encoding components of the neuromuscular junction (NMJ) have been described in FADS and/or LMPS (Kariminejad et al. 2016a). This includes:
    1. Mutations in the genes *CHRNA1* (Michalk et al. 2008), *CHRND* (Michalk et al. 2008), and *CHRNG* encoding the alpha, delta, and gamma subunits of the acetylcholine receptor (AChR), respectively.
    2. Mutations in *RAPSN* (Vogt et al. 2008), encoding a postsynaptic protein that connects and stabilizes AChR at the NMJ, *DOK7* (Vogt et al. 2009), and recently identified *MuSK* (Wilbe et al. 2015), encoding muscle skeletal receptor tyrosine kinase, have been associated with LMPS and/or FADS.
3. Lethal multiple pterygium syndrome: the extreme end of the *RYR1* spectrum (Kariminejad et al. 2016b)
    1. *RYR1* encodes the skeletal muscle isoform ryanodine receptor 1, an intracellular calcium channel with a central role in muscle contraction.
    2. Mutations in *RYR1* have been associated with congenital myopathies, which form a continuous spectrum of pathological features including a severe variant with onset in utero with fetal akinesia and arthrogryposis.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Germline mutations in *RYR1* are associated with fetal akinesia deformation sequence/ lethal multiple pterygium syndrome (McKie et al. 2014).
4. Classification by Hall et al. (1982), Hall (1984), Froster et al. (1997), and Entezami et al. (1998)
   1. Based on the following concomitant abnormalities
      1. Age of onset of intrauterine growth retardation
      2. Timing and extent of neck swelling
      3. Presence or absence of bony fusions and bone modeling errors
   2. Type I (Gillin-Pryse-Davis syndrome) (Gillin and Pryse-Davis 1976)
      1. Multiple pterygia
      2. Pulmonary hypoplasia
      3. Genital anomalies
      4. Facial anomalies
      5. Strongly flexed extremities with a reduced muscle mass
   3. Type II (Chen syndrome) (Chen et al. 1984)
      1. Multiple pterygia
      2. Hygroma colli
      3. Facial anomalies
      4. Shortened extremities
      5. Undermodeled long bones
      6. Cartilaginous fusion of joints and bony fusion of the spinous processes of the vertebrae
      7. Polyhydramnios
      8. Hypoplastic lungs and heart
      9. Diaphragmatic hernia
   4. Type III (van Regemorter syndrome) (Van Regemorter et al. 1984)
      1. Multiple pterygia
      2. Pulmonary hypoplasia
      3. Facial anomalies
      4. Thin extremities with reduced muscle mass
      5. Fusions of the long tubular bones
   5. Type IV (Herva syndrome) (Herva et al. 1985)
      1. Multiple pterygia
      2. Degeneration of the anterior horn cells of the spinal cord
      3. Found particularly in Finland
5. Classification by de Die-Smulders et al. (1990a)
   1. Early LMPS
      1. A group with presumed genetic heterogeneity
      2. Lethality in the second trimester
      3. Hydrops fetalis
      4. Cystic hygroma
   2. Late LMPS
      1. Survival into the third trimester
      2. Absence of fetal hydrops
   3. Finnish-type LMPS
      1. Fetal hydrops from the 15th gestational week
      2. Lethality at average gestation of 29 weeks
      3. Occasional pterygia of the neck and elbows
      4. Distinct neuropathologic findings
6. Pathogenesis (Moerman et al. 1990)
   1. Combination of the following two sequences:
      1. Fetal akinesia deformation sequence
         1. Resulting from myoneural dysfunction (generalized amyoplasia) and/or intrauterine growth constraint leading to fetal akinesia
         2. Fetal akinesia, in turn, leading to growth retardation, pulmonary hypoplasia, short umbilical cord, limb positional defects, and facial anomalies
      2. Jugular lymphatic obstruction sequence: delay in development of the connection between jugular lymph sacs and the internal jugular vein resulting in dilatation of tributary lymphatics and peripheral lymphedema
   2. Fragile collagen proposed as a possible pathogenesis (Hartwig et al. 1989; Gericke 1991)
7. A gene responsible for some cases of lethal MPS (LMPS) and Escobar variant of MPS has now been identified.
   1. Caused by mutation in the *CHRNG* gene (Hoffmann et al. 2006; Morgan et al. 2006)
   2. Caused by mutations in the *CHRNA1* and *CHRND* genes (Michalk et al. 2008)

Clinical Features

1. Prenatal history
   1. Nonimmune fetal hydrops
   2. Diminished fetal activity
   3. Maternal hydramnios
   4. Often presented with fetal demise
2. Characteristic facial features
   1. Ocular hypertelorism
   2. Antimongoloid slant of the palpebral fissures
   3. Epicanthal folds
   4. Markedly flattened nasal bridge with hypoplastic nasal alae
   5. Micrognathia
   6. Lethal pterygium syndrome with facial clefting (Bartsocas-Papas syndrome) (Francesco and Nicola 1988; Turnpenny and Hole 2000)
   7. Apparently low-set malformed ears
3. Neck
   1. Short
   2. Cystic hygroma
4. Chest
   1. Small chest
   2. Hypoplastic lungs
   3. Hypoplastic heart
5. Multiple pterygia
   1. Symmetrical
   2. Sites
      1. Chin-to-sternum
      2. Cervical
      3. Axillary (Froster-Iskenius et al. 1988)
      4. Antecubital
      5. Crural
      6. Popliteal
6. Other limb anomalies
   1. Multiple contractures: always present
   2. Camptodactyly
   3. Calcaneovalgus foot deformities
7. Gastrointestinal anomalies
   1. Intestinal malrotation
   2. Short bowel
   3. Thin colon
   4. Colonic atresia
   5. Absent vermiform appendix
8. Genitourinary anomalies
   1. Hydronephrosis
   2. Unilateral renal dysplasia
   3. Cryptorchidism
9. Other associated anomalies
   1. Kyphoscoliosis
   2. Near-complete absence of diaphragmatic muscle
   3. Aortic coarctation
   4. Absent abdominal wall muscle
   5. Adrenal hypoplasia
   6. Short umbilical cord
   7. Rare cerebral anomalies
      1. Hydranencephaly (Mbakop et al. 1986)
      2. Holoprosencephaly
      3. Dilated ventricles with intracerebral cyst

Diagnostic Investigations

1. Radiography
   1. Craniofacial abnormalities
      1. Scalp edema
      2. Microbrachycephaly
      3. Flattened mandibular angle
   2. Hypoplasia and undermodeling of the bones
      1. Thin crowded ribs
      2. Markedly hypoplastic scapulae
      3. Hypoplastic iliac wings, ischia, and pubic bones
      4. Lack of normal curvature at the cervicothoracic junction
   3. Bony fusion
      1. Marked bony fusion of posterior spinous processes
      2. Radioulnar synostosis
2. Histologic studies of the skeletal system
   1. Cartilaginous and bony fusion of the spinous processes
   2. Fusion of epiphyseal cartilages of distal humerus and proximal ulna
   3. Poorly developed joint space
   4. An abnormal growth plate
   5. Weak safranin staining of the resting cartilages
   6. Placenta (Brink et al. 2003)
      1. Scalloped chorionic villi
      2. Intravillous trophoblast invaginations

7. Muscular and neural abnormalities (Spearritt et al. 1993; Cox et al. 2003)
3. Chromosome analysis: normal
4. Molecular diagnosis for *CHRNA1*, *CHRND*, *CHRNG*, *RAPSN*, *DOK7*, *MuSK*, and *RYR1* gene mutations (McKie et al. 2014; Kariminejad et al. 2016a)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal recessive inheritance: 25%
      2. X-linked recessive inheritance: 50% risk of having an affected brother if the mother is a carrier
   2. Patient's offspring: a lethal entity not surviving to reproductive age
2. Prenatal diagnosis by ultrasonography: possible (Isaacson et al. 1984; Hogge et al. 1985; Martin et al. 1986; Lockwood et al. 1988; de Die-Smulders et al. 1990b; Entezami et al. 1998; Sciarrone et al. 1998; Hertzberg et al. 2000)
   1. Nonimmune fetal hydrops
   2. Cystic hygroma
   3. Diminished fetal activity/absent limb movement
   4. Short and fixed limbs (multiple joint contractures with cutaneous webs)
   5. Maternal hydramnios
   6. Other ultrasonographically detectable anomalies
      1. Diaphragmatic hernia
      2. Scoliosis
      3. Pterygia
      4. Malformed ribs
   7. Ultrasonographic features at first trimester of pregnancy (Meizner et al. 1993; Chen et al. 2005; Gundogan et al. 2006)
      1. Cystic hygroma
      2. Generalized edema
      3. Ascites
      4. Markedly increased nuchal translucency
      5. No fetal movement/fetal posture (Anthony et al. 1993)
      6. Flexed upper and lower limbs
      7. Cutaneous webs across both elbow joints
      8. Hypoplastic left heart
3. Management: a lethal entity

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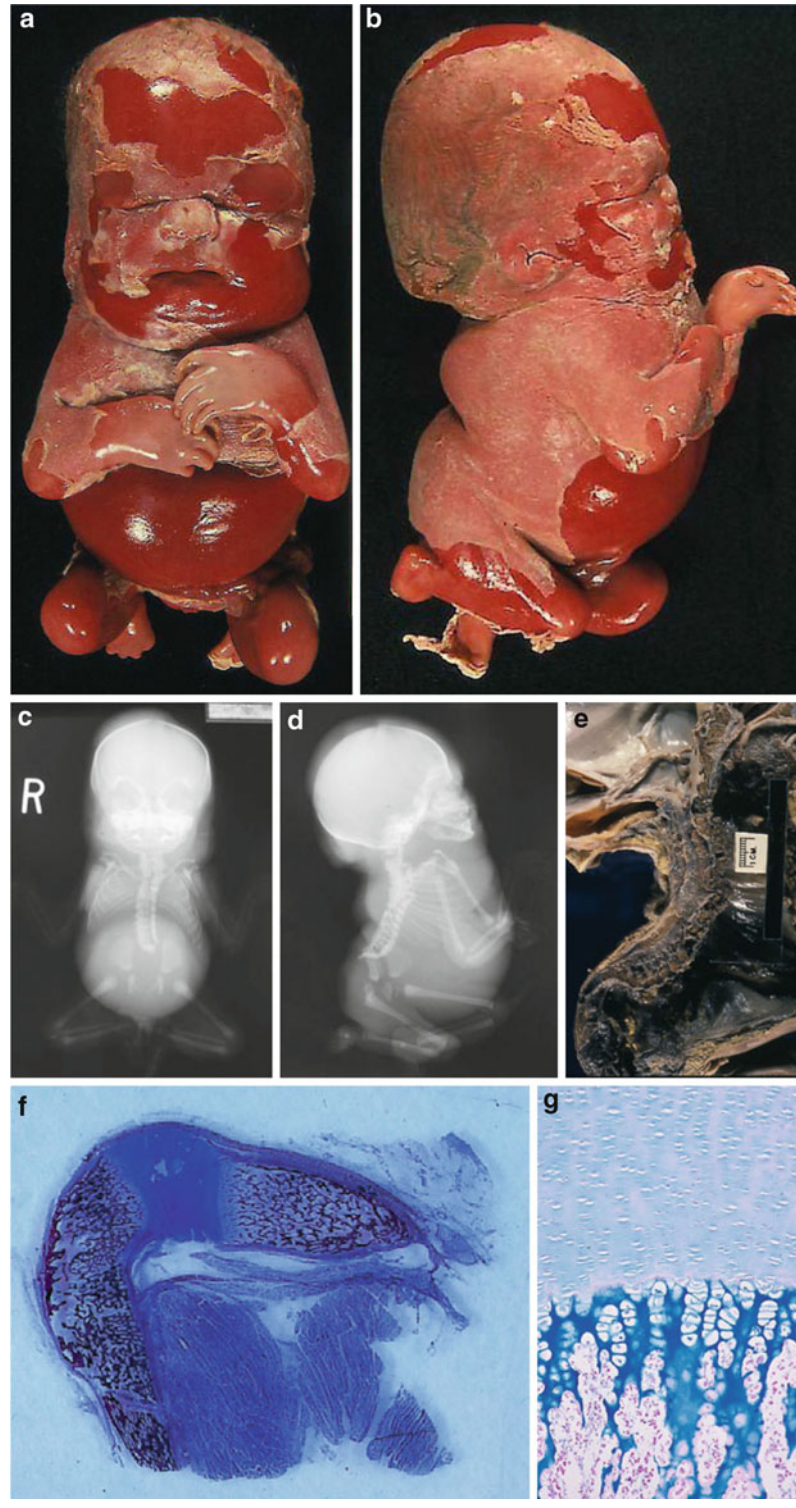

Fig. 1 The macerated 32-week stillborn (**a**, **b**) with Chen syndrome showing multiple pterygia involving the neck, axillae, antecubital, crural, popliteal, and interphalangeal areas, hygroma coli, and facial anomalies (hypertelorism, antimongoloid slant of the palpebral fissures, a shortened nose, depressed nasal bridge and tip of the nose, a long philtrum, a receding chin, and apparently low-set and malformed ears). Contractures of the fingers were present with ulnar deviation of the hands. Polyhydramnios and fetal hydrops were noted by ultrasonography at 30 weeks of gestation. Autopsy showed hypoplastic lungs and heart and a large left diaphragmatic hernia (containing intestine, pancreas, and part of the stomach and ascites). Radiographs (**c**, **d**) and postmortem section (**e**) revealed a large cystic hygroma, hypoplastic vertebral bodies, fusion of the posterior elements extended from the cervical into the midthoracic spine, angulated cervicothoracic junction, and undermodeled long bones. Representative section of the elbow (**f**) showed fusion of epiphyseal cartilages of the distal humerus and proximal ulna resulting in bending of the proximal portion of the ulna and a deficient joint space. The resting cartilage (**g**) was distinctly demarcated from the physeal growth plate, which showed slightly retarded but normally arranged chondrocytic column

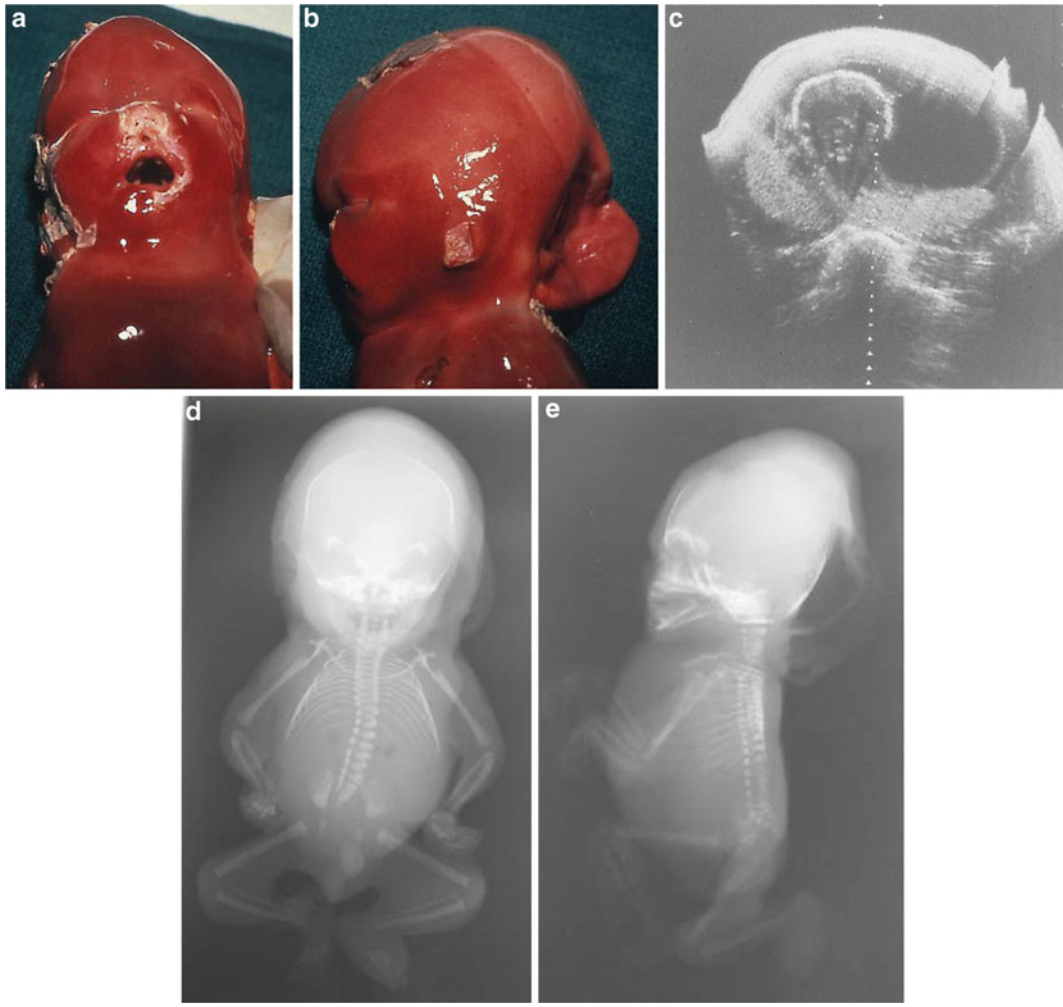

Fig. 2 A malformed macerated 28-week fetus (**a**, **b**) with Chen syndrome showing impressive skin webbing at the neck, axillae, antecubital, crural, and popliteal areas, and abnormal facies (markedly flattened nasal bridge with anteverted and hypoplastic nasal alae, low-set ears, and a small mouth with cleft soft palate). In addition, there were contractures of the hands and fingers and rocker bottom feet. The prenatal ultrasound at 25 weeks of gestation (**c**) showed a large cystic hygroma at the back of the head. Radiographs (**d**, **e**) revealed massive edema of the scalp contiguous with the neck pterygia, hypoplastic vertebral bodies, multiple fusions of the posterior elements of the cervical and lumbosacral spine bodies, and incipient fusion of the radius and ulna bilaterally. Post mortem study revealed markedly hypoplastic lungs and heart

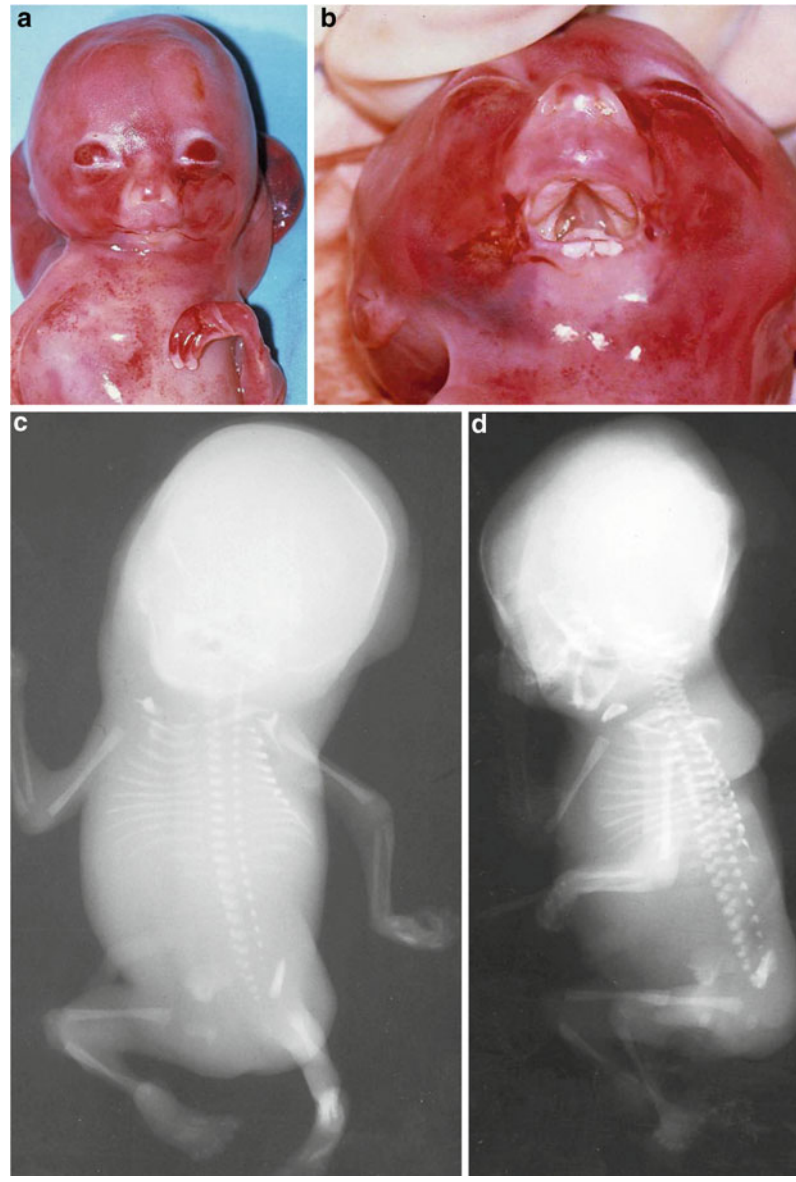

Fig. 3 A 19-week fetus with Chen syndrome (**a**, **b**) showing a large cystic hygroma, detected by prenatal ultrasonography, multiple pterygia involving neck, axillae, elbows, fingers, and knees with contractures, illustrated by radiographs (**c**, **d**). Distinctive facial features include hypertelorism, flat nasal bridge, cleft palate, and micrognathia. Postmortem study revealed hypoplastic lungs and heart, fusion of cartilage of the elbow joints, and hypoplastic cervical vertebral bodies with posterior elements beginning to come together but were not yet fused

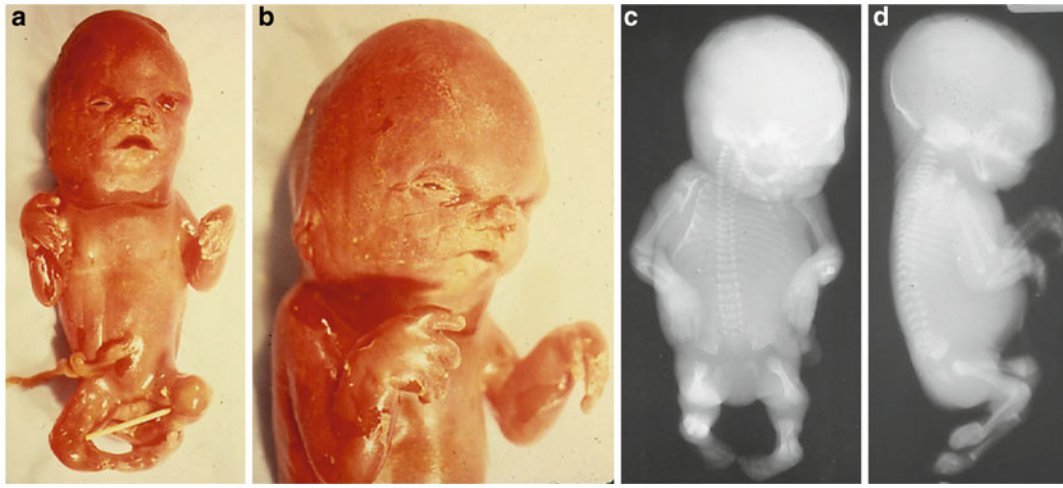

Fig. 4 A fetus with lethal multiple pterygium (**a**, **b**) syndrome showing multiple pterygia involving neck, axilla, elbows, and knees associated with multiple contractures illustrated by radiographs (**c**, **d**). There were hypertelorism, small nose, and micrognathia

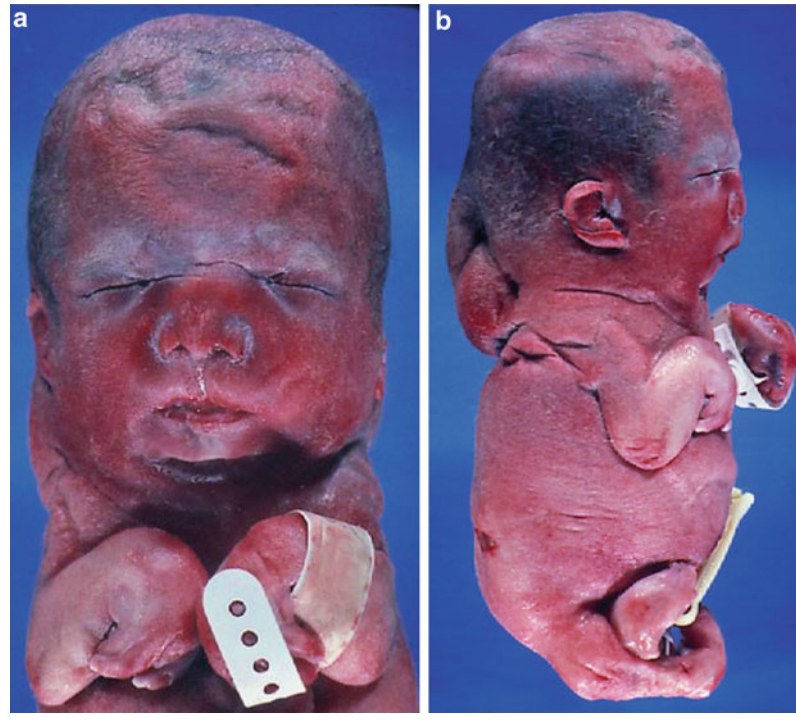

Fig. 5 (**a**, **b**) A stillbirth with lethal multiple pterygium syndrome showing flexion of all four limbs with multiple pterygia involving neck, axillae, elbows, and knees; short neck; and cystic hygroma colli. There were antimongoloid slant of the palpebral fissures, hypertelorism, flat nasal bridge, micrognathia, and high-arched palate. The upper extremities were held in extreme flexion with ulnar deviation of both hands and camptodactyly. The lower limbs were rotated externally and flexed in a crossed position with bilateral calcaneus deformities of the feet. Postmortem findings include multiloculated cystic hygroma, hypoplastic lungs, and kyphoscoliosis

Loeys-Dietz Syndrome

Contents

Loeys-Dietz syndrome (LDS), a newly recognized connective tissue disorder, shares overlapping features with Marfan syndrome (MFS) and the vascular type of Ehlers-Danlos syndrome (EDS), including aortic root dilatation and skin abnormalities (Aalberts et al. 2008).

Synonyms and Related Disorders

Loeys-Dietz aortic aneurysm syndrome (Dietz et al. 2005); Marfan syndrome-related disorders; TGFBR1-related Loeys-Dietz syndrome; TGFBR2-related Loeys-Dietz syndrome

Genetics/Basic Defects

1. An autosomal dominantly inherited disorder of connective tissue.
2. Caused by heterozygous mutations in the gene encoding type I or II transforming growth factor beta (TGF-β) receptor.
3. An altered signaling of the TGF-β cytokine family.
    1. Plays an important role in cell proliferation and differentiation, apoptosis and extracellular matrix formation, underlining both LDS and MFS.
    2. Causes disarrayed elastic fibers and loss of elastin content in the aortic media, predisposing to dilatation and dissection of the aortic wall.
    3. Disruption of the normal TGF-β signaling takes place at the level of the TGF-β receptors. Mutations in either the TGF-β receptor 1 or 2 genes (Loeys et al. 2006; LeMaire et al. 2007; Mizuguchi and Matsumoto 2007; Drera et al. 2008) have been identified in one third and two thirds of LDS patients, respectively. However, in MFS an abnormal fibrillin protein causes an increased activity of TGF-β, leading to the typical phenotypic characteristics of the MFS.
4. Mutations in the *TGFBR* gene may be associated with greater phenotypic heterogeneity than previously reported (Akutsu et al. 2007).
5. Patients with a *TGFBR1* or *TGFBR2* mutation showed extensive clinical overlap between patients with MFS type 1, MFS type 2, and

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LDS type 2A and 2B (Singh et al. 2006; Stheneur et al. 2008; Söylen et al. 2009).

6. Increased transforming growth factor-β (*TGF-β*) activity plays a crucial role in the pathogenesis of MFS and related disorders, such as Loeys-Dietz syndrome (LDS), which is caused by mutation in TGF-β signaling-related genes (Takeda et al. 2016).
7. LDS classification (MacCarrick et al. 2014).
    1. LDS 1 (thoracic aortic aneurysm and dissection) (*TGFBR1*)
    2. LDS 2 1 (thoracic aortic aneurysm and dissection; Marfan syndrome type 2) (*TGFBR2*)
    3. LDS 3 (aneurysms-osteoarthritis syndrome) (*SMAD3*)
    4. LDS 4 (aneurysm, aortic and cerebral, with arterial tortuosity and skeletal manifestations) (*TGFB2*)
8. Marfan syndrome-related disorders and mutated genes (Pearson et al. 2008; Verstraeten et al. 2016).
    1. Marfan syndrome: *FBN1*, *TGFBR*1, *TGFBR2*
    2. LDS: *FBN1*, *TGFBR*1, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*, *SMAD2*
    3. MASS (*M*itral valve, *A*orta, *S*kin and *S*keletal) phenotype: *FBN1*
    4. Neonatal Marfan syndrome: *FBN1*
    5. Familial thoracic aortic: aneurysms and dissections: *FBN1*, *TGFBR1*, *TGFBR2*
    6. Isolated ectopia lentis: *FBN*1
    7. Shprintzen-Goldberg craniosynostosis syndrome: *FBN1*, *TGFBR2*
    8. Autosomal dominant Weill-Marchesani syndrome: *FBN1*
    9. Loeys-Dietz syndrome (Loeys et al. 2006): *TGFBR1*, *TGFBR2*

Clinical Features

1. A wide range of intra- and interfamilial variability involving cutaneous, skeletal (Sousa et al. 2011), and cardiovascular systems (Loeys et al. 2005)
2. Clinical types (Aalberts et al. 2008)
    1. Type I (about 75% of cases): recognized by craniofacial characteristics (hypertelorism, bifid uvula, or cleft palate).
    2. Type II (about 25% of cases): absence of facial characteristics (However, certain common facial features have been recently observed in type II patients.).
    3. Generalized arteriopathy: the most salient feature in LDS whether in type I or type II.
    4. Aortic root aneurysms are present in 98% of LDS patients (Augoustides et al. 2009).
    5. Dural ectasia has recently been observed in LDS patients (Sheikhzadeh et al. 2014).
    6. Both types with interfamilial and intrafamilial phenotypic variability.
3. LDS type I
    1. Overlapping features with MFS
        1. Aortic root dilatation/aneurysm
        2. Arachnodactyly (long slender fingers)
        3. Dolichostenomelia (thin body habitus and long extremities)
        4. Pectus deformity
        5. Joint laxity
    2. Typical characteristics
        1. Aortic root aneurysm (98%)
        2. Aneurysms of other vessels (52%)
        3. Generalized arterial tortuosity (84%)
    3. Typical and easily recognizable facial characteristics
        1. Ocular hypertelorism (increased distance between the pupils) (90%)
        2. Cleft palate or bifid uvula (90%)
        3. Other facial features
            1. Blue sclera (40%)
            2. Malar hypoplasia (60%)
            3. Exotropia
            4. Proptosis
            5. Retrognathia (50%)
    4. Musculoskeletal manifestations
        1. Craniosynostosis (premature closure of cranial sutures) (48%)
            1. Premature fusion of the sagittal suture (resulting in dolichocephaly) most commonly involved
            2. Coronal suture synostosis (resulting in brachycephaly)
            3. Metopic suture synostosis (resulting in trigonocephaly)

2. Dolichostenomelia (18%)
3. Cervical spine instability
4. Pectus deformity (68%)
5. Arachnodactyly (70%)
6. Scoliosis (50%)
7. Joint laxity (68%)
8. Talipes equinovarus (45%)
9. Camptodactyly (38%)

5. Cutaneous manifestations
   1. Velvety skin (28%)
   2. Translucent skin (32%)
6. Congenital heart defects
   1. Patent ductus arteriosus (35%)
   2. Atrial septal defect (22%)
   3. Bicuspid aortic valve
   4. Bicuspid pulmonary valve
   5. Mitral valve prolapse
7. Developmental delay (15%)
8. Absence of ectopia lentis (lens subluxation) (0%) and other ocular manifestations seen in MFS

4. LDS type II
   1. Aortic root aneurysm with dissection (100%)
   2. Other aortic aneurysm (73%)
   3. Arterial tortuosity (67%)
   4. Overlapping features with the vascular type of EDS
      1. Skin abnormalities
         1. Easy bruising (67%)
         2. Translucent skin (64%)
         3. Velvety skin (83%)
         4. Skin hyperextensibility (20%)
         5. Atrophic scars (50%)
      2. Joint laxity (100%)
      3. Rupture of visceral organs
         1. Vascular rupture during pregnancy (50%)
         2. Uterine rupture (33%)
         3. Splenic or bowel rupture (25%)
      4. Uterine hemorrhage (17%)
      5. Inguinal hernia (36%)
   5. Facial features observed in most patients, although not exclusive to LDS II (Adès 2008)
      1. Dolichocephaly
      2. A tall broad forehead
      3. Frontal bossing
      4. A high anterior hairline
      5. Hypoplastic supraorbital margins
      6. A "jowly" appearance (particularly in the first 3 years of life)
      7. Translucent and redundant facial skin (often most pronounced in the periorbital region)
      8. Prominent upper central incisors in late childhood/adulthood
      9. An open-mouthed myopathic face
      10. The adult faces appeared prematurely aged
5. Cardiovascular involvement
   1. Type I
      1. Mean craniofacial-severity-index score (scores range from 0 to 11 with higher scores indicating more severe abnormalities): 4.8 years
      2. Mean age at first major event: 24.5 years
      3. Age at death: 22.6 years (0.5–45.0)
      4. Cause of death: thoracic aortic dissection (19%), abdominal aortic dissection (5%), subclavian artery dissection (0%), and cerebral bleeding (3%)
      5. Age at first cardiovascular surgery 16.9 years (1.2–46.0)
      6. Distribution of aneurysms: ascending aorta (84%), transverse aorta (5%), descending thoracic aorta (6%), abdominal aorta (8%), thoracic arterial branches (27%), head or neck arterial branches (11%), and abdominal arterial branches (3%)
   2. Type II
      1. Mean craniofacial-severity-index score: 0.8 year
      2. Mean age at first major event: 29.8 years
      3. Age at death: 31.8 years (18.0–47.0)
      4. Cause of death: thoracic aortic dissection (23%), abdominal aortic dissection (12%), subclavian artery dissection (4%), and cerebral bleeding (0%)
      5. Age at first cardiovascular surgery: 26.9 years (14.0–38.0)
      6. Distribution of aneurysms: ascending aorta (85%), transverse aorta (23%), descending thoracic aorta (19%), abdominal aorta (15%), thoracic arterial

branches (8%), head or neck arterial branches (8%), and abdominal arterial branches (15%)

6. Differential diagnosis (Kalra et al. 2011)
   1. Vascular type of Ehlers-Danlos syndrome (please see the chapter on "► Ehlers-Danlos Syndrome").
   2. Marfan syndrome (please see the chapter on "► Marfan Syndrome").
   3. Shprintzen-Goldberg syndrome (Marfanoid craniosynostosis syndrome).
      1. Phenotypes overlapping with some LDS patients with mutations in TGFBR1 or TGFBR2.
      2. Not associated with cleft palate, arterial tortuosity or risk of aneurysm, or dissection other than at the aortic root.
      3. Most affected individuals have no vascular pathology.
      4. Sequencing of TGFBR1 and TGFBR2 in five individuals with classic SGS identified no mutations (data not shown). Nevertheless, given the extent of phenotypic overlap between SGS, MFS, and selected individuals with mutations in either TGFBR1 or TGFBR2, the pathogenesis of SGS probably also relates to alteration in TGF-β signaling.
   4. Familial thoracic aortic aneurysm and dissections.
      1. Cardinal features: progressive dilation of the ascending aorta and thoracic aortic dissections
      2. Unlike LDS, cardiovascular abnormalities are typically the only manifestations of disease.
   5. Congenital contractural arachnodactyly (CCA).
      1. LDS and CCA share many features, including not only arachnodactyly but also camptodactyly, club foot, scoliosis, and aortic dilation that may progress over time
      2. Whereas aortic tortuosity/aneurysms are typically widespread in patients with LDS, dilation is restricted to the aorta in CCA and is not present in all individuals; moreover, no dissections have so far been reported in CCA patients
   6. Arterial tortuosity syndrome, a rare autosomal-recessive disorder with a clinical phenotype of aortic/arterial tortuosity, skeletal and cutaneous involvement, may closely resemble LDS.
   7. Children who present with diffuse hypotonia, joint laxity, and/or joint contractures and in whom a diagnosis of arthrogryposis, Larsen syndrome, or Beal syndrome is being entertained should undergo thorough genetic evaluation to rule out a *TGFBR1* or *TGFBR2* mutation.
   8. Larsen syndrome or Beals syndrome: presenting as joint contractures and joint hypermobility in the neonatal period (Yetman et al. 2007).

Diagnostic Investigations

1. Diagnosis of LDS.
   1. Based on characteristic clinical findings in the proband and family members
   2. Craniofacial examination for evidence of bifid uvula, cleft palate, and craniosynostosis
   3. Ophthalmologic examination by an ophthalmologist with expertise in connective tissue disorders
      1. Slit-lamp examination through a maximally dilated pupil for exclusion of lens subluxation or luxation
      2. Careful refraction and visual correction, especially in young children at risk for amblyopia
      3. Specific assessment for retinal detachment and blue sclerae
   4. Magnetic resonance angiography (MRA) or CT scan with 3D reconstruction from head to pelvis: to identify arterial aneurysms and arterial tortuosity throughout the arterial tree
   5. Radiographs to detect skeletal manifestations (e.g., severe scoliosis, cervical spine instability) that may require attention by an orthopedist

6. Multidetector CT angiography (Johnson et al. 2007)
    1. Enlargement of aortic root
    2. Marked tortuous carotid arteries/vertebral artery
7. Molecular genetic testing of *TGFBR1* and *TGFBR2*, the only two genes known to be associated with LDS, available on a clinical basis

2. Genetic testing of relatives at risk.
    1. To clarify genetic status of family members at risk if the causal *TGFBR1* or *TGFBR2* mutation is known in the proband
    2. To evaluate relatives at risk for signs of LDS, including echocardiography and extensive vascular imaging if the mutation is not known in the proband
3. Next generation sequencing approach for thoracic aortic aneurysm genetic testing overcomes the intrinsic hurdles of consecutive Sanger sequencing of all candidate genes and presents a powerful tool for the elaboration of clinical phenotypes assigned to different genes (Proost et al. 2015).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. If a parent of the proband is affected: the risk to the sibs is 50%
        2. If parents are clinically unaffected: the risk to the sibs of a proband appears to be low but greater than that of the general population because of reported rare cases of somatic (Watanabe et al. 2008) and germline mosaicism
    2. Patient's offspring
        1. A 50% chance of inheriting the mutation and the disorder.
        2. Since the penetrance of disease-causing *TGFBR1* and *TGFBR2* mutations is reported to be near 100%, offspring who inherit a mutant allele from a parent will have LDS, although the severity cannot be predicted.
2. Prenatal diagnosis (Loeys and Dietz 2013)
    1. Ultrasonography
        1. Ultrasound examination in the first two trimesters: not sensitive in detecting manifestations of LDS although prenatal occurrence of aortic dilatation has been described
        2. Aortic root aneurysm identified in a fetus of 19 week of gestation (Viassolo et al. 2006)
    2. Molecular genetic testing
        1. Prenatal diagnosis for pregnancies at increased risk for LDS is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15–18 weeks' gestation or chorionic villus sampling (CVS) at approximately 10–12 weeks' gestation.
        2. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.
        3. Linkage analysis should be used with caution unless *TGFBR1* or *TGFBR2* marker alleles can be shown to cosegregate with disease in a large family.
        4. Preimplantation genetic diagnosis: available for families in which the disease-causing mutations have been identified.
3. Management
    1. Careful follow-up and aggressive surgical treatment mandatory because of the following reasons:
        1. Aortic dissection and rupture in LDS tend to occur at a young age versus MFS.
        2. Vascular pathology can be seen throughout the entire arterial tree.
    2. Echocardiographic assessment of the aortic root diameter and its growth
    3. MR angiography from head to pelvis to discover other possible aneurysms
    4. Surgical fixation of cervical spine instability to prevent spinal cord damage
    5. Standard treatment of clubfeet and severe pes planus

6. Standard management of cleft palate and craniosynostosis, preferably by a craniofacial team
7. High risk of pregnancy following aortic root replacement in Loeys-Dietz syndrome: high risk of dissection (Braverman et al. 2016)
8. Prevention of secondary complications: consider subacute bacterial endocarditis prophylaxis in those undergoing dental work or other procedures expected to contaminate the bloodstream with bacteria
9. Initiate β-blockade therapy to reduce further aortic root dilatation or alternatively treat with angiotensin II receptor antagonist
10. Indications for surgical intervention in Loeys-Dietz syndrome (aggressive thoracic aortic aneurysm disease) (Williams et al. 2007)
    1. Adults
        1. Aortic root >4.0 cm or expanding rapidly (>0.5 cm/year)
        2. Descending thoracic aorta >5.0 cm or expanding rapidly (>0.5 cm/year)
        3. Abdominal aorta >4.0 cm or expanding rapidly (>0.5 cm/year)
        4. Rapid expansion of peripheral aneurysms
    2. Children
        1. Severe craniofacial features: aortic root z-score >3.0 or expanding rapidly (>0.5 cm/year), or mild craniofacial features: aortic root z-score >4.0 or expanding rapidly (>0.5 cm/year).
        2. Effort should be made to delay surgery until the annulus reaches 1.8 cm, allowing placement of a valve-sparing graft of sufficient size to accommodate growth.
        3. Large size or rapid expansion of the descending aorta or other vessels.
11. Situations and agents to avoid
    1. Contact sports
    2. Competitive sports
    3. Isometric exercise
    4. Agents that stimulate the cardiovascular system including routine use of decongestants
    5. Activities that cause joint injury or pain

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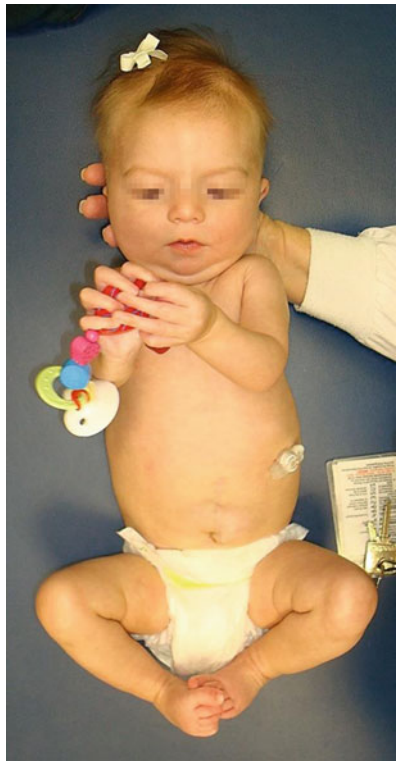

Fig. 1 A 5-month-old infant girl with molecularly confirmed Loeys-Dietz syndrome with *TGFBR1* exon 4 mutation c.722C > T (Ser241Leu). She was evaluated initially for possible neonatal Marfan syndrome because of very long fingers and toes. At 3 weeks of age, she was diagnosed to have intestinal malrotation which was surgically repaired and a Nissen fundoplication was performed. She had seizures since birth (eyes rolling up, occasional twitching, and head pulling back for a very short period). MRI of the brain showed bilateral caudal thalamic groove cyst. At 3 months of age, she was noted to be abnormally pale and was found to have bleeding due to a ruptured wandering spleen in the pelvis which was surgically removed. She had a surgical incision hernia at the site of the first surgery in addition to her original inguinal hernia. Multiple echocardiograms showed no aortic root dilatation but the patient was put on β-blocker for aortic root dilatation prevention. Family history was noncontributory. Note the ocular hypertelorism, dolichostenomelia, and arachnodactyly

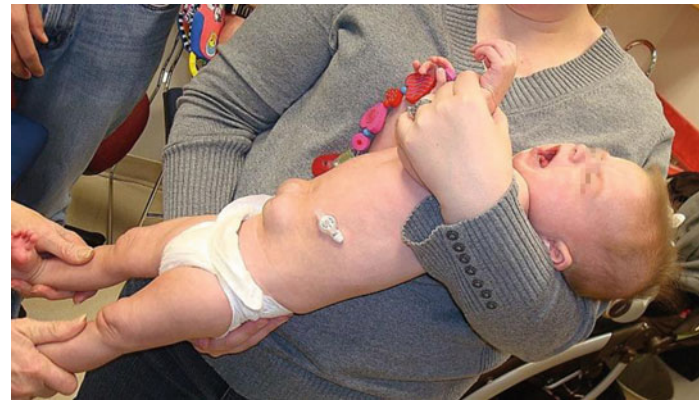

Fig. 2 Note the large incisional umbilical hernia

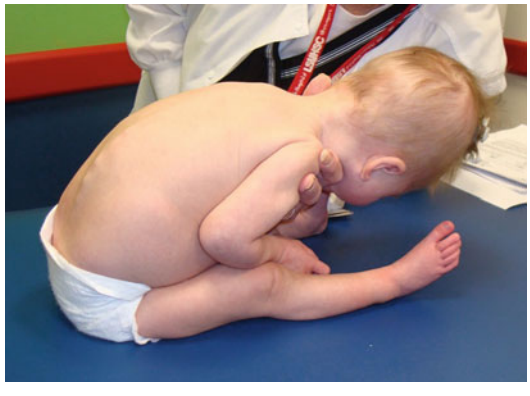

Fig. 3 Note the marked hypotonia and long and slender extremities

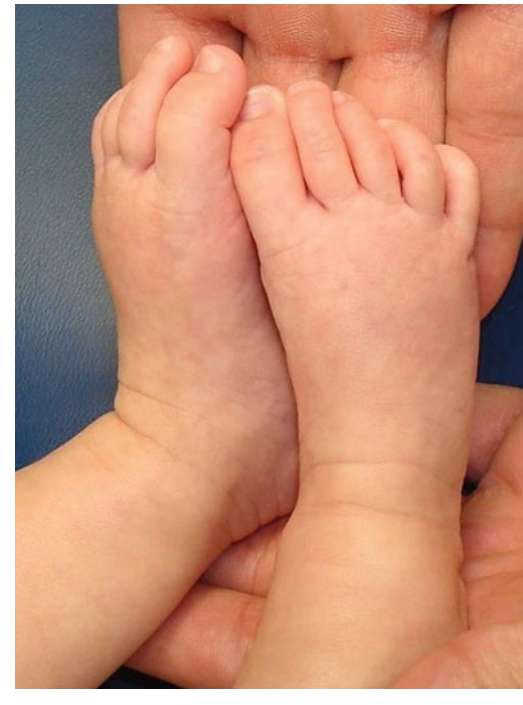

Fig. 4 Note the long toes

Lowe Syndrome

Contents

Lowe syndrome, also known as oculocerebrorenal syndrome, is a rare X-linked recessive disorder. It was initially recognized in 1952 by Lowe and colleagues who described the triad of congenital cataracts, mental retardation, and generalized aminoaciduria (Lowe et al. 1952). In 1954, a renal Fanconi syndrome was recognized as being associated with the syndrome (Bickel and Thursby-Pelham 1954) and in 1965, an X-linked recessive pattern of inheritance was determined (Richards et al. 1965). Its prevalence is estimated to be several cases per 100,000 males.

Synonyms and Related Disorders

Dent-2 disease; Oculocerebrorenal syndrome

Genetics/Basic Defects

1. Inheritance:
   1. X-linked recessive disorder predominantly affecting males, although several affected females have been reported (Abbassi et al. 1968)
   2. New mutations in 31.6% of affected males
   3. Germ line mosaicism in 4.5%
2. The gene involved (*OCRL1*):
   1. Map locus: Xq26.1, based on:
      1. Balanced X-autosome translocations with a break point in band Xq25–Xq26 in two unrelated female patients (Attree et al. 1992)
      2. Linkage analysis with RLFP in families with multiple affected individuals (Silver et al. 1987; Reilly et al. 1988, 1990)
   2. Mapped in 1977 (Nussbaum et al. 1997)
   3. Cloned in 1992
   4. Encoding *OCRL1*, a 105-kD enzyme with phosphatidylinositol 4,5-bisphosphate 5-phosphatase (PtdIns-4,5-P_2) activity localized to the Golgi complex:
      1. Loss or reduction of the enzyme demonstrated in affected males
      2. Carrier status of OCRL in females not readily determined by assays of the enzyme due to the X-linked nature of *OCRL1* and random X inactivation

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Mutations of *OCRL1* gene responsible for Lowe syndrome (Lin et al. 1997; Satre et al. 1999):
   1. Nonsense mutations and deletions causing frameshifts and premature termination
   2. Deletions (Peverall et al. 2000)
   3. Missense mutations in domains conserved among all the known PtdIns(4,5)P_2 5-phosphatases
   4. Germ line mosaicism (Satre et al. 1999)
4. An exonic deletion of *OCRL1* gene affecting the catalytic 5-phosphatase domain is related to a severe phenotype in Lowe syndrome (Peces et al. 2013).
5. Carrier females with typical lens opacities (Gardner and Brown 1976; Reilly et al. 1988).
6. Affected females as a result of:
   1. Unfavorable lyonization
   2. Turner syndrome
   3. X-autosome translocation through the relevant gene
7. Dent-2 disease (a mild variant of Lowe syndrome (Bökenkamp et al. 2009)):
   1. Dent disease:
      1. An X-linked tubulopathy characterized by low-molecular-weight proteinuria, hypercalciuria, and nephrolithiasis/nephrocalcinosis (1)
      2. In more than half the patients, Dent disease is caused by mutations affecting the voltage-gated chloride channel and chloride/proton antiporter (ClC-5).
   2. Dent-2 disease:
      1. In approximately 15% of patients with a Dent phenotype, mutations in the oculocerebrorenal syndrome of Lowe gene (*OCRL*) encoding a phosphatidylinositol 4,5-bisphosphate 5-phosphatase has been found (Hoopes et al. 2005; Utsch et al. 2006; Sekine et al. 2007; Cho et al. 2008).
      2. These patients are classified as having "Dent-2 disease" to distinguish them from most patients with an *OCRL* mutation who have the more severe oculocerebrorenal syndrome of Lowe phenotype (Charnas et al. 1991) which is characterized by a proximal tubulopathy (Bökenhauser et al. 2008; Kleta 2008), congenital cataract, severe mental retardation, and behavioral disturbances.

Clinical Features

1. Variable age of onset and severity of clinical manifestations
2. Eye abnormalities (Ginsberg et al. 1981; Charnas and Gahl 1991; Lavin and McKeown 1993; Al-Uzri 2014):
   1. Congenital cataracts (the hallmark of the disease):
      1. Developed prenatally
      2. Always present prior to birth
   2. Congenital glaucoma with or without buphthalmos (50–60%)
   3. Microphthalmos
   4. Nystagmus
   5. Decreased visual acuity (blindness)
   6. Corneal scarring and keloid formation:
      1. Develops spontaneously without trauma
      2. Onset usually after age 5
      3. Causes significant visual impairment
3. Renal abnormalities:
   1. Fanconi syndrome of renal tubules (the cardinal features):
      1. Bicarbonaturia
      2. Proximal tubular acidosis
      3. Generalized aminoaciduria
      4. Hyperphosphaturia leading to osteomalacia, renal rickets, and pathologic fractures
      5. Hypercalciuria
      6. Proteinuria
      7. Glycosuria (not a feature of the renal tubular dysfunction)
      8. Impairment in urine concentration (polyuria)
      9. Carnitine wasting
   2. Variable age of onset and severity of the tubular dysfunction:
      1. Failure to thrive.
      2. Recurrent infections.
      3. Metabolic collapse.

4. Severe hypokalemia or hypocalcemia requiring replacement therapy in a minority of patients. This is probably a part of preterminal exacerbation of tubular dysfunction.
5. Slowly progressive renal failure may occur in the second to fourth decade of life.

4. CNS (prominently involved organ) and behavioral abnormalities:
   1. Cardinal features:
      1. Neonatal/infantile hypotonia
      2. Delay in motor milestones
      3. Cognitive impairment
      4. Areflexia by 1 year of age
   2. Mental retardation (common but not cardinal feature)
   3. Seizures
   4. Neuropathologic and neuroimaging abnormalities
   5. Stereotypic behaviors (Kenworthy and Charnas 1995; Al-Uzri 2014):
      1. Temper tantrum (Lowe tantrum)
      2. Aggression
      3. Irritability
      4. Stubbornness
      5. Rigidity of thought
      6. Self-injury
      7. Repetitive nonpurposeful movements
5. Musculoskeletal abnormalities (Holtgrewe and Kalen 1986):
   1. Secondary consequences of hypotonia, renal tubular acidosis, and/or hypophosphatemia:
      1. Short stature
      2. Joint hypermobility
      3. Dislocated hips
      4. Genu valgum
      5. Scoliosis
      6. Kyphosis
      7. Platyspondylia
      8. Fractures
   2. Primary abnormality of excessive connective tissue growth:
      1. Nontender joint swelling
      2. Subcutaneous nodules
6. Typical facies:
   1. Frontal bossing
   2. Characteristic deep-set eyes
   3. Inattentiveness
7. Other features:
   1. Increased hemorrhagic risk (Lane et al. 2010)
   2. Cryptorchidism
8. Natural history:
   1. Succumb to either severe renal insufficiency and dehydration or infection
   2. Survival to adulthood if metabolic abnormalities are adequately treated
9. Manifestation in the carriers:
   1. Lens involvement:
      1. Micropunctate cataracts clustered in a radial wedge pattern
      2. Occasional dense posterior cortical cataract
   2. Sensitivity of carrier detection by slit-lamp examination (>90%), due to random inactivation of Lowe syndrome allele in the proportion of cells in the lens of female carriers
   3. Germ line or somatic mosaicism documented
   4. Positive family history of early cataracts in mother, maternal female relatives, and institutionalized maternal uncles

Diagnostic Investigations

1. Blood chemistry:
   1. Blood gas for metabolic acidosis
   2. Electrolyte disturbances (likely absent in neonates and young infants)
2. Urine:
   1. Aminoaciduria
   2. Hyperphosphaturia
   3. Low-molecular-weight (LMV) proteinuria: characterized by the excretion of proteins such as retinal-binding protein and *N*-acetyl glucosaminidase seen in:
      1. Lowe syndrome: LMW proteinuria can be seen early in life even in the absence of clinically significant aminoaciduria or other renal tubular abnormalities (Laube et al. 2004).

2. The allelic disorder Dent disease.
3. Many other diseases associated with the Fanconi syndrome.
4. Glycosuria
5. Low urine osmolality
6. Elevated 24 h volume

3. Serum enzyme values:
   1. Elevated CK
   2. Elevated SGOT
   3. Elevated LDH
   4. Elevated α2-globulin
4. Measurement of inositol polyphosphate 5-phosphatase OCRL1 activity in cultured skin fibroblasts (Lewis et al. 2008):
   1. Males: to confirm the diagnosis in affected males (Suchy et al. 1995; Zhang et al. 1995):
      1. Affected males have less than 10% normal activity of the enzyme.
      2. Such testing is abnormal in more than 99% of affected males.
   2. Carrier females. The activity is not accurate for carrier detection because of lyonization (random X chromosome inactivation), which results in a wide range of "normal" activity in females (Lin et al. 1999).
5. Karyotype. Translocations between an autosome and an X chromosome with a break point through the OCRL locus (Xq26.1) have been observed (Hodgson et al. 1986; Mueller et al. 1991).
6. Radiography:
   1. Rickets/osteoporosis
   2. Pathological fractures
   3. Frontal bossing
   4. Kyphoscoliosis
   5. Cervical spine anomalies
   6. Platyspondyly
   7. Hip subluxations/dislocation
7. Neuroimaging:
   1. Cranial MRI:
      1. Mild ventriculomegaly (33%)
      2. Multiple tiny periventricular cysts (no clinical significance)
      3. Two patterns of brain lesions (Ono et al. 1996; de Carvalho-Neto et al. 2009):
         1. Hyperintensities on T2-weighted images
         2. Periventricular cystic lesions (Demmer et al. 1992)
   2. MR spectroscopy (Sener 2004; Allmendinger et al. 2014):
      1. Shows an elevation at 3.56 ppm, likely corresponding to elevated levels of myo-inositol. This suggests the abnormal parenchymal signal is due to gliosis, given that myoinositol is a glial marker.
      2. The MR spectra also showed normal choline and *N*-acetyl aspartate (NAA) peaks, which also suggests gliosis, as demyelination typically produces an elevated choline and reduced NAA peak.
   3. Neuropathologic examination of the brain:
      1. Normal in some cases
      2. Diffuse or focal myelin pallor without myelin breakdown
      3. Ventriculomegaly
      4. Mild cerebral abnormalities
      5. Isolated cases of subependymal cysts
      6. Mesencephalic porencephaly
      7. Postencephalitic changes
      8. Blunted and foreshortened frontal lobes
      9. Acute pontine necrosis
      10. Cerebellar hypoplasia
      11. Aberrant neuronal migration
      12. Multiple tiny cysts without inflammatory changes
8. Affected male patients:
   1. Biochemical assay of reduced activity (<10%) of PtdIns (4,5)P_2 5-phosphatase in cultured fibroblasts to confirm diagnosis of patients with OCRL. Peripheral blood cannot be tested since the enzyme is not present in lymphocytes.
   2. Molecular analysis to detect mutations in the *OCRL* gene in about 95% of affected males:
      1. Sequence analysis
      2. Fluorescence in situ hybridization analysis (FISH), with cosmid probes that span the entire *OCRL1* gene
9. Carrier females:
   1. Karyotyping to rule out X-autosome translocation with a break point through the *OCRL* locus
   2. Carrier detection:

1. Biochemical assay of reduced activity of PtdIns (4,5)P_2 5-phosphatase in cultured fibroblasts is not suitable for determining OCRL carrier status, since random X inactivation could result in a wide range of enzyme activity that may overlap with the normal range.
2. An obligatory carrier based on evaluation of the family pedigree.
3. Slit-lamp examination (Gardner and Brown 1976; Roschinger et al. 2000) for numerous punctate opacities, especially in prepubertal females, is a better method and it has a low false-negative rate.
4. By direct detection of mutations when the mutation is previously identified (in about 95% of carrier females).
5. By mutation scanning of high-risk females by denaturing high-performance liquid chromatography (DHPLC) when:
    1. The affected male is not available.
    2. The diagnosis has been confirmed by enzyme analysis.
6. By linked markers when the mutation is unknown.

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib:
        1. A 25% risk of having an affected boy and a 25% risk of having a carrier daughter if the mother is a carrier (Loi 2006)
        2. A low but finite recurrence risk (estimated to be about 1.5%) in case of a new mutation due to possibility of nonpenetrance or gonadal mosaicism in the mother
    2. Patient's offspring: affected males not known to reproduce
2. Prenatal diagnosis available for pregnancies at risk:
    1. Determine fetal gender by amniocentesis or CVS
    2. Biochemical assay for deficiency of PtdIns (4,5)P_2 5-phosphatase from cultured amniotic fluid cells (Suchy et al. 1998) or cultured CVS if the fetal karyotype shows 46, XY (not suitable for determining OCRL carrier status for females)
    3. Molecular analysis (Gazit et al. 1990):
        1. By direct detection of mutations when the *OCRL* disease-causing mutation in the family is known
        2. By linked markers in informative families when the mutation is unknown (Wadellius et al. 1989)
    4. Offer prenatal diagnosis by enzymatic analysis (Suchy et al. 1998) to every mother of a son with Lowe syndrome because of the relatively high rate (4.5%) of germ line mosaicism, even with the following situations:
        1. Negative family history
        2. Negative dilated slit-lamp examination
        3. DNA testing showing that the mother is not a carrier
3. Management:
    1. Ocular management:
        1. Cataract extraction to avoid amblyopia
        2. Refraction for aphakia
        3. Control of glaucoma
        4. Removal of corneal keloids: often with recurrence and enlargement of the lesions
    2. Speech and physical therapy for developmental delay
    3. Medications:
        1. Anticonvulsants
        2. Behavior-modifying medications if needed
    4. Replacement/supplementation (Charnas et al. 1991):
        1. Phosphate and sodium-potassium citrate for renal tubular acidosis (urinary bicarbonate, water, and phosphate losses) and bone disease (rickets)
        2. L-carnitine
        3. Vitamin D supplements as indicated
    5. Anesthetic risks (Saricaoğlu et al. 2004):
        1. Chronic metabolic acidosis
        2. Existing hypokalemia, a risk for serious cardiac arrhythmia

3. A risk of glaucoma
4. Hypophosphatemic rickets causing fragility of bone structures:
    1. Requires attention while positioning
    2. Difficulty in maintaining the airway due to craniofacial abnormalities and abnormal teeth structure

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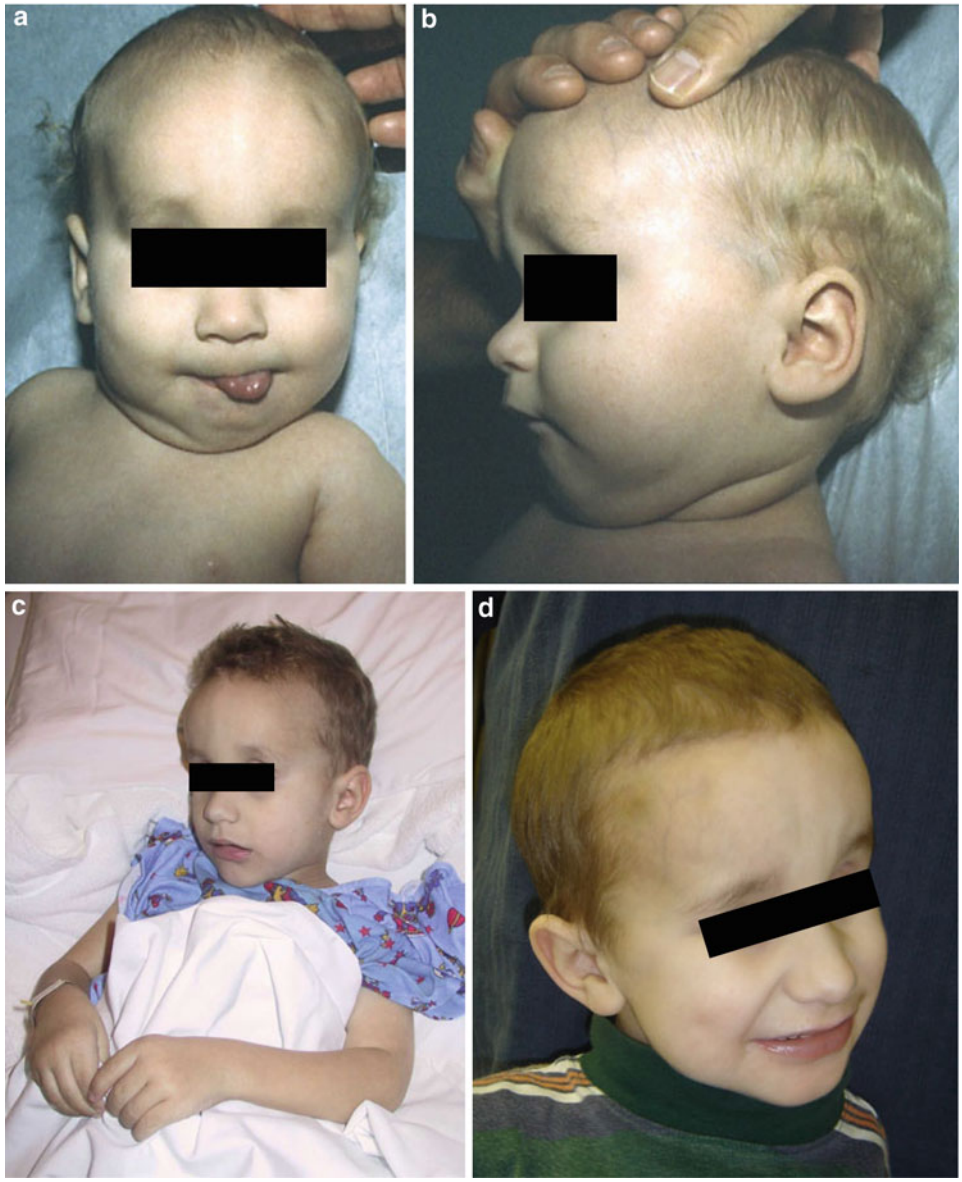

Fig. 1 (**a**–**d**) One-and-half-year-old boy with Lowe syndrome showing frontal bossing and deep-set eyes. He had a history of profound hypotonia, failure to thrive, cataracts, glaucoma, seizures, and generalized aminoaciduria. The diagnosis was confirmed by assay of markedly deficient phosphatidylinositol bisphosphate phosphatase activity in the cultured fibroblasts (0.05, control: 2–5 mmol/min/mg protein). The recent photos were taken at 6 and 9 years of age

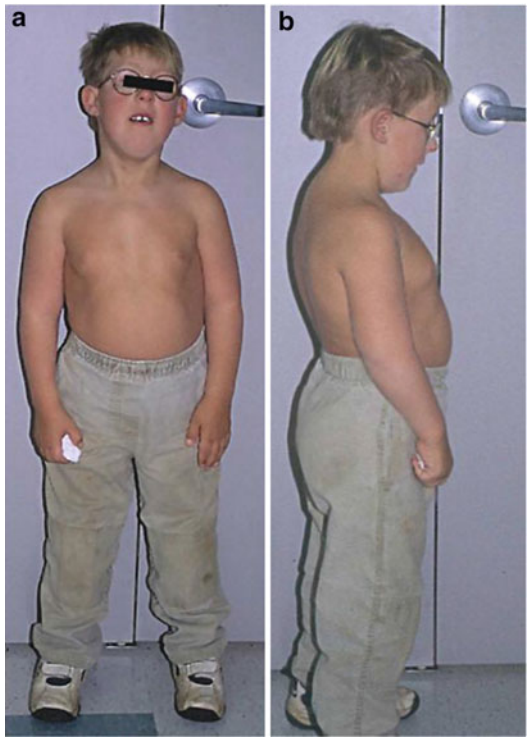

Fig. 2 (**a**, **b**) A 10-year-old boy with Lowe syndrome showing short stature and visual impairment. The diagnosis was confirmed by assay of markedly deficient phosphatidylinositol bisphosphate phosphatase activity (0.05 with normal control of 2–5 nmol/min/mg protein) in the cultured fibroblasts

Fig. 3 This 12-year-old Hispanic boy from Panama was admitted for evaluation of global developmental delay and multiple congenital anomalies. He had a history of hypotonia, bilateral congenital cataracts which was repaired, seizures, and bony deformities. Blood chemistry showed CK [314 U/L (39-308)], LDH [452 U/L (87-241)]. AST [66 U/L (15-37)], PTH intact [91.7 pg/mL (12.4-76.8)], phosphorus [3.4 mg/dL (4.5-5.5)], and alpha-2-macroglobulin [316 mg/dL (131-293)]. Urine amino acids quantitative showed severe generalized aminoaciduria. Urinalysis showed high phosphorus (>90) and high protein (205). The clinical and laboratory findings are compatible with Lowe syndrome

Lymphangiomas and Lymphangiomatosis

Contents

Lymphangiomas are histologically benign but may have life-threatening potential with increasing size and encroachment of adjacent vital structures. Lymphangiomatosis is an extremely rare pathological condition where multiple lymphangiomas are present and may affect the visceral organs (lung, liver, and spleen), soft tissues, subcutaneous tissues, skin, and bones (long bones, pelvis, skull, vertebrae).

Synonyms and Related Disorders

Cystic hygroma; Generalized lymphangiomatosis; Gorham disease (Gorham-Stout syndrome, vanishing bone disease, massive osteolysis)

Genetics/Basic Defects

1. Lymphangiomas
    1. Basic pathological process of lymphangiomas (Whimster 1976; Stringel 1993)
        1. Large, multiloculated cisterns extend deep into the dermis and laterally beyond the obvious clinical lesions.
        2. Deep lymphangiomas show no evidence of communication with the adjacent normal lymphatics.
        3. The cause of failure of these primitive lymph sacs to connect to the rest of the lymphatic system is unknown.
    2. Relatively common benign proliferations of the lymphatic vessels, with abnormal connections to the lymphatic system representing 5-6% of childhood masses (Bhatti et al. 1985)
    3. Commonly occur in the area of primitive lymph sacs, such as the neck (where lymphangioma is referred to as "cystic hygroma") or the axilla (Grossman and Yousem 2003)
2. Lymphangiomatosis
    1. Heterogeneous disorders.
    2. Characterized by generalized or multifocal proliferation of lymphatic vessels that are lined by endothelia in osseous or extraosseous tissues (Faul et al. 2000).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. The majority of lesions occur in the thoracic (chest and mediastinum) (Faul et al. 2000) and neck region (Mirra 1989).
4. Histologically benign but infiltrates widely.

Clinical Features

1. Lymphangiomas
   1. Anatomic locations (Anderson and Kennedy 1992)
      1. Neck (75%)
      2. Axillary region (20%)
      3. Retroperitoneum and abdominal viscera (2%)
      4. Limbs and bones (2%)
      5. Cervicomediastinum (1%)
   2. Usually solitary
   3. May accompany other congenital syndromes, such as trisomies 13, 18, and 21, Turner syndrome, and Noonan syndrome (Ozturk and Yousem 2007)
   4. Asymptomatic unless pressing on adjacent structures with swelling and/or pain
2. Lymphangiomatosis
   1. Symptoms: depend on location and extent of involvement
   2. Can be devastating due to multi-organ involvement and/or osteolysis
   3. Generalized lymphangiomatosis (Yang and Goo 2006)
      1. Frequently involves the bones, mediastinum, spleen, liver, lungs, neck, and pleura.
      2. Asymptomatic in many patients.
      3. Respiratory difficulty due to pleural involvement.
      4. Pathologic fracture due to osteolytic lesions.
      5. Rarely lymphangiomatosis may involve the larynx causing obstruction of the airway tract.
   4. Diffuse intrapulmonary lymphangiomatosis, coined to describe lymphangiomatosis limited to the lungs and thoracic cavity with bilateral and diffuse involvement (Tazelaar et al. 1993; Satria et al. 2011)
      1. Nonspecific symptoms
         1. Wheezing
         2. Cough
         3. Chest tightness
         4. Shortness of breath
         5. Chest pain
         6. Dyspnea
      2. Other manifestations (Faul et al. 2000; Alvarez et al. 2004; Radhakrishnan and Rockson 2008)
         1. Cervical lymphangioma
         2. Pericardial effusions
         3. Chyloptysis
         4. Hemoptysis
         5. Protein-wasting enteropathy
         6. Lymphedema
         7. Splenic lesions
         8. Mediastinal compression
         9. Lymphangiomatosis with lytic bone lesions (also known as Gorham-Stout disease) (Gorham & Stout 1955; Nikolaou et al. 2014)
      3. Primary cause of death
         1. Respiratory failure
         2. Infections
         3. Accumulation of chylous fluid
   5. Renal lymphangiomatosis (benign cystic lymphangioma or renal lymphangiectasia) (Celebi et al. 2012)
      1. Does not usually impair kidney function but may lead to mechanical complications because of local compression effects (Chen et al. 2009)
      2. Rare signs and symptoms
         1. Flank pain
         2. Hematuria
         3. Proteinuria and ascites, due to lymphatic drainage through the urine (chyluria) and do not represent renal disease (Cheng et al. 2006)
         4. Hypertension

Diagnostic Investigations

1. Diagnostic challenge: Information from following scan types is useful in deriving the diagnosis. Imaging recommendation is

usually ultrasound and MRI. Bone scan and CT are not too much helpful and with radiation.

1. Plain film radiography: depends on disease extent
    1. Massive chylothorax
    2. Pulmonary infiltrates
    3. Splenomegaly
    4. Translucent bone lesions characterized by progressive dissolution of part or all of one or more adjacent bones
2. Magnetic resonance imaging of diffuse lymphangiomatosis (Maki et al. 1999; Ozturk and Yousem 2007)
3. Lymphoscintigraphy: provides direct evidence of the abnormal lymphatic flows associated with lymphangiomatosis (Beveridge et al. 2010)
4. Computed tomography (Raman et al. 2009)
    1. Thoracic lymphangiomatosis (Yekeler et al. 2005)
        1. Diffuse, bilateral, symmetric, and interlobular septal and peribronchovascular thickening.
        2. Usually spare alveolar spaces.
        3. Lymphatic proliferation diffusely infiltrates the mediastinum and thickens the visceral and parietal pleura.
    2. Extrathoracic lymphangiomatosis (Alvarez et al. 2004)
        1. Lytic bone lesions
        2. Splenomegaly
        3. Splenic lesions
        4. Disseminated intravascular coagulation or other coagulopathy
6. Bone scanning
7. Renal ultrasonography, CT, and MRI for renal lymphangiomatosis: detect multiple cystic-tubular structures that do not involve the parenchyma (Chen et al. 2009)

2. Histology and immunohistochemistry analysis (Ramani and Shah 1993).
    1. Characterized by multifocal proliferation of lymphatic vessels that are lined by cytologically benign endothelia.
    2. Endothelial cells lining the majority of the proliferating lymphatics showed intense immunostaining with FVIII-Rag and CD31 and focal immunoreactivity with UEA-1 in a minority of the lymphatics.
3. Pulmonary function tests for pulmonary lymphangiomatosis.

Genetic Counseling

1. Recurrence risk: apparently not significantly increased
2. Prenatal diagnosis and treatment
    1. Plain ultrasonography (Axt-Fliedner et al. 2002)
        1. Congenital lymphangiomas
            1. Most commonly noted in the neck, axilla, and anterolateral thorax
            2. May be detected antenatally as early as 8–10 weeks of gestation
            3. May be associated with skin edema, hydrops fetalis, and polyhydramnios
            4. Overall prognosis: poor with a mortality rate ranging from 50% to 100% (Pijpers et al. 1988), particularly for lesions identified in the nuchal region owing to frequent association with chromosomal anomalies
        2. Prenatal ultrasound features
            1. Present as multicystic, multiseptated structures varying in size and form (Chervenak et al. 1983; Benacerraf and Frigoletto 1987; Katz et al. 1992).
            2. Variable thickness with no solid components.
            3. Prenatal diagnosis of fetal lymphangiomatosis should be followed by targeted ultrasound and serial ultrasound scans.
    2. 3D ultrasounds: show better for extension and calculate the volume
    3. Droppler ultrasounds: to assess blood flow to exclude other vascular malformations
    4. Fetal MRI: provides essential information about the diagnosis and the anatomy of giant fetal neck masses and adjacent airways (Hubbard et al. 1998; Cozzi et al. 2010)
    5. Ex utero intrapartum treatment (EXIT): to secure fetal airway in cases of giant cervical lymphangioma complicated by fetal upper

airway obstruction (Liechty and Crombleholme 1999; Ogamo et al. 2005)
6. Elective cesarean section: avoids complications due to the exposed fetal mass during vaginal delivery
7. Parental counseling (Rasidaki et al. 2005)
    1. Prognosis depends on the location and extent of the lesion.
    2. There may be an association with chromosomal or other abnormalities.
    3. Neonatal outcome of large fetal lymphangioma is generally poor.
    4. Axillary or chest wall lymphangiomas may not carry a marked risk for aneuploidy or untoward pregnancy outcome.
    5. Fetal karyotyping may be indicated.
    6. There may be a much more optimistic prognosis with noncervical lymphangiomas.

3. Management (Blei 2011)
    1. General principle
        1. Dictated by the nature of symptoms, anatomic location, and associated problems
        2. Require concomitant or sequential therapy
    2. Systemic therapy
        1. Bisphosphonates and vitamin D: results ranging from stabilization to lack of response (Hammer et al. 2005; Lehmann et al. 2009; Heyd et al. 2011; Venkatramani et al. 2011)
        2. Direct intralesional instillation of bisphosphonate (Sun et al. 2011)
        3. Interferon alpha: successful in some cases (Venkatramani et al. 2011)
        4. Adjunctive therapy with interferon alpha-2b, low anticoagulant, low molecular weight heparin, radiotherapy, and surgery (Brodszki et al. 2011)
        5. Tyrosine kinase inhibitors: bevacizumab or propranolol (Grunewald et al. 2010; Ozeki et al. 2011)
        6. A clinical trial investigating the safety and efficacy of sirolimus for complex vascular anomalies including lymphangiomatosis and Gorham syndrome currently underway
    3. Surgery
        1. Sclerotherapy with bleomycin, doxycycline, OK-432, and other agents (Aoki et al. 1996; Guvenc et al. 2005): variable results
        2. Orthopedic surgery including bone grafts and reconstruction, arthroplasty, fracture management, and allograft-resurfacing composite (Paley et al. 2005; Burgess et al. 2006; Browne et al. 2011; Ruggieri et al. 2011; Tan et al. 2011)
        3. Total lymphectomy of mediastinum, ligation of all lymphatic vessels on the diaphragm and the thoracic inlet, and bilateral pleurectomy in cases of thoracic lymphangiomatosis (Steinacher et al. 2009)
        4. Lung and liver transplantation for lymphangiomatosis (Tepetes et al. 1995; Miller et al. 1988; Ra et al. 2007; Kinnier et al. 2008; Ooi et al. 2011): variable results
    4. Radiation therapy
        1. To prevent disease progression
        2. Result in stable or improved disease in 80% of a series of 8cases and in 77.3% of 44 previously published cases (Heyd et al. 2011)

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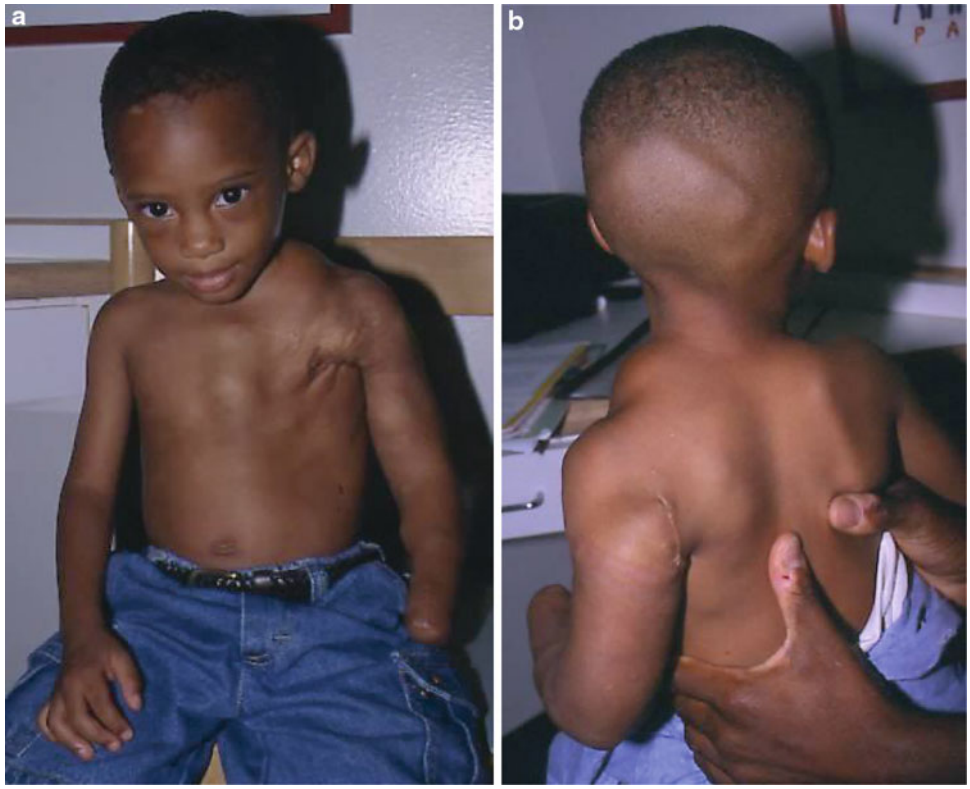

Fig. 1 (**a**, **b**) This young boy had lymphangiomatosis, characterized by massive swellings of the left shoulder, anterior and lateral thorax, upper arm, and hand at birth. The boy had extensive surgeries to excise the lesions. The left hand was amputated

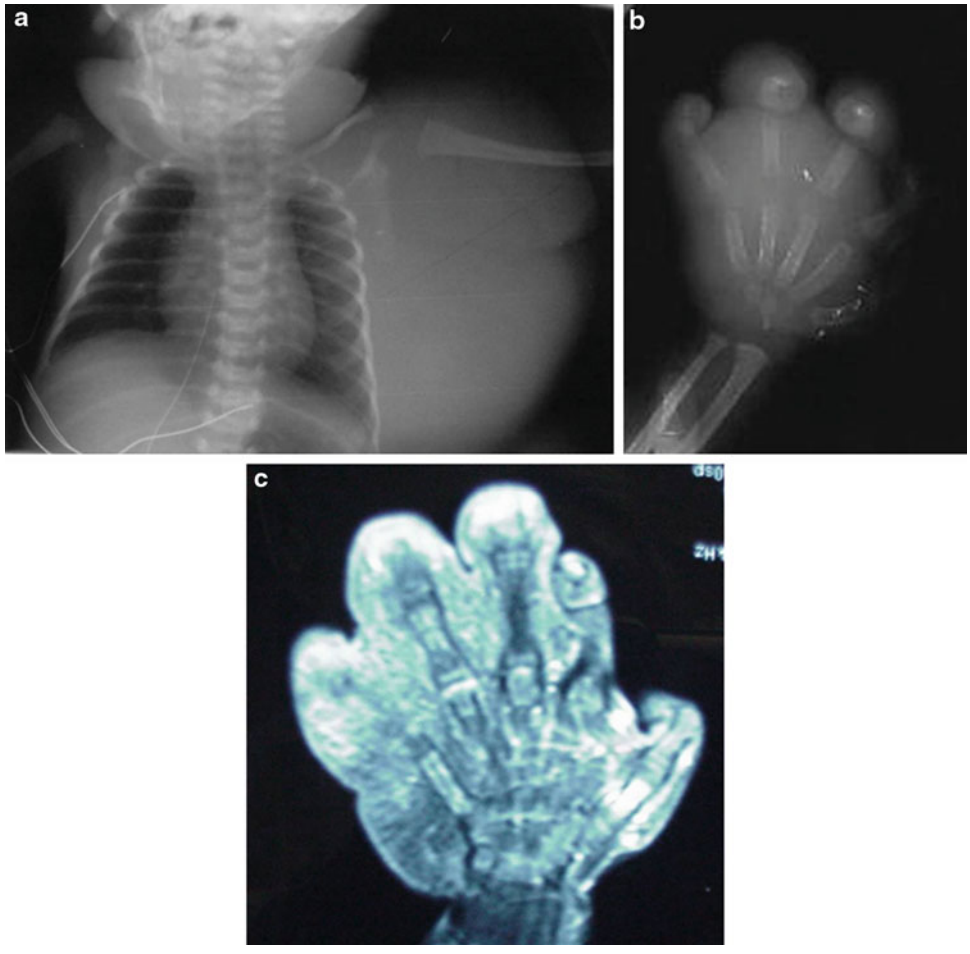

Fig. 2 (**a**–**c**) Radiography of the chest showed a huge lobulated soft tissue mass over the shoulder, proximal humerus, and left chest wall (**a**). Radiography (**b**) and MR image (**c**) of the left hand showed diffuse enlarged soft tissue with infiltrative process in the subcutaneous region. No focal abnormality was seen in the visualized bones

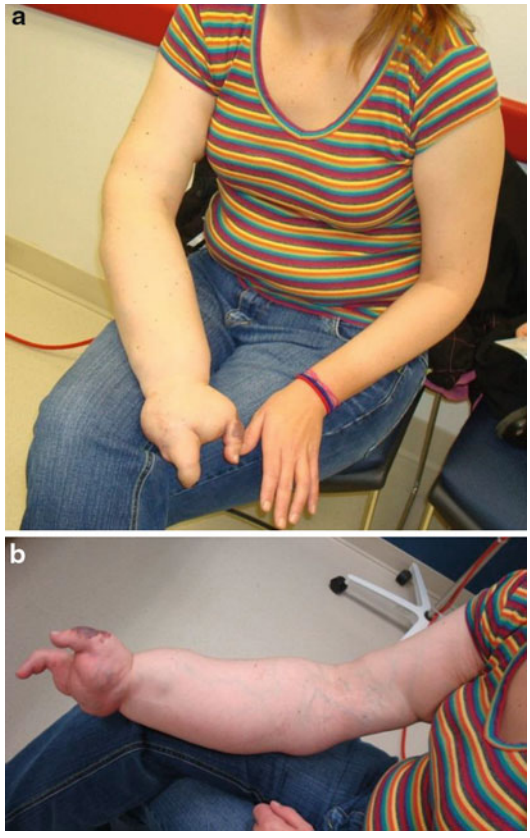

Fig. 3 (**a**, **b**) This mother with lymphangiomatosis was seen because her daughter has Poland syndrome with hypoplastic left upper arm. The mother had lymphangiomatosis involving her whole right upper extremities (**a**, **b**). She had three fingers excised and a hemangioma on the right thumb; her lymphangiomatosis also involved the breast (mastectomy), spleen, and adrenal gland

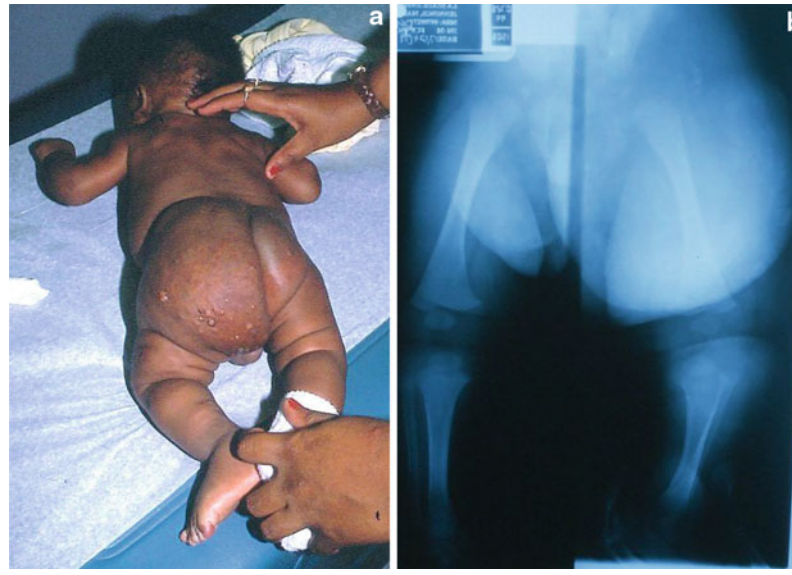

Fig. 4 (**a**, **b**) This neonate presented with lymphangioma having an enlarged left buttock (**a**). The plain radiography showed soft tissue density in the left buttock. There was no focal bone abnormality (**b**)

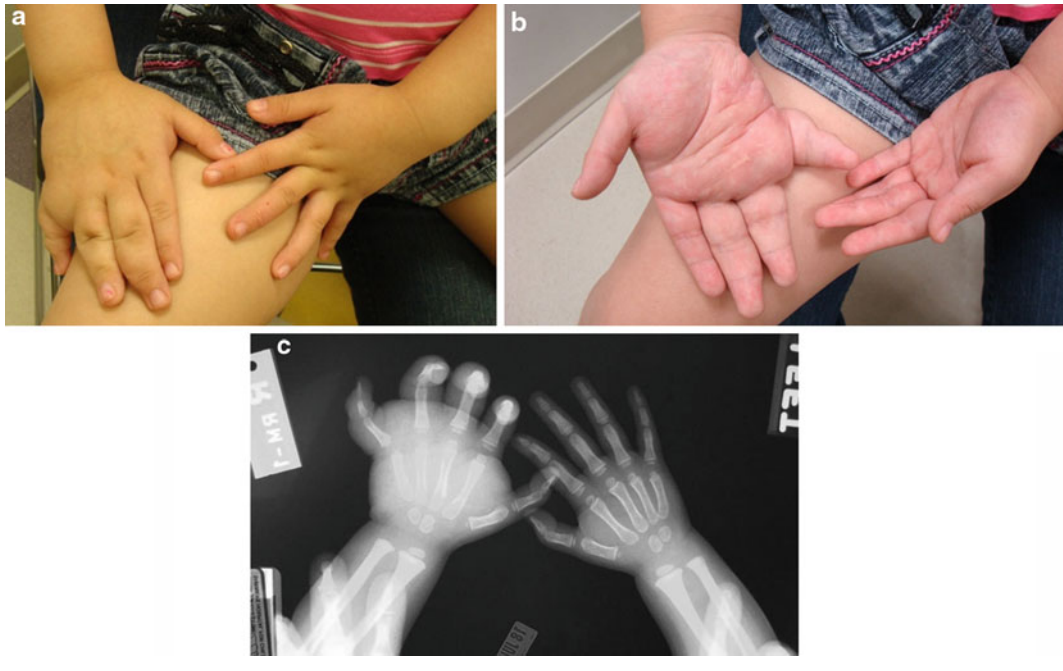

Fig. 5 (**a**–**c**) This 4-year-old boy was evaluated for soft tissue swelling of the right hand and fingers. At 10 months of age, he was operated for recurrent lymphangioma in the right hand with extensive involvement of the right hand and palmar and dorsal with severe perineural and peri-arterial scarring

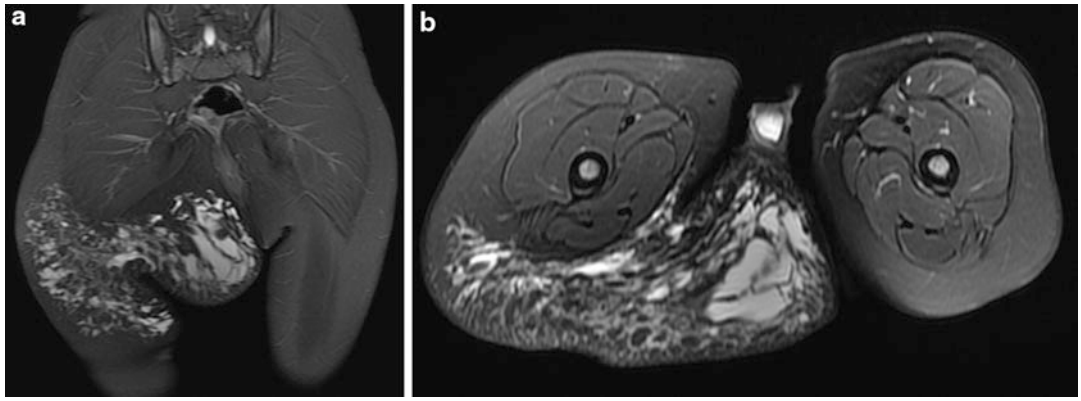

Fig. 6 (**a**, **b**) This patient was a 2-year 3-month-old male who presented for evaluation of his swollen right buttock. The parents noticed discrepancy in the size of buttocks after birth. The mother felt that the right buttock had been enlarging. There was no drainage, discolorations, or tenderness noticed. MRI (**a**, **b**) showed a large infiltrating complex mass lesion in the subcutaneous fat right of the right buttock. It was comprised of T2-weighted hyperintense collections with septations and minimal enhancement. The gluteal and thigh musculature were not involved (Courtesy of Dr. Grace Guo)

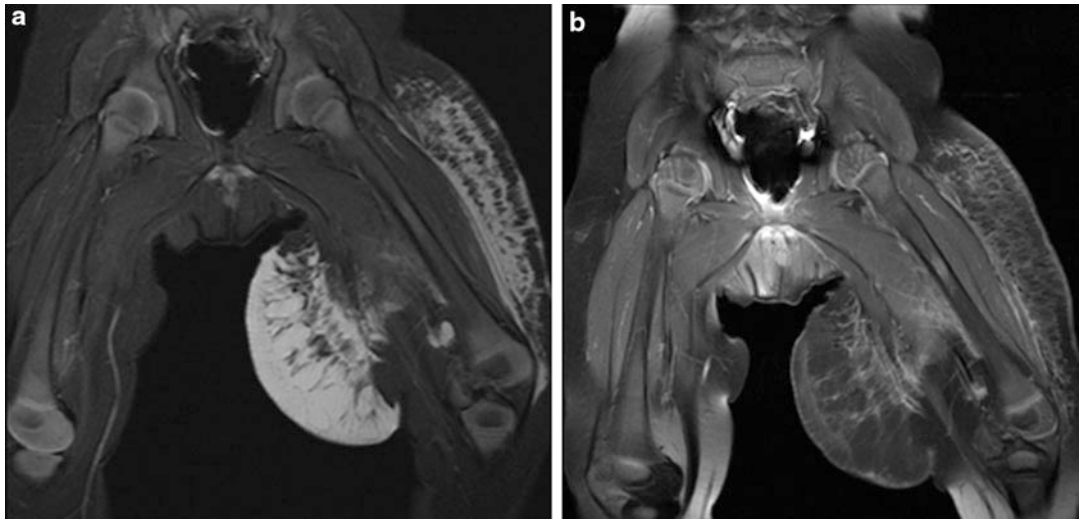

Fig. 7 (**a**, **b**) The patient was a 7-month-old girl with a history of left leg hemihypertrophy. MRI showed a large infiltrative lesion in the subcutaneous fat of the left thigh with high T2 signal abnormality (**a**) and minimal enhancement of septations (**b**). Abnormal signal did not involve the musculature. The bone marrow was normal in appearance (Courtesy of Dr. Grace Guo)

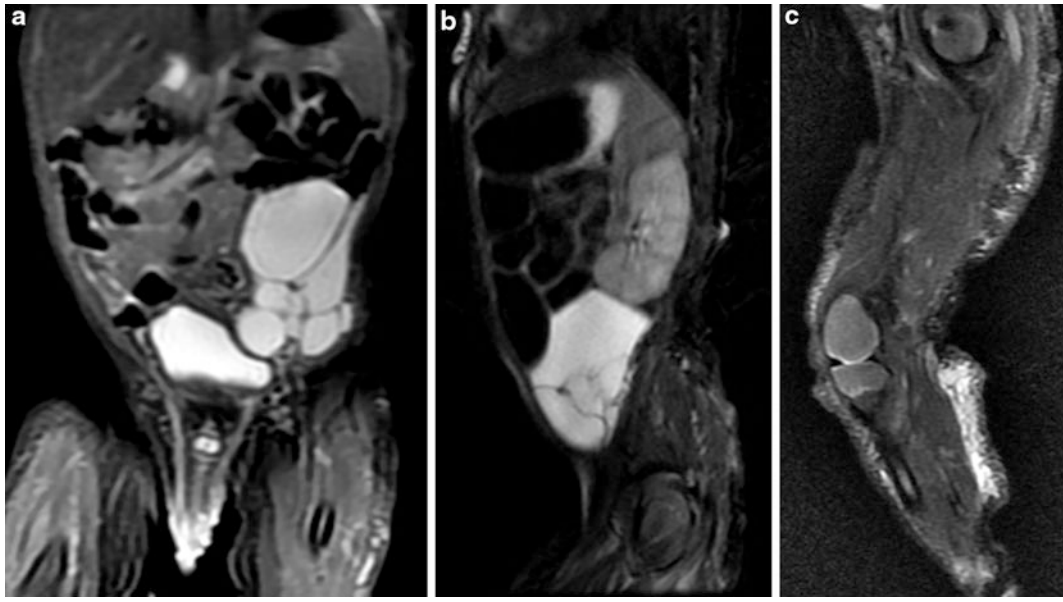

Fig. 8 (**a**–**c**) This one-week-old boy was seen because of superficial venous capillary malformations of the left lower extremity. Prenatal ultrasound showed maternal hydramnios and an abdominal cyst. On examination, the diameter of the left lower extremity was larger than the right lower extremity. There was an extensive vascular malformation of the left lower extremity extending onto the lower portion of the trunk, gluteal region, and thigh. The majority of visible portion appeared to be capillary malformation with the purple color. The clinical diagnosis of Klippel-Trenaunay-Weber syndrome with intra-abdominal lymphatic malformation and superficial venous capillary malformations of the left lower extremity was made. MRI showed a multicystic lesion in the left lower quadrant and the pelvis with displacement of the adjacent bowel loops and bladder (**a**, **b**), compatible with lymphatic malformation. There was also soft tissue abnormality that extends posterior to the left gluteal muscles and extends along the posterior lateral aspect of the thigh (**c**) with flow voids and enhancement. MRI shows two large veins laterally extending from the dorsal and ventral aspects of the hindfoot through the leg and thigh which drain into a large vein entering the pelvis to join with the left iliac vein (not shown). Correlating with clinic findings, the lesions are compatible with venous capillary malformations (Courtesy of Dr. Grace Guo)

Macrodactyly

Contents

Macrodactyly is a rare congenital anomaly resulting in overgrowth of all the mesenchymal elements of the digit including phalanges, tendons, nerves, and vessels. Currently, the term macrodystrophia lipomatosa refers to a form of progressive macrodactyly with osseous involvement associated with diffuse overgrowth of adipose tissue (Yaghmai et al. 1976; Baruchin et al. 1988; Viola et al. 1991).

Synonyms and Related Disorders

Congenital localized gigantism; Digital gigantism; Lipofibromatous hamartoma of nerve or type I macrodactyly; Macrodystrophia lipomatosa; Proteus syndrome

Genetics/Basic Defects

1. Exact etiology: unknown
2. Possible mechanisms (Inglis 1950)
    1. Abnormal nerve supply
    2. Abnormal blood supply
    3. Abnormal humoral mechanism
3. Molecular genetics of isolated congenital macrodactyly
    1. Caused by somatic activation of the PI3K/AKT cell-signaling pathway
    2. Genetically and biochemically related to other overgrowth syndromes (Rios et al. 2013)
4. Macrodactyly of the hand (Flatt 1994; Cerrato et al. 2013)
    1. Nonhereditary, rare, congenital overgrowth disorder
    2. Accounts for 0.9% of upper extremity congenital anomalies
    3. Unlike neoplastic lesions, digital enlargement involves all tissue types and maintains general patterns of growth and anatomic relationships within the affected portion of the hand
    4. Hypertrophy and tortuosity of the digital nerve: a striking features in macrodactyly of the hand
5. Macrodactyly of the foot (Hendrix et al. 2000)
    1. Relatively rare congenital deformity
    2. An incidence of 1 in 18,000 (Kowtharapu et al. 2009)
    3. An enlarged digit or digits, including the phalanges, tendons, nerves, blood vessels, subcutaneous fat, nails, and skin

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_278

4. Absence of hypertrophy and tortuosity of the digital nerve (Syed et al. 2005)

Clinical Features

1. Onset: recognized at birth or neonatal period.
2. No sex predilection.
3. Usually involve unilateral but bilateral involvement has been reported (Aydos et al. 2003).
4. Affects one or more digits and rarely one entire extremity (Bansal and Harmit 1989).
5. Favored sites: second to third digits corresponding to the median nerve and medial plantar nerve in upper and lower limbs, respectively (Sone et al. 2000).
6. Least likely affected site: fifth digit.
7. Lower extremity more commonly involved than the upper extremity.
8. Abnormal growth usually ceases at puberty.
9. Patients often present for cosmetic reasons.
10. Secondary osteoarthritis may ensue in the involved joints in adolescence or early adulthood causing mechanical problems.
11. Psychological distress can be severe and school-aged ridicule is likely because macrodactyly of the fingers may be difficult to conceal (Ghavami 2007).
12. McKusick's classification of macrodactyly (Tentamy and McKusick 1978).
    1. An isolated anomaly
        1. True type
        2. Pseudo type: digit is enlarged because of soft tissue involvement without bony enlargement
    2. A part of a syndrome, i.e.,
        1. Congenital partial gigantism
        2. Proteus syndrome
        3. Neurofibromatosis
        4. Ollier disease
        5. Maffucci syndrome
        6. Klippel-Trenaunay-Weber syndrome
        7. Trevor's disease
        8. Congenital lymphedema
13. Other classifications of true macrocephaly.
    1. Respect to the course of growth (Barsky 1967)
        1. Progressive macrodactyly: the affected enlarged digits grow disproportionally faster than the rest of the limb; more common than the static macrodactyly
        2. Static macrodactyly: affected enlarged digits grow proportionally to the rest of the limb
    2. Hyperostotic type (Kelikian 1974)
        1. Continued growth of bone elements with osteocartilaginous plaques around the joint
        2. Cartilaginous component of the periarticular deposits predominates in the early stage
        3. Cartilage gradually replaced by bone
        4. Eventually joint motion is mechanically blocked
    3. Four types of macrodactyly (Upton 2005)
        1. Type I: macrodactyly with lipofibromatosis of a nerve, either of a static or progressive subtype
        2. Type II: macrodactyly associated with neurofibromatosis
        3. Type III: associated hyperostosis
        4. Type IV: associated hemihypertrophy
14. Differential diagnosis (Singla et al. 2008)
    1. Proteus syndrome
        1. Hallmark: random or mosaic distribution of its manifestations throughout the body
        2. Hemihypertrophy
        3. Associated abnormalities
            1. Partial gigantism of hands or feet.
            2. Cerebriform connective tissue nevi (McCuaig et al. 2012).
            3. Calvarial changes: hyperostotic lesions.
            4. Pulmonary cysts.
            5. Pigmented nevi.
            6. Intra-abdominal lipomas.
            7. Vascular malformations.
            8. Some consider macrodactyly to be a localized form of Proteus syndrome.

2. Klippel-Trenaunay-Weber syndrome (please see the chapter of "▶ Klippel-Trenaunay Syndrome")
   1. Port-wine stains
   2. Excess growth of bones and soft tissue and varicose vein
3. Lymphangiomatosis (please see the chapter)
   1. Diffuse swelling.
   2. Pitting edema.
   3. Osseous growth not observed.
   4. Long TR/TE sequences show high-signal intensity lesion with low-signal-intensity septations of variable thickness.
4. Hemangiomatosis (please see the chapter)
   1. A bruit may be palpable.
   2. Osseous growth not observed.
   3. Long TR/TE sequences show high-signal intensity lesion with internal flow voids and vigorous enhancement.
5. Fibrolipomatous hamartoma of nerve
   1. Mature fat infiltrating the neural sheath.
   2. Majority of the lesions occurring in the median nerve.
   3. Macrodactyly is present in 30–66% of cases (Cavallaro et al. 1993).
   4. MRI features: speckled appearance correlating with its histologically known architecture, i.e., neural fascicles separated by fat and connective tissue.
6. Neurofibromatosis (please see the chapter)
   1. Cutaneous lesions.
   2. Marked hyperintensity on T2W images.

Diagnostic Investigations

1. Imaging (Ho et al. 2007; Singla et al. 2008; Upadhyay et al. 2011)
   1. Plain radiography
      1. Hypertrophy of soft tissue and bone
      2. Translucencies in the soft tissue due to increased adipose tissue
      3. Phalanges
         1. Elongated, broad, and splayed, especially the distal phalanx, sometimes giving rise to a mushroomlike appearance
         2. Secondary osteoarthritic changes-like joint space narrowing, subchondral cysts, and osteophytes often develop in adolescence or early adulthood (Silverman and Enzinger 1985)
   2. CT scan: to demonstrate the proliferation of fat along the nerve territory (Curry et al. 1988; Brodwater et al. 2000)
   3. MRI (Soler et al. 1997; Wang et al. 1997; Sone et al. 2000; Pandey 2007)
      1. Shows abundant adipose tissues in the involved areas.
      2. This fat has the same signal intensity as the normal subcutaneous fat.
         1. High signal on T1W
         2. Intermediate signal on T2W
         3. Low signal on fat-suppressed sequences
      3. Contrary to lipoma, the abnormal fat in this disorder is not encapsulated.
      4. Linear hypointense bands may be noted within this redundant adipose tissue representing fibrous strands (low-signal-intensity linear strands on T1W images).
      5. Fatty infiltration of the involved muscles; as well as, the bony overgrowth and cortical thickening of the enlarged bones can be well demonstrated.
2. Pathology
   1. Hallmark: increased amount of adipose tissue embedded within a fine mesh of fibrous tissue.
   2. An excess fat deposition within the nerve sheath, bone marrow, periosteum, muscles, and subcutaneous tissues.
   3. Neural enlargement may be observed, which is caused by infiltration of the nerve sheath by the adipose tissue, and there is no increase in the number of axons.
   4. The median nerve in the upper extremity and the planter nerves of the lower extremity are most commonly affected (Goldman and Kaye 1977).

Genetic Counseling

1. Recurrence risk: a sporadic occurrence; recurrence risk apparently not significantly increased
2. Prenatal diagnosis
    1. Ultrasonography detected an isolated macrodactyly in a fetus at 24 weeks of gestation (Yuksel et al. 2009).
    2. Molecular genetic analysis: not reported.
3. Management
    1. Surgeries (Cerrato et al. 2013)
        1. Soft tissue debulking (surgical removal of adipose or soft tissue).
        2. Osteotomy for volume reduction or partial amputation (surgical removal of bone either longitudinally, transversely, or both).
        3. Closing wedge osteotomy.
        4. Epiphysiodesis.
        5. Digit transfer.
        6. Toe transfer.
        7. Full ray amputation.
    2. Treatment of macrodactyly of the lower extremity (Hendrix et al. 2000)
        1. Goals
            1. To obtain a pain-free and functional foot that can fit appropriately and comfortably into a shoe approximately the same size as the contralateral normal foot.
            2. Clinical results: difficult to achieve and necessitate multiple procedures.
        2. Ablation procedures: standard treatment in the past
        3. Phalangeal resection
        4. Syndactylization
        5. Phalangeal amputation
        6. Shortening of the digit, with and without tissue debulking
        7. Osteotomy for bony deformities
        8. Epiphysiodesis in children: Although longitudinal growth is arrested, appositional growth continues and multiple surgical procedures are necessary before correction is obtained.
        9. Amputation especially in progressive types of macrodactyly
        10. Radical resection with tissue debulking remains the most definitive method of treatment (Tsuge 1967; Kalen et al. 1988)

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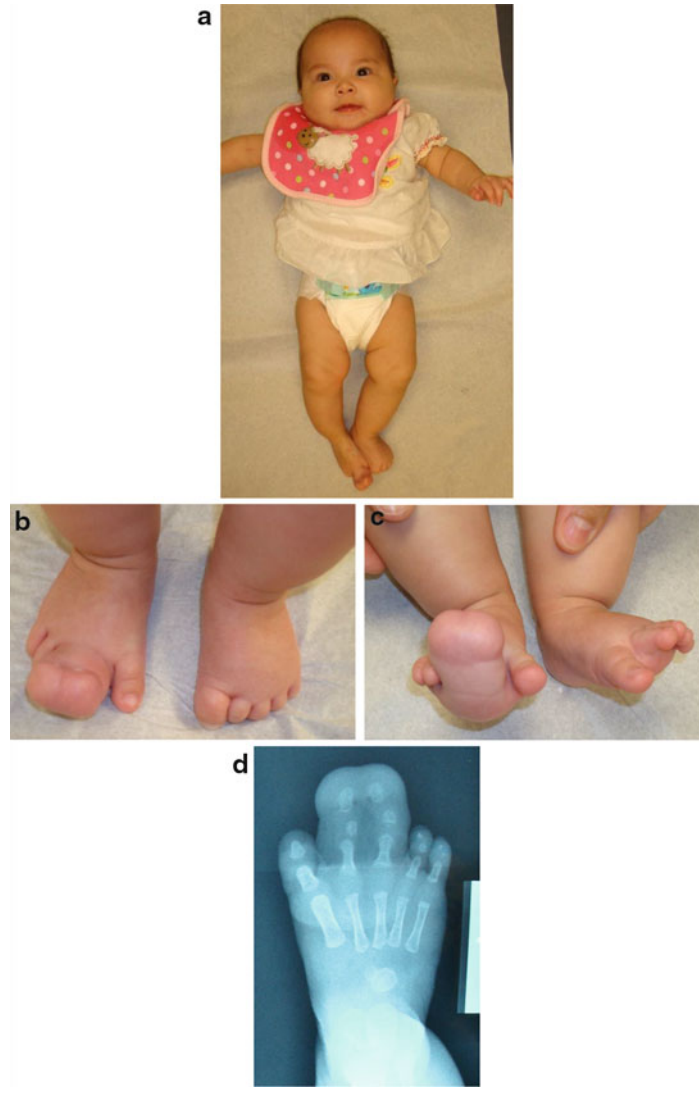

Fig. 1 (**a**–**d**) This 5-month-old female infant was seen for her macrodactyly of the right toes (**a**). Dorsal (**b**) and plantar (**c**) photographs showing macrodactyly of the second and third toes of the affected right foot with complete cutaneous syndactyly. AP radiograph (**d**) showed overgrowth of the bones and soft tissues with complete fusion of the soft tissues along the second and third toes. She also has situs inversus abdominus

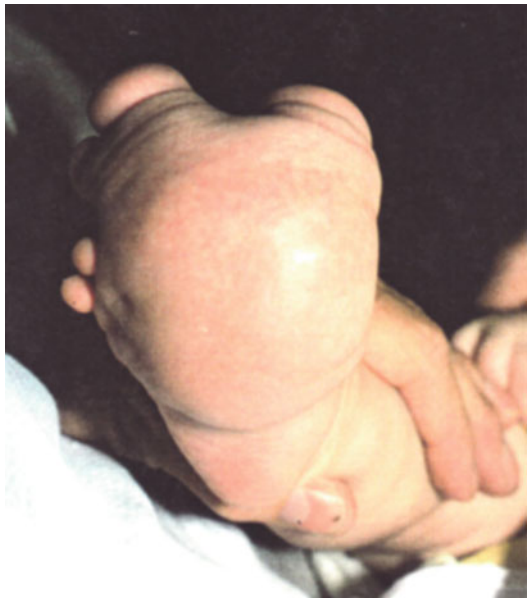

Fig. 2 The infant was born with macrodactyly of the right forefoot including the right first toe through third toe with syndactyly between second and third toes. This picture was taken at approximately 7 months of age. At 9 month of age, resection of the first, second, and third ray was performed with debulking of tumorous tissue of the right foot. MRI showed extensive infiltration of the right foot by primarily fatty density tissue extending from the plantar aspect between the toes to the dorsal aspect of the right foot and extending posteriorly and medially into the ankle. This fatty density tissue has soft tissue interspersed within it in swirls. These findings most likely represent fibromatosis

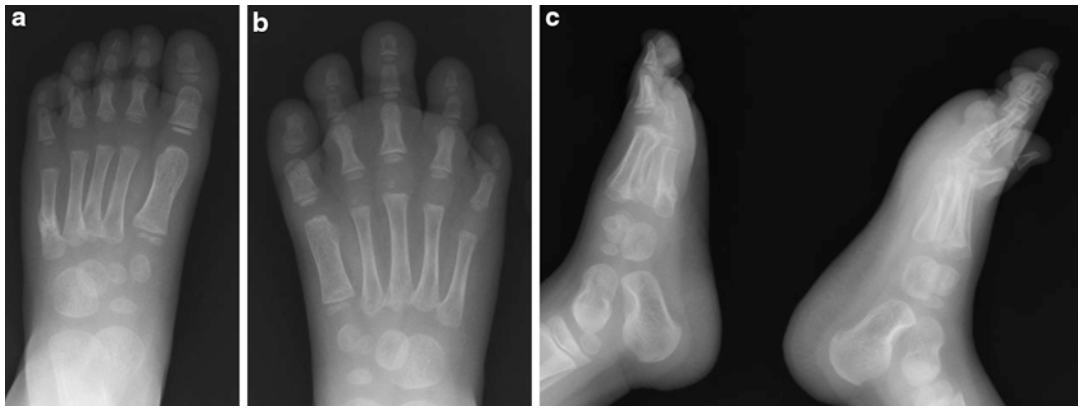

Fig. 3 This 2-year-old girl was seen for overgrowth of her right foot. Radiographs of bilateral feet showed asymmetry of the feet with overgrowth of bony structures as well as soft tissues on the right compared with the left (healing fracture was present in the left fifth metatarsal, otherwise normal left foot). It predominantly affects the right second, third, and fourth digits. In addition, the lateral cuneiform and cuboid are larger on the right than on the left. The upper and lower extremities are otherwise normal (Courtesy of Dr. Grace Guo)

Marfan Syndrome

Contents

Marfan syndrome (MFS) is an inherited connective tissue disorder, noteworthy for its worldwide distribution, relatively high prevalence, clinical variability, and pleiotropic manifestations involving primarily the ocular, skeletal, and cardiovascular systems, some of which are life threatening. Its estimated frequency is 2–3 per 10,000 individuals.

Genetics/Basic Defects

1. Inheritance.
   1. Autosomal dominant.
   2. New mutation in about 25–30% of the cases.
   3. About 70–75% of individuals diagnosed with Marfan syndrome have an affected parent.
2. Caused by a wide variety of mutations in the fibrillin-1 (*FBN1*) gene located on chromosome 15q21.1 (Dietz et al. 1991a, b; Giampietro et al. 2002).
3. Molecular defects in the fibrillin gene are responsible for the impaired structural integrity of the skeletal, ocular, and cardiovascular systems (Dietz and Pyeritz 1995).
4. Almost all mutations are specific (unique) to a particular individual or family (Robinson and Godfrey 2000).
5. *FBN1* mutation is helpful diagnostically only if it has been previously found in the person who independently meets the criteria for Marfan syndrome.
6. Criteria for causal *FBN1* mutation (Loeys et al. 2010).
   1. Mutation previously shown to segregate in Marfan family
   2. De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
   3. Nonsense mutation
   4. In frame and out of frame deletion/insertion
   5. Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
   6. Missense affecting/creating cysteine residues
   7. Missense affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues: D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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8. Linkage of haplotype for n ≥ 6 meioses to the FBN1 locus
7. A compound heterozygous Marfan patient with two defective fibrillin alleles resulting in a lethal phenotype (Kartunnen et al. 1994).
8. No obvious correlation between location of mutation and phenotypic severity (except an apparent clustering of mutations associated with the most severe form of Marfan syndrome, i.e., neonatal Marfan syndrome).
9. Pathophysiological consequence of the elastic fiber degeneration: reduced distensibility in response to the pulse pressure wave or increased stiffness (Dean 2002).
10. Intrafamilial and interfamilial variability of clinical expression.
11. Fibrillin-1 mutations also observed in related disorders of connective tissue (type I fibrillinopathies) (Aoyama et al. 1995; Pyeritz 1996; Robinson and Godfrey 2000; Dietz 2009; Loeys et al. 2010).
    1. Autosomal dominant ectopia lentis (bilateral ectopia lentis without the typical skeletal and cardiovascular manifestations of the Marfan syndrome)
    2. Shprintzen-Goldberg syndrome
        1. Unclear inheritance pattern
        2. Marfanoid habitus
        3. Craniosynostosis
        4. Mental retardation
        5. Rarely aortic root dilatation
        6. Mitral valve prolapse
        7. Majority of cases are not caused by *FBN1* mutations
    3. Autosomal dominant Weill-Marchesani syndrome
        1. Ectopia lentis
        2. Short stature
    4. Familial ectopic lentis
        1. An autosomal dominant condition
        2. Bilateral ectopia lentis
        3. Scoliosis in some cases
        4. No cardiovascular manifestations
    5. Familial aortic aneurysm
        1. Ascending aortic aneurysm and dissection
        2. No ectopia lentis
        3. No specific skeletal findings
    6. MASS phenotype
        1. An autosomal dominant condition
        2. Acronym MASS stands for:
            1. *M*itral valve prolapse
            2. *A*ortic root dilation without dissection
            3. *S*keletal abnormalities
            4. *S*kin abnormalities
    7. Mitral valve prolapse syndrome
        1. An autosomal dominant condition
        2. Mitral valve prolapse
        3. Associated with subtle skeletal features that are reminiscent of the Marfan syndrome
    8. New variant of Marfan syndrome
        1. Skeletal features of Marfan syndrome
        2. Joint contractures
        3. Knee joint effusions
        4. Ectopia lentis
        5. No cardiovascular manifestations
    9. Marfan-like (marfanoid) skeletal abnormalities
        1. Tall stature
        2. Scoliosis
        3. Pectus excavatum
        4. Arachnodactyly
12. Other disorders overlap with Marfan syndrome (Dietz 2009; Loeys et al. 2010).
    1. Loeys-Dietz syndrome: please see the chapter on "▶ Loeys-Dietz Syndrome"
        1. An autosomal dominant condition.
        2. Shares many features of Marfan syndrome but ectopia lentis is absent.
        3. Unique features.
            1. Craniofacial involvement (bifid uvula/cleft palate, hypertelorism, craniosynostosis)
            2. Skin: soft, velvety, and translucent
            3. Easy bruising
            4. Generalized arterial tortuosity and aneurysms
            5. Dissection throughout the arterial trees
        4. Other features.
            1. Clubfoot
            2. Cervical spine instability
        5. Caused by mutations in either the *TGFBR1* or *TGFBR2* gene (Loeys et al. 2005, 2006).

6. Loeys-Dietz syndrome types 1 and 2: designate those with and without severe craniofacial involvement, respectively (Loeys et al. 2006).

2. Other related disorders due to defects in components of the TGFβ pathway (Cook et al. 2015)
   1. Shprintzen-Goldberg syndrome
   2. Aneurysm-osteoarthritis syndrome
   3. Syndromic thoracic aortic aneurysms
3. Congenital contractural arachnodactyly
   1. Caused by fibrillin-2 (*FBN2*) mutations (highly homologous to BBN1, mapped to chromosome 5q23-31)
   2. Characteristic features
      1. Marfanoid habitus
      2. Arachnodactyly
      3. Camptodactyly
      4. Crumpled ears
      5. Mild contractures of the elbows, knees, and hips
      6. Mild muscle hypoplasia especially of the calf muscles
4. Ehlers-Danlos syndrome: please see the chapter on "► Ehlers-Danlos Syndrome"
5. Homocystinuria
   1. An autosomal recessive condition
   2. Caused by cystathionine β-synthase deficiency resulting from mutations in the *CBS* gene
   3. Characteristic clinical features
      1. Variable mental retardation.
      2. Ectopia lentis and/or severe myopia.
      3. Skeletal abnormalities (including excessive height and limb length).
      4. Excessive overlap with Marfan syndrome (a long and lean body habitus, pectus deformity, scoliosis, mitral valve prolapse, highly arched palate, hernia, and ectopia lentis).
      5. A tendency for intravascular thrombosis and thromboembolic events: Thromboembolic events can be life threatening. Approximately half of affected individuals are responsive to pharmacologic doses of vitamin B6, highlighting the need to consider this diagnosis.
6. Stickler syndrome: please see the chapter on "► Stickler Syndrome"
7. Fragile X syndrome: please see the chapter on "► Fragile X Syndrome"

Clinical Features

Ghent criteria: For the diagnosis of Marfan syndrome in the first (index) case in a family, major criteria must be found in at least two different organ systems and minor criteria in a third body system. If a fibrillin-1 mutation is identified, a major criterion in one system and involvement of another system are required. In a relative of an individual with confirmed Marfan syndrome, a major criterion in one body system and involvement of another system are all that are needed for the diagnosis (de Paepe et al. 1996; Pyeritz 2000).

1. Skeletal system (requires at least two majors or one major plus two minors): Affected patients are usually tall and thin with respect to the family profile. Limbs are disproportionately long compared with the trunk (dolichostenomelia). Arachnodactyly is a very common feature.
   1. Major criteria (requires at least four manifestations)
      1. Pectus carinatum.
      2. Pectus excavatum requiring surgery.
      3. Reduced upper-to-lower body segment ratio (<0.85 in Caucasians and <0.78 in African descents) or arm span-to-height ratio greater than 1.05. Arms and legs may be unusually long in proportion to the torso.
      4. Positive wrist (Walker-Murdoch) and thumb (Steinberg) signs for arachnodactyly. Two simple maneuvers may help demonstrate arachnodactyly. First, the thumb sign is positive if the thumb, when completely opposed within the clenched hand, projects beyond the ulnar border. Secondly, the

wrist sign is positive if the distal phalanges of the first and fifth digits of one hand overlap when wrapped around the opposite wrist.
5. Scoliosis $\geq$20 or spondylolisthesis. More than 60% of patients have scoliosis. Progression is more likely with curvature greater than 20° in growing patients.
6. Reduced extension of the elbows ($<$170°).
7. Medial displacement of the medial malleolus, resulting in pes planus.
8. Protrusio acetabuli (intrapelvic protrusion of the acetabulum; abnormally deep acetabulum with accelerated erosion) of any degree (ascertained by pelvic radiograph). Prevalence is about 50%.

2. Minor criteria
1. Pectus excavatum of moderate severity
2. Joint hypermobility
3. High arched palate with dental crowding
4. Typical face
1. Dolichocephaly
2. Malar hypoplasia
3. Enophthamos
4. Retrognathia
5. Down-slanting palpebral fissures

2. Ocular system (requires one major or at least two minors).
1. Major criterion: ectopia lentis (usually superior temporal dislocation, almost always bilateral, occurs in up to 80% of affected individuals). This may present at birth or develop during childhood or adolescence.
2. Minor criteria
1. Abnormally flat cornea (measured by keratometry)
2. Increased axial length of the globe (measured by ultrasound)
3. Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

3. Cardiovascular system (requires one major or one minor): the most serious problems associated with Marfan syndrome.
1. Major criteria
1. Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva. The prevalence of aortic dilatation in Marfan syndrome is 70–80%. It presents at an early age and tends to be more common in men than women.
2. Dissection involving the ascending aorta.

2. Minor criteria
1. Mitral valve prolapse with or without mitral valve regurgitation. The prevalence of mitral valve prolapse is 55–69%.
2. Dilatation of main proximal pulmonary artery in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 years.
3. Calcification of mitral annulus in patients less than 40 years of age.
4. Dilatation or dissection of abdominal or descending thoracic aorta in patients less than 50 years of age.

4. Pulmonary system (requires one minor).
1. Major criterion: none
2. Minor criteria
1. Spontaneous pneumothorax: occurs in about 5% of patients
2. Apical blebs (on chest radiography)

5. Skin and integument (requires one minor).
1. Major criterion: none
2. Minor criteria
1. Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy, or repetitive stress. Stretch marks are usually found on the shoulder, mid back, and thighs.
2. Recurrent or incisional hernia

6. Dura (requires the major criterion).
1. Major criterion: lumbosacral ectasia (ballooning or widening of the dural sac) by CT or MRI. Fewer than 20% of patients experience serious dural

ectasia. Dural ectasia is thought to be caused by CSF pulsations against weakened dura.
2. Minor criteria: none.

7. Family history (requires one major).
   1. Major criteria
      1. Having a parent, child, or sibling who meets the diagnostic criteria independently
      2. Presence of a mutation in *FBN1* known to cause the MFS
      3. Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed MFS in the family
   2. Minor criterion: none
8. Other features not in the Ghent criteria.
   1. Ocular features
      1. Myopia (most common ocular feature)
      2. At increased risk for retinal detachment, glaucoma, and early cataract formation
   2. Skeletal system
      1. Bone overgrowth
      2. Disproportionately long extremities for the size of the trunk (dolichostenomelia)
      3. Overgrowth of the ribs pushing the sternum in (pectus excavatum) or out (pectus carinatum)
      4. Mild, severe, or progressive scoliosis
9. Natural history: age-related nature of some clinical manifestations and variable phenotypic expression.
   1. At birth, early in life, and childhood
      1. Dolichostenomelia
      2. Arachnodactyly
      3. Manifestations of other organ systems usually not present at birth, making the diagnosis during neonatal period difficult in the absence of family history
      4. Asthenic habitus
      5. Lens dislocation or lens subluxations (a hallmark feature) commonly diagnosed during the first year of life (not present at birth)
   2. Childhood and puberty
      1. Skeletal manifestations apparent during childhood
      2. Pectus deformities and scoliosis worsen during puberty
      3. Upper normal or larger than normal aortic root size in early childhood
      4. Rapidly increasing magnitude of dilatation during puberty
   3. Adulthood
      1. Lumbosacral dural ectasia manifesting as progressive dilatation of the dura with consequent erosion of vertebral bone during adulthood
      2. Aortic disease as the major cause of cardiovascular morbidity and reduced life expectancy (initial life expectancy: 32 ± 16 years)
      3. Increased life expectancy attributes to successive elective and emergent aortic surgery and to the use of β-adrenergic receptor antagonists for the prevention of the progression of aortic root dilatation (current life expectancy: 41 ± 18 years)
10. Revised Ghent nosology for the Marfan syndrome (Loeys et al. 2010).
    1. Established by an international expert panel.
    2. Puts more weight on the cardiovascular manifestations in which aortic root aneurysm and ectopia lentis are the cardinal clinical features.
       1. In the absence of any family history, the presence of aortic root aneurysm and ectopic lentis is sufficient for the unequivocal diagnosis of MFS.
       2. In the absence of either of aortic aneurysm or ectopic lentis, the presence of a bona fide *FBN1* mutation or a combination of systemic manifestations is required. The following new scoring system has been designed for systemic features: The score of ≥ 7 indicates systemic involvement (maximum total of 20 points).
          1. Wrist and thumb sign: 3 (wrist or thumb sign: 1)

2. Pectus carinatum deformity: 2 (pectus excavatum or chest asymmetry: 1)
3. Hindfoot deformity: 2 (plain pes planus: 1)
4. Pneumothorax: 2
5. Dural ectasia: 2
6. Protrusio acetabuli: 2
7. Reduced US/LS and increased arm/height and no severe scoliosis: 1
8. Scoliosis or thoracolumbar kyphosis: 1
9. Reduced elbow extension: 1
10. Facial features (3/5): 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
11. Skin striae: 1
12. Myopia >3 diopters: 1
13. Mitral valve prolapse (all types): 1

3. In this revised nosology, *FBN1* testing, although not mandatory, has greater weight in the diagnostic assessment.
4. Special considerations are given to the diagnosis of MFS in children and alternative diagnoses in adults.
5. These new guidelines may delay a definitive diagnosis of MFS but will decrease the risk of premature or misdiagnosis and facilitate worldwide discussion of risk and follow-up/management guidelines.

11. Neonatal Marfan syndrome.
    1. Diagnosed early in life because of striking and severe clinical manifestations (Gross et al. 1989)
        1. Two symptoms that are uncommon in severe Marfan syndrome presenting at birth but very common in neonatal Marfan syndrome (Hannekam 2005)
            1. Congenital pulmonary emphysema
            2. Mitral or tricuspid insufficiency (multivalvular involvement)
        2. Congestive heart failure
        3. Joint contractures
        4. Death usually within the first year of life
    2. Characteristic aged facial appearance
        1. Deep-set eyes
        2. Down-slanted palpebral fissures
        3. Crumpled ears
        4. High arched palate
    3. Striking arachnodactyly of the fingers and toes
    4. Pectus deformities
    5. Scoliosis
    6. Flexion contractures
    7. Pes planus
    8. Aortic root dilatation
    9. Ectopia lentis
    10. A cluster of mutations in exons 24–27 as well as in exons 31–32

Diagnostic Investigations

1. Annual physical examination including blood pressure measurement
2. Slit-lamp examination for lens dislocation
3. Electrocardiogram for symptomatic palpitations, syncope or near-syncope, and conduction disturbance
4. Echocardiography (Geva et al. 1987) and targeted imaging studies to carefully monitor the cardiovascular status
    1. Cross-sectional echocardiography for detecting aortic root dilatation
    2. Standard echocardiography for assessing mitral valve prolapse, left ventricular size and function, left atrial size, and tricuspid valve function
    3. Transesophageal echocardiography for visualizing the distal ascending and descending aorta and assessing prosthetic valves
    4. Doppler echocardiography for detecting and assessing the severity of aortic and mitral regurgitation
5. Radiography
    1. Chest X-ray for apical blebs, enlargement of cardiac silhouette, and detecting dissecting aneurysm of aorta
    2. Pelvic X-ray for additional diagnostic criteria of protrusio acetabuli
    3. Feet X-ray for medial displacement of the medial malleolus, responsible for pes planus

6. Computed tomography (CT) and magnetic resonance imaging (MRI)
    1. MRI: best choice for assessing chronic dissection of any region of the aorta
    2. CT or MRI of the lumbosacral spine for detecting dural ectasia
7. Cardiovscular MR (CMR) imaging (or CT) of the entire aorta (Dommand and Mohiaddin 2013)
    1. CMR: free from ionizing radiation; well visualization of aneurysm formation, dissection, and previous surgery; unsurpassed at characterizing vascular and myocardial tissue
    2. Advise every 5 years if normal aortic dimensions beyond root
    3. Advise at least annually if aneurysm formation beyond root
8. Avoid coronary angiography due to increased dissection risk (Dommand and Mohiaddin 2013)
9. Aortograph: still considered by many to be the gold standard for diagnosing acute aortic dissection although sensitivity is not 100% and there are associated risks
10. Molecular analysis of *FBN1* mutations by sequence analysis, mutation scanning, deletion analysis, or linkage analysis (may be used to determine if an individual has inherited an FBN1 allele that is associated with Marfan syndrome in family members)
    1. *FBN1* mutation screening not only confirms the diagnosis but also facilitates determination of prognosis and timely management (Loeys et al. 2001; Halliday et al. 2002; Chen 2014)
    2. Mutations detected nearly always specific to each family
    3. *FBN1* mutations observed in 20–80% of patients depending upon the clinical selection of patients and the mutation detection method used
        1. Mutation scanning
        2. Targeted mutation analysis
        3. Sequencing of entire coding region
    4. Genotype-phenotype correlations (Pyeritz 2000; Loeys et al. 2001)
        1. Little correlation observed in several hundred mutations reported to date
        2. Severe MFS detected in infancy (inappropriately termed neonatal MFS) usually caused by point mutations or small deletions in frame in the epidermal growth factor (ECF)-like motifs in the middle third of the fibrillin-1 protein
        3. Less severe phenotype, verging on the MASS phenotype, usually caused by chain-terminating mutations resulting in essence in null mutants
        4. Marked variability among individuals with the same mutation
    5. *FBN1* mutations of various types reported
        1. Classic Marfan syndrome
        2. Nonclassical Marfan related phenotypes
    6. Molecular diagnosis practical in the following two situations (Pyeritz 2000)
        1. Information about a known *FBN1* mutation in a person with MFS applied to relatives
        2. Linkage analysis using sufficient intragenic and tightly linked polymorphisms to MFS families with several available and willing relatives
11. Histology of the aorta
    1. Elastic fiber fragmentation and disarray
    2. Paucity of smooth muscle cells
    3. Deposition of collagen and the mucopolysaccharide between the cells of the media

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Recurrence risk: small if neither parent is affected
        2. Gonadal mosaicism reported as the cause of multiple affected offspring being born to unaffected parents
        3. Fifty percent if one parent is affected
    2. Patient's offspring
        1. Fifty percent if the spouse is normal

2. "Homozygous" MFS reported in case of an affected spouse
3. "Compound heterozygosity" at the *FBN1* locus confirmed at the molecular level; the affected child had a severe phenotype leading to early death

2. Prenatal diagnosis
   1. Ultrasonography insensitive in the first two trimesters for detecting a fetus with MFS
   2. Presumptive prenatal diagnosis of fetal Marfan syndrome by fetal echocardiography at 34 weeks of gestation (Lopes et al. 1995)
      1. Cardiomegaly
      2. Pericardial effusion
      3. Prolapse of the tricuspid and mitral valves with mitral and tricuspid regurgitation
      4. Dilatation of Valsalva with typical "clover-lead" appearance
      5. Aortic and pulmonary regurgitation
   3. Main clinical cardiovascular features for the prenatal diagnosis of Marfan syndrome (Lopes et al. 2006)
      1. Cardiomegaly
      2. Dilated great vessels
      3. Dysplastic atrioventricular valves with tricuspid regurgitation and aneurysms of the pulmonary artery and/or sinus of Valsalva
   4. Prenatal diagnosis of Marfan syndrome can be confirmed in affected families by gene identification using chorionic villus sampling (Godfrey et al. 1993; Rantamaki et al. 1995).
      1. Only if the family's mutation is known in an affected parent
      2. Neonatal Marfan syndrome, mostly sporadic, appears to be more severe than those in familiar forms (Gross et al. 1989). Inability to predict exons 24–32 mutation to be associated with "classic, atypically severe or neonatal" Marfan syndrome (Tieck et al. 2001)
      3. Presence of sufficient affected family members available for genetic linkage analysis if linkage with markers in and around the *FBN1* locus can be established
   5. Preimplantation diagnosis accomplished but complicated by the potential for selective PCR amplification of the normal allele as with all autosomal dominant conditions (Eldadah et al. 1995; Kilpatrick et al. 1996; Blaszczyk et al. 1998; Sermon et al. 1999)
3. Management (Pyeritz and McKusick 1979; Nienaber and Von Kodolitsch 1999; Castellano et al. 2014)
   1. Address patients' perceptions of Marfan syndrome and its associated pain, fatigue, and depressive symptoms to enhance patient adaptation.
   2. Stress benefits of medication use (β-blockers or calcium-channel blockers to retard aortic root dilatation and dissection) and restriction of physical activities (to delay the onset of a severe cardiovascular event and prevent other syndrome-related problems such as lens dislocation).
      1. β-Blockers
         1. Should be considered in all Marfan patients, particularly in the younger age group
         2. Not suitable for patients with asthma, cardiac failure, or bradyarrhythmias
      2. Other treatments aimed at reducing the ejection impulse
         1. Calcium antagonists
         2. Angiotensin converting enzyme (ACE) inhibitors
   3. Lifestyle changes
      1. Avoid competitive and collision/contact sports which are potentially dangerous due to underlying aortic weakness and dilatation, valvular insufficiency, ocular abnormalities, and skeletal problems (Braverman 1998)
      2. Avoid blows to the head such as boxing and high diving.
      3. Protect against blows to the globe (racquet sports) with cushioned spectacles.

4. Avoid activities involving isometric work to prevent excessive elevations of systolic blood pressure and sudden death.
    1. Weight lifting
    2. Climbing steep inclines
    3. Gymnastics
    4. Water skiing
    5. Pull-ups
5. Avoid rapid decompression associated with quick ascents in elevators, scuba diving, and flying in unpressurized aircraft to protect against pneumothorax.
6. Favor noncompetitive, isokinetic activity performed at a nonstrenous aerobic pace.
    1. Golfing
    2. Walking
    3. Fishing

4. Surgical intervention recommended for affected individuals with significantly dilated or dissected aortic roots or aortic aneurysm (Baumgartner et al. 1999)
5. Management of scoliosis (Sponseller et al. 1997)
    1. Bracing
    2. Physical therapy
    3. Surgery for severe scoliosis
6. Pectus repair
    1. Repair of pectus excavatum to improve respiratory mechanics: should be delayed until midadolescence to lessen the chance of recurrence
    2. Repair of pectus carinatum performed mainly for cosmetic purpose
7. Pneumothorax
    1. Chest tube: an appropriate initial therapy
    2. Bleb resection and pleurodesis recommended after one recurrence
8. Ocular management (Koenig and Mieler 1996)
    1. Removal of dislocated lens (pars plana lensectomy and vitrectomy), only in the following few instances, due to an increased risk of retinal detachment related to lens extraction
        1. Dislocation of a lens in the anterior chamber, especially when it touches the corneal endothelium
        2. Significant lens opacity
        3. Evidence of lens-induced uveitis and glaucoma
        4. Inadequate visual acuity that is not correctable by refraction and iris manipulation
        5. Imminent complete luxation of the lens
    2. Lasers to restore a detached retina
9. Pregnancy in women with MFS (Curry et al. 2014)
    1. Preconceptional counseling of maternal risks during pregnancy and risk of transmitting the condition to offspring.
    2. A significantly increased risk of cardiovascular complications during pregnancy.
        1. Particularly risk of dissecting aortic aneurysm
        2. Increase in aortic root diameter
        3. Worsening mitral or aortic regurgitation, as seen in echocardiography
        4. Myocardial infarction
        5. Pulmonary edema
        6. Arrhythmia
        7. Endocarditis
        8. Cardiac death
        9. Aortic surgery within 6 months of delivery
    3. Obstetric complications.
        1. Antepartum hemorrhage
        2. Pregnancy-induced hypertension
        3. Pre-eclampsia
        4. Eclampsia
        5. Gestational diabetes
        6. Preterm labor/rupture of membranes
        7. Postpartum hemorrhage
        8. Thromboembolism
    4. Fetal/neonatal complications.
        1. Preterm birth
        2. Respiratory distress syndrome
        3. Intraventricular hemorrhage
        4. Fetal demise

5. Perinatal/neonatal mortality
5. Need for close surveillance during pregnancy.
6. Avoid pregnancy if echocardiography suggests a high risk of life-threatening cardiovascular compromise. Pregnancy bears a 1% risk of fatal complication; the risk rises with increasing aortic root diameter.
7. β-Blockers recommended in pregnant women to prevent aortic dilatation.
8. Cesarean section should be offered at 38 weeks gestation if aortic root diameter is greater than 4.5 cm (Child 1997).
9. Favorable outcomes in a tertiary referral center (Allyn et al. 2013).
    1. Pre- or early pregnancy evaluation
    2. Early β-blocker therapy
    3. Serial echocardiographic assessments
    4. Multidisciplinary planning of mode of delivery
    5. Avoidance of hemodynamic stress on the aortic root with appropriate analgesia/anesthesia technique
10. More extensive screening for Marfan syndrome and a search for additional risk factors are desirable because of high fatality rate in Marfan syndrome aortic root dissection (Groenink et al. 1999).
11. Genetic counseling that addresses patients' perception of Marfan syndrome and its associated pain, fatigue, and depressive symptoms may enhance patient adaptation to the condition (Peters et al. 2001a).
12. Genetic counseling should address beliefs about medication use and physical activity restrictions, as perception of these health behaviors may have a significant impact on how adults with Marfan syndrome adhere to these recommendations and cope with their condition (Peters et al. 2001b).
13. Dramatic increase in life expectancy (Silverman et al. 1995).
    1. Median (50%) cumulative probability of survival in 1993 was 72 years compared with 48 years in 1972.
    2. Overall improvement in population life expectancy.
    3. Benefits arising from cardiovascular surgery.
    4. Greater proportion of milder cases due to increased frequency of diagnosis.
    5. Medical therapy including β-blockers.

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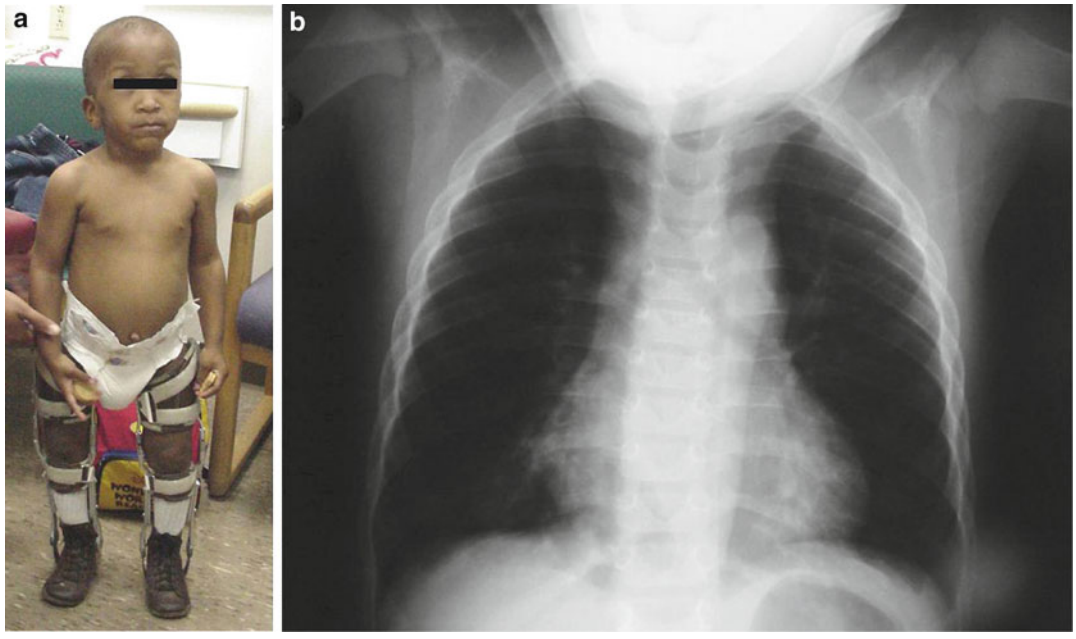


Fig. 1 (**a**, **b**) A boy with severe Marfan syndrome showing arachnodactyly, joint contractures, and aortic root dilatation, illustrated by the chest radiography

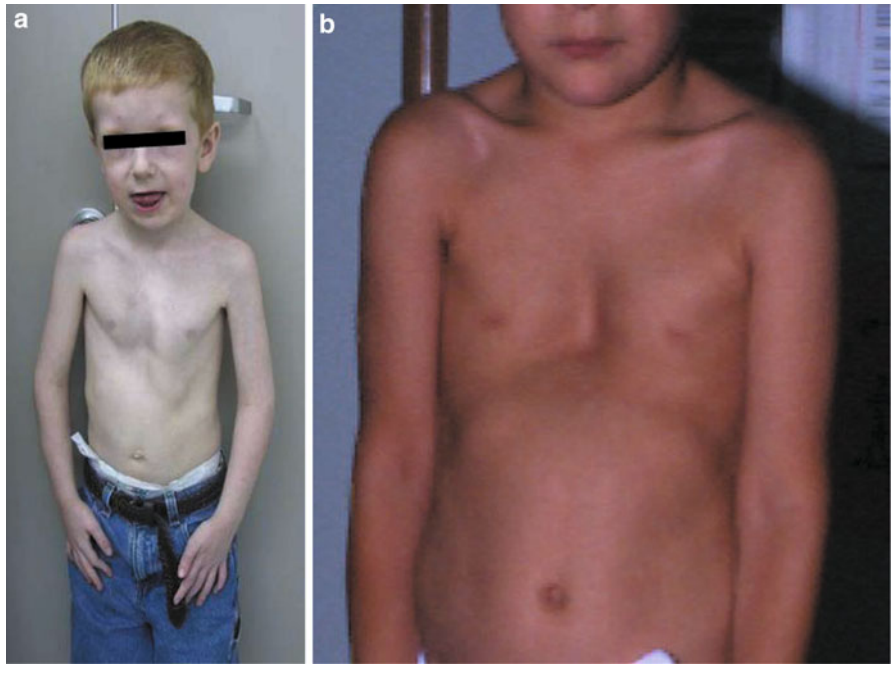


Fig. 2 (**a**, **b**) Two children with Marfan syndrome showing pectus and arachnodactyly. The first patient had dural ectasia detected by MRI. The second patient had aortic root dilatation and mitral valve prolapse

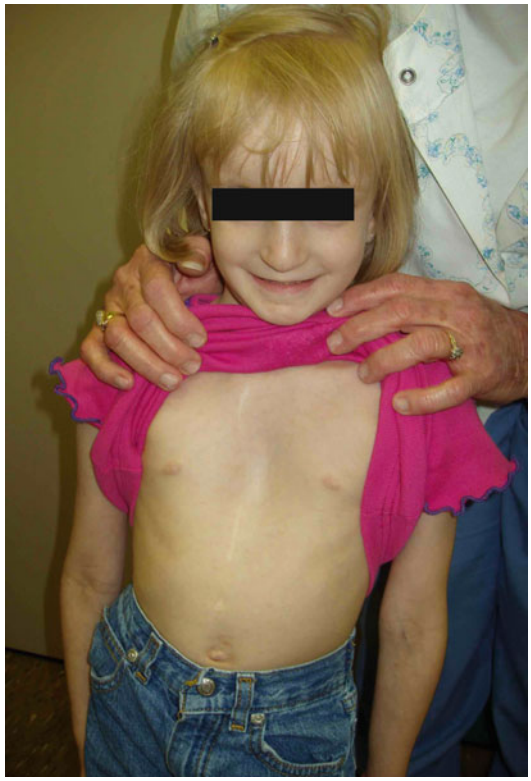


Fig. 3 A 4-year-old girl with Marfan syndrome showing pectus excavatum and the operation scar from surgical correction of marked aortic dilatation. She also has hyperextensible joints and scoliosis

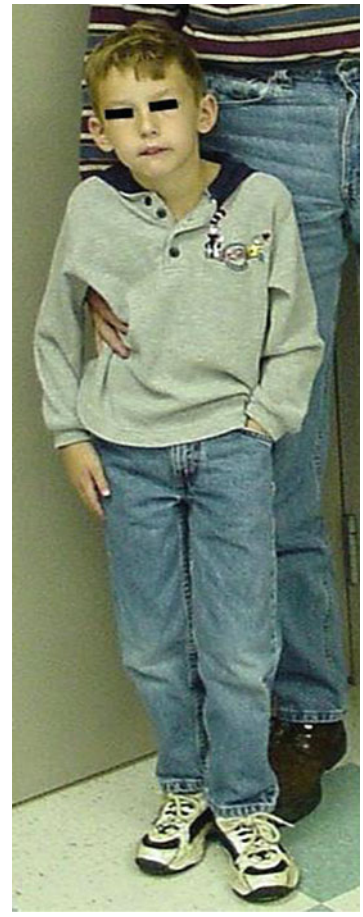


Fig. 4 A 5-year-old boy with Marfan syndrome showing tall and slender body habitus. He was noted to have mitral valve prolapse and aortic root dilatation at age 2. In addition, he has bilateral lens dislocations and scoliosis

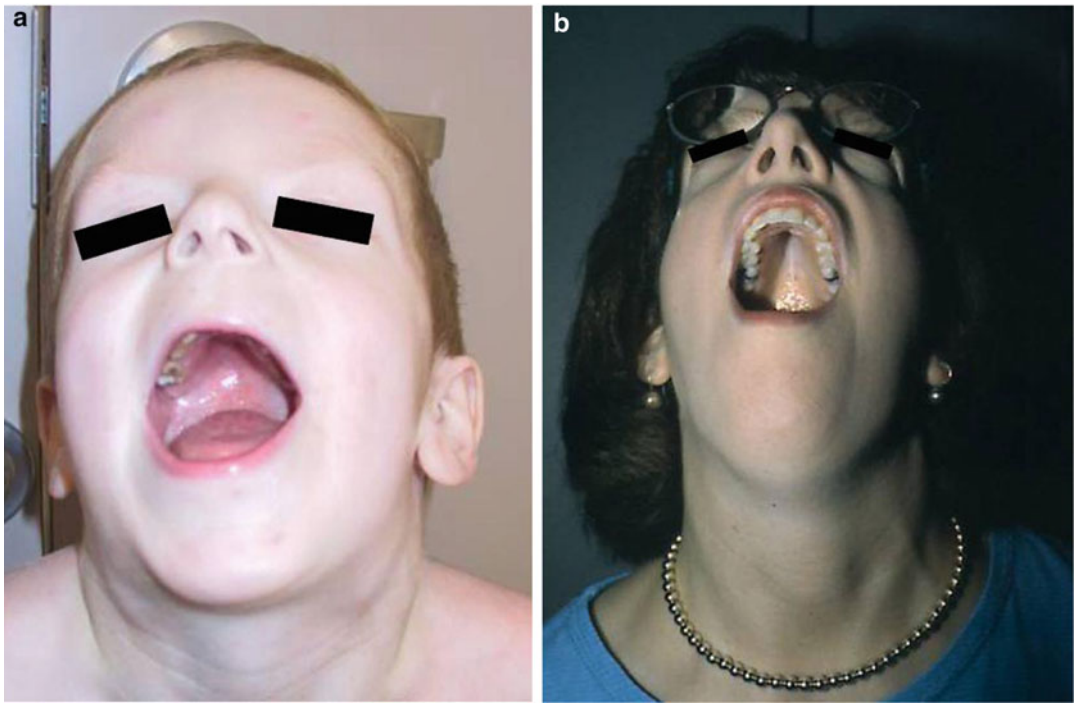


Fig. 5 (**a**, **b**) A child and an adult with Marfan syndrome showing high arched palate

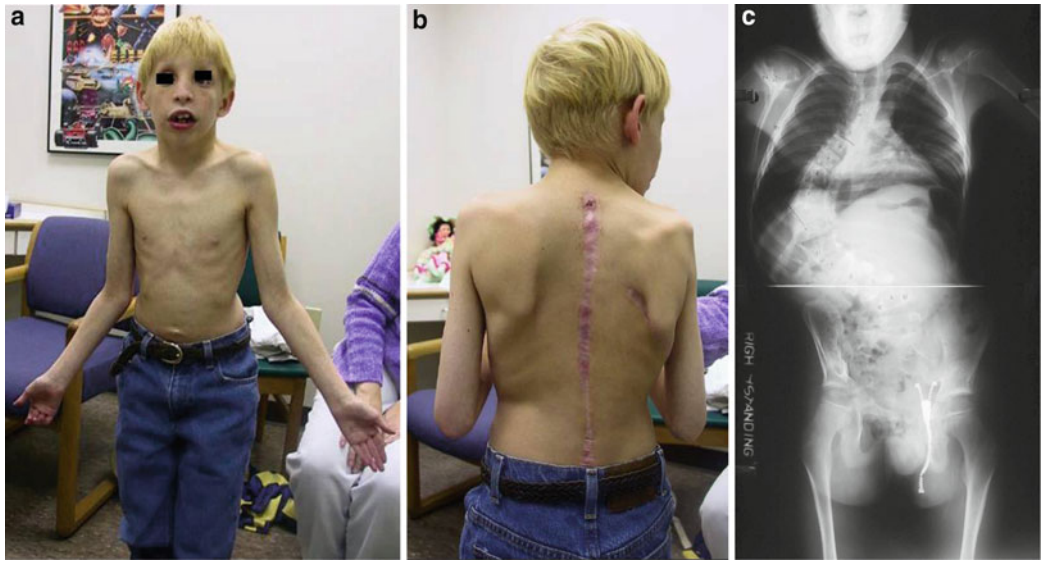


Fig. 6 (**a**–**c**) A child with Marfan syndrome showing cubitus valgus, arachnodactyly, and postsurgical spinal fusion for severe scoliosis (Illustrated by radiograph)

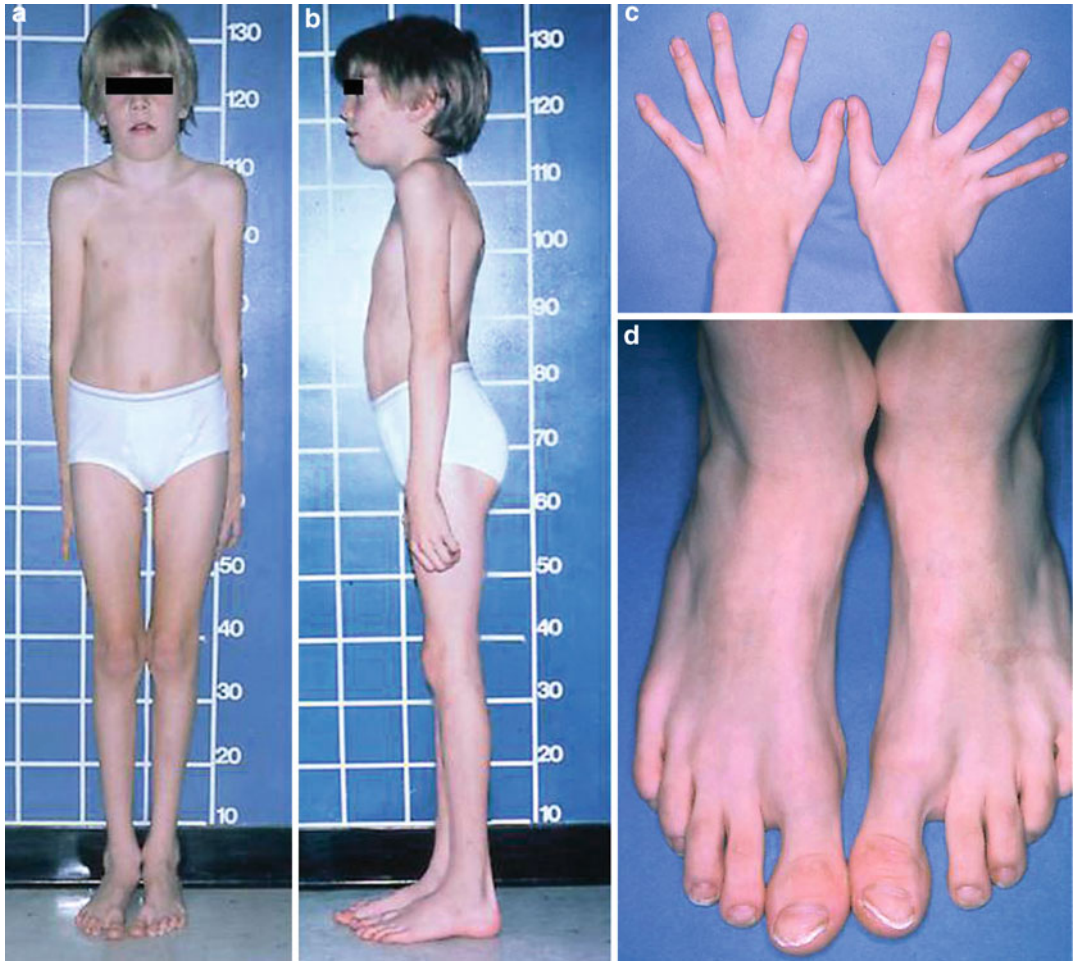


Fig. 7 (**a**–**d**) A boy with Marfan syndrome showing a slender/tall habitus and arachnodactyly

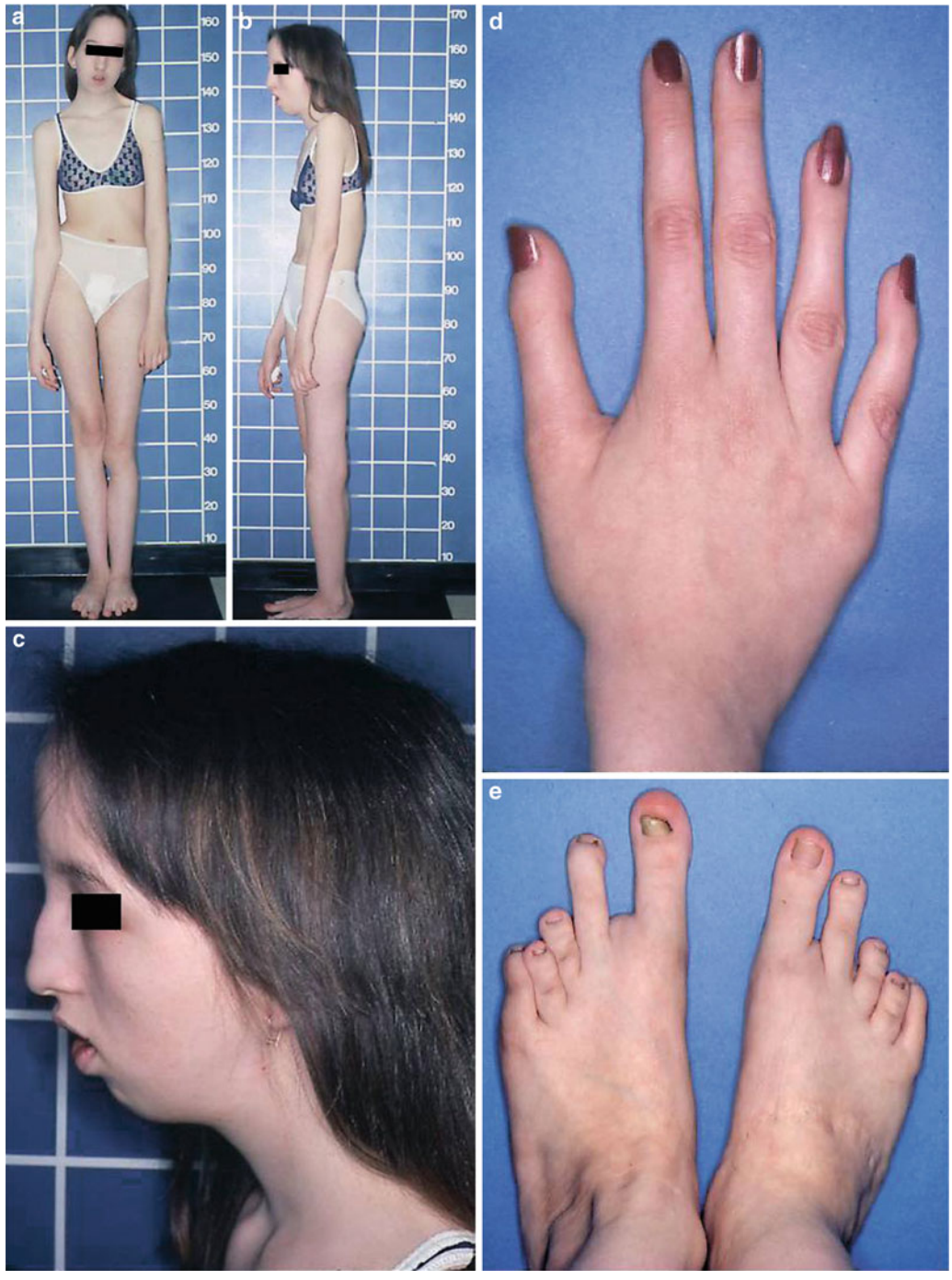


Fig. 8 (**a**–**e**) A girl with Marfan syndrome showing a slender/tall habitus, typical facies, arachnodactyly, and toe anomalies

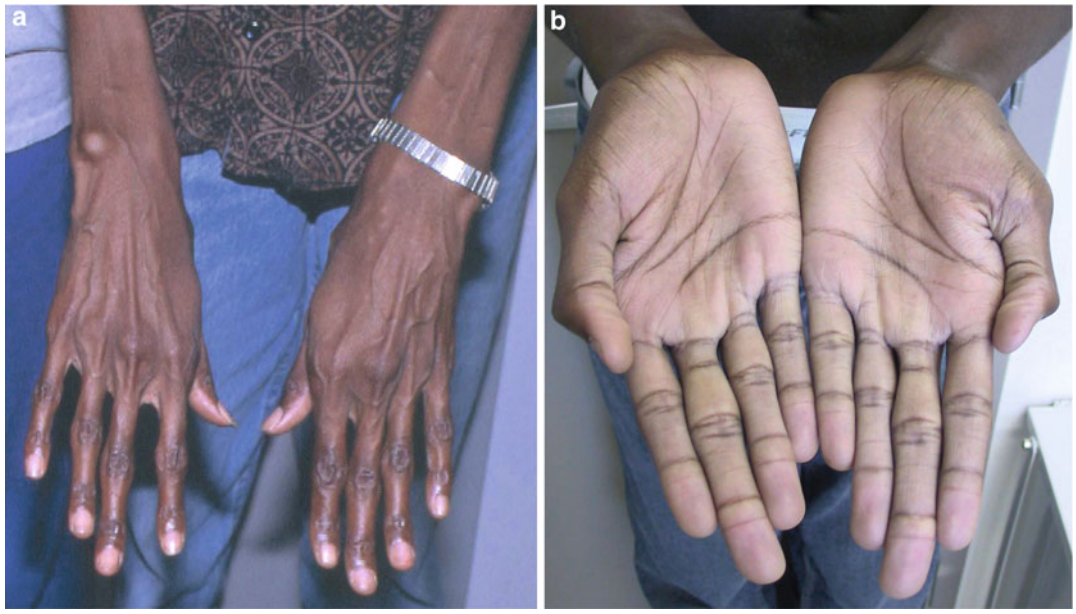


Fig. 9 (**a**, **b**) Arachnodactyly in two adult patients with Marfan syndrome

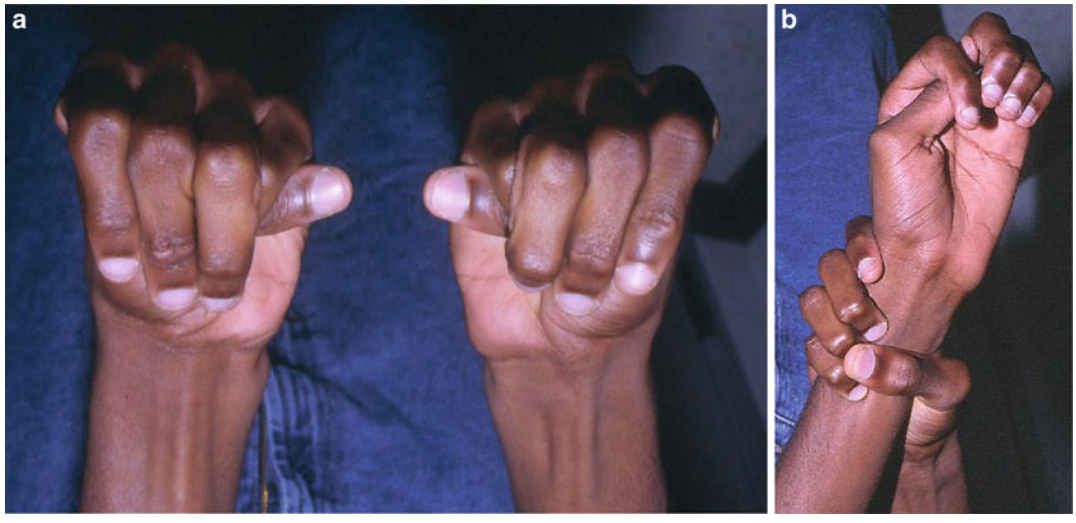


Fig. 10 (**a**, **b**) Thumb and wrist signs

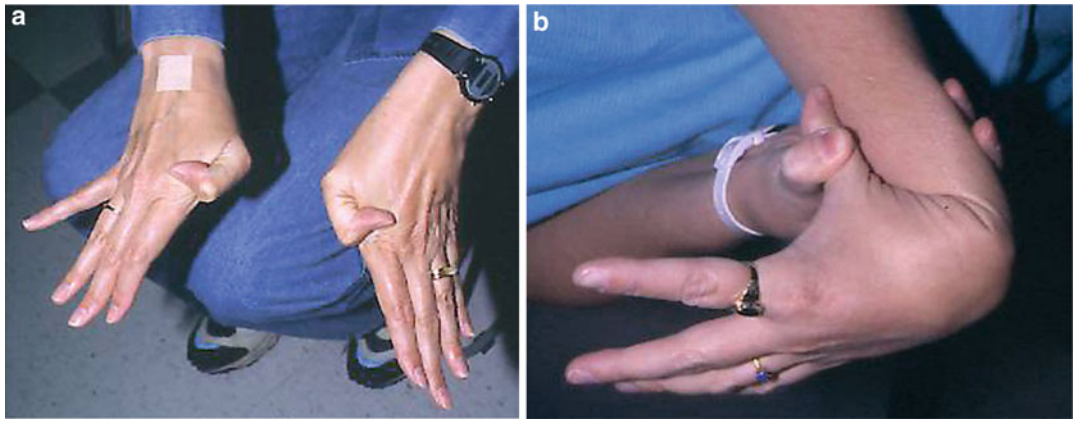
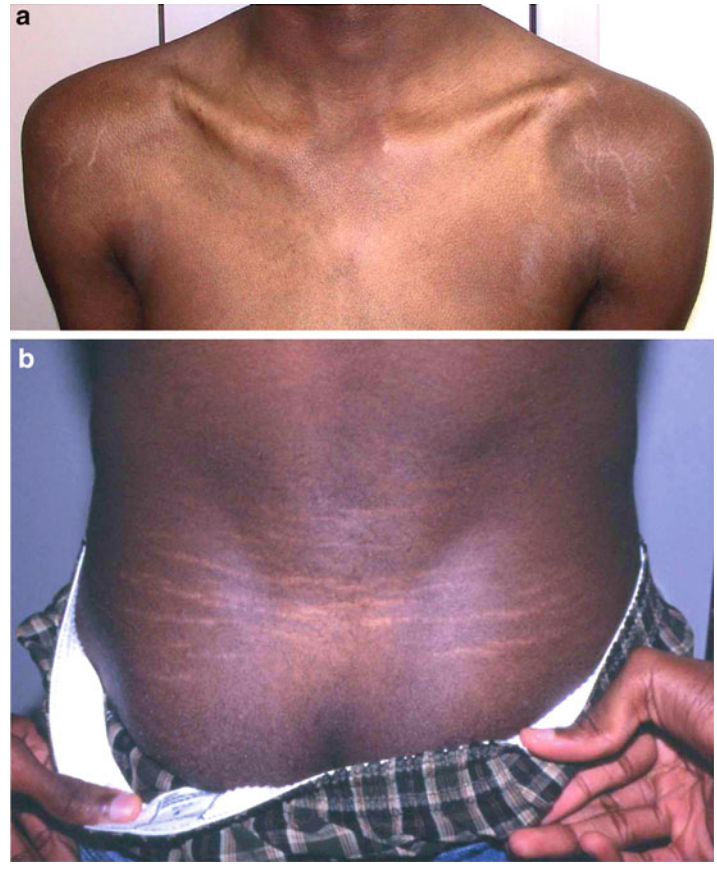


Fig. 11 (**a**, **b**) Hypermobile joints in two patients with Marfan syndrome

Fig. 12 (**a**, **b**) Stretch marks in the shoulders in one patient and in the buttock region in other patient with Marfan syndrome



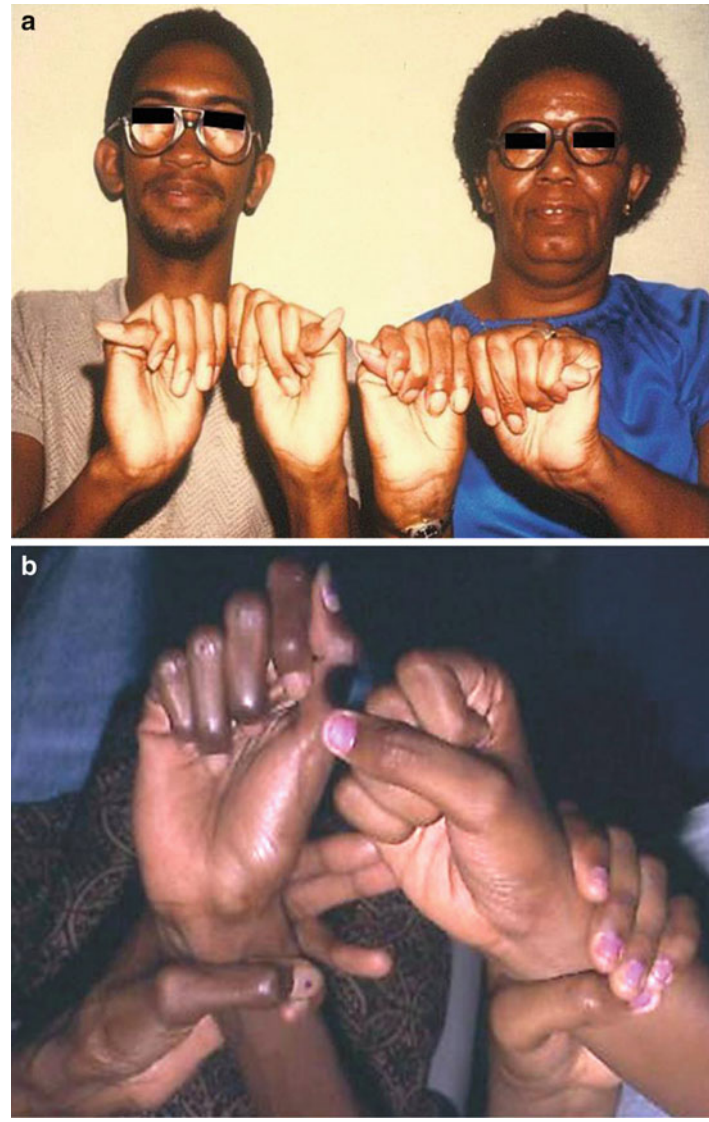


Fig. 13 (**a**, **b**) Familial Marfan syndrome in a mother and a son showing extreme myopia (lens dislocation) and thumb and wrist signs

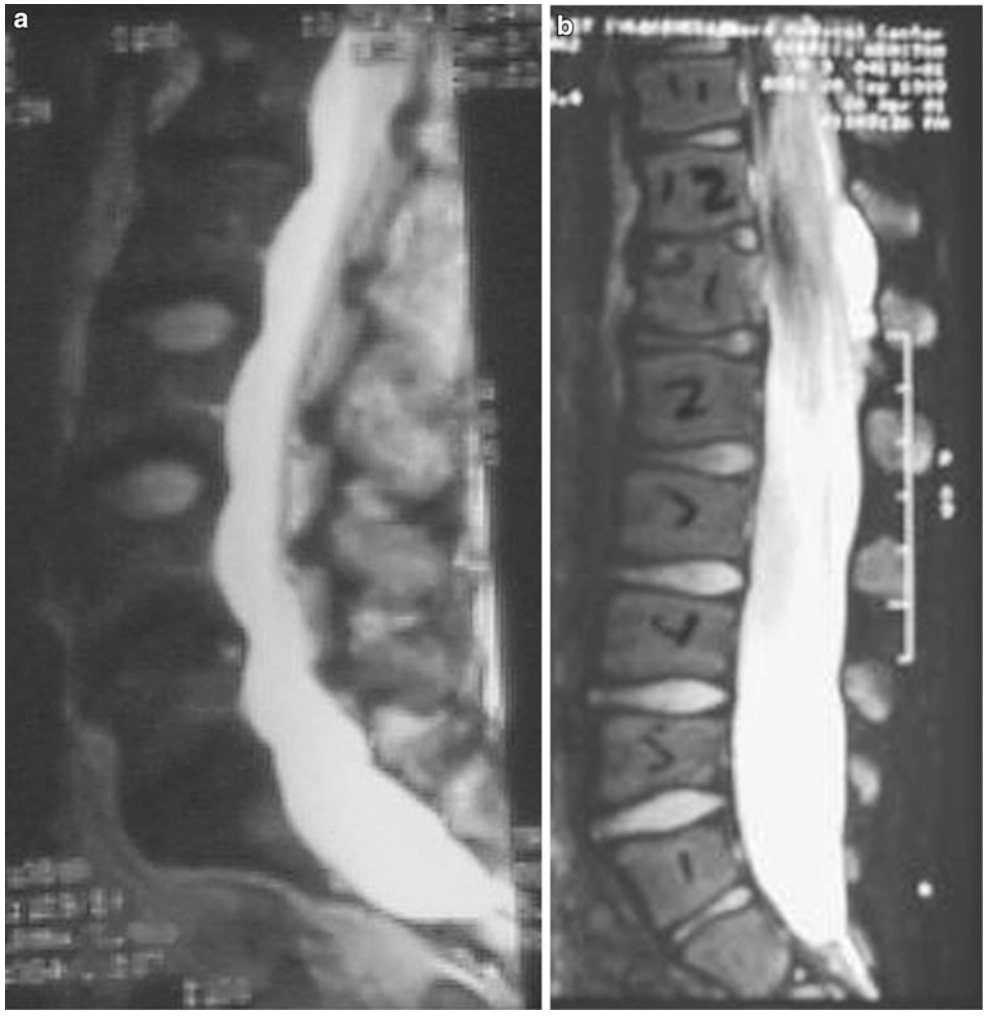


Fig. 14 (**a**, **b**) MRI of the lumbosacral spine in two patients showing dural ectasia

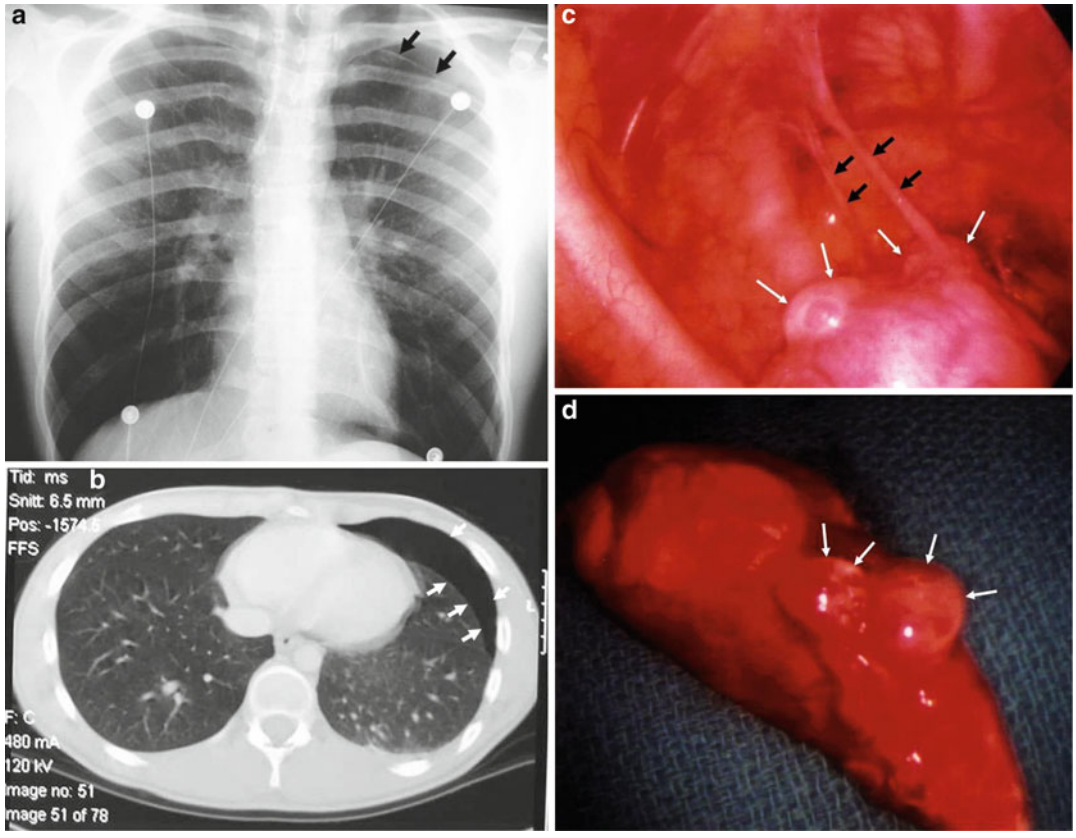


Fig. 15 (**a**–**d**) A 20-year-old male with Marfan syndrome with repeat spontaneous pneumothorax from ruptures of apical blebs. The chest X-ray shows collapsed left lung with pleural line (*arrows*). The CT of the chest shows pneumothorax on the right lung (*arrows*). Thoracoscope image from the right lung shows two bands representing the old adhesions due to previously ruptured apical blebs (*black arrows*) and two intact blebs (*white arrows*). The wedge biopsy specimen of the right apex shows two emphysematous blebs (*white arrows*) which were demonstrated in the previous figure

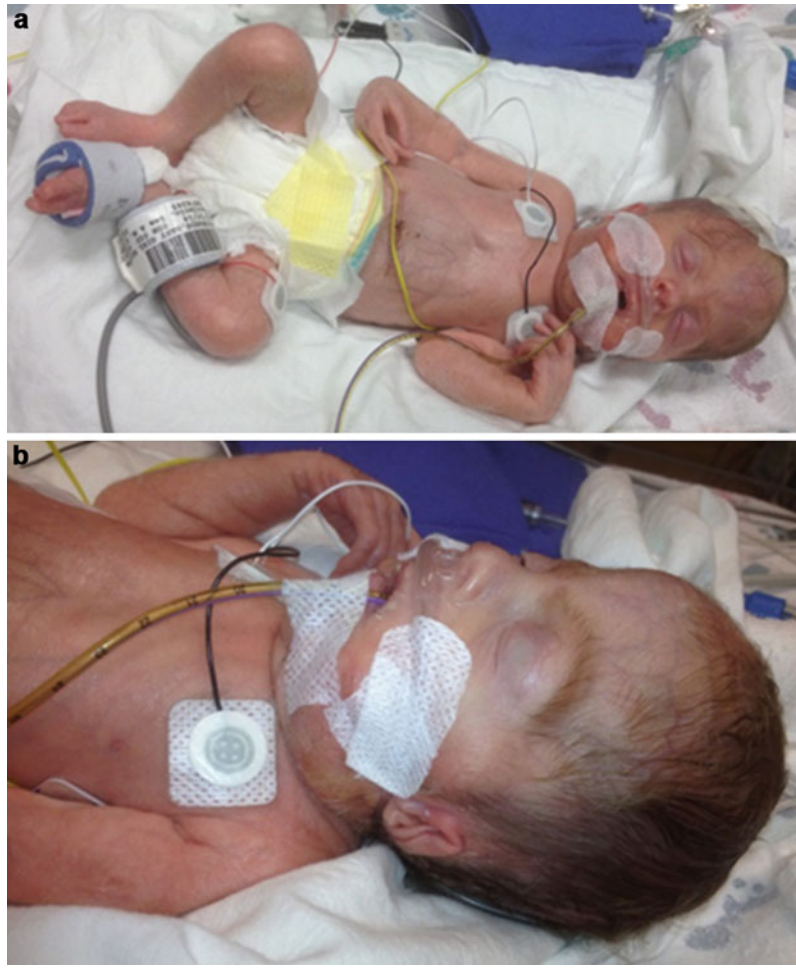


Fig. 16 (**a, b**) This premature baby girl (**a, b**) was born at 30 4/7 weeks gestation via cesarean section due to pregnancy-induced hypertension and omphalocele. Craniofacial features were characterized by trigonocephaly, anti-mongoloid slant of the palpebral fissures, cleft palate, and crumpled low-set ears. The neck was short. Fingers and toes were long. Echocardiograms showed a large patent ductus arteriosus and obstructive right ventricular muscle bundle at 70 %. Due to family history of her mother with Marfan syndrome and baby's clinical features of cardiac anomalies and long fingers and toes, *FBN1* gene test for neonatal Marfan syndrome and full gene sequence of *FBN1* were performed (Mayo Clinical Laboratories). A pathogenic variant was not detected in exons 24–32 of *FBN1*gene which has been reported in individual with neonatal Marfan syndrome to harbor mutations in exons 24–32 of the *FBN1* gene. However, one copy of the following mutations was detected in *FBN1*: exon 2, nucleotide c.240dupT, and amino acid p.Ile81Tyrfs*48.This pathogenic FBN1 variant is consistent with Marfan syndrome. In addition, chromosome microarray analysis identified a complex 9p rearrangement, resulting in a terminal deletion from 9p24.3 to 9p22.2, spanning approximately 17.5 megabases. FISH studies using a 9p subtelomere probe (Abbott Molecular) and a probe within the duplicated interval (CTD-2054C7) confirmed the deletion and are consistent with an inverted duplication. Similar complex 9p rearrangements have been reported in patients with developmental delay, intellectual disability, trigonocephaly, facial dysmorphism, hypotonia, and additional phenotypic features (Recalcati et al. 2012; Di Bartolo et al. 2012) (Courtesy of Dr. Lea Bonifacio)

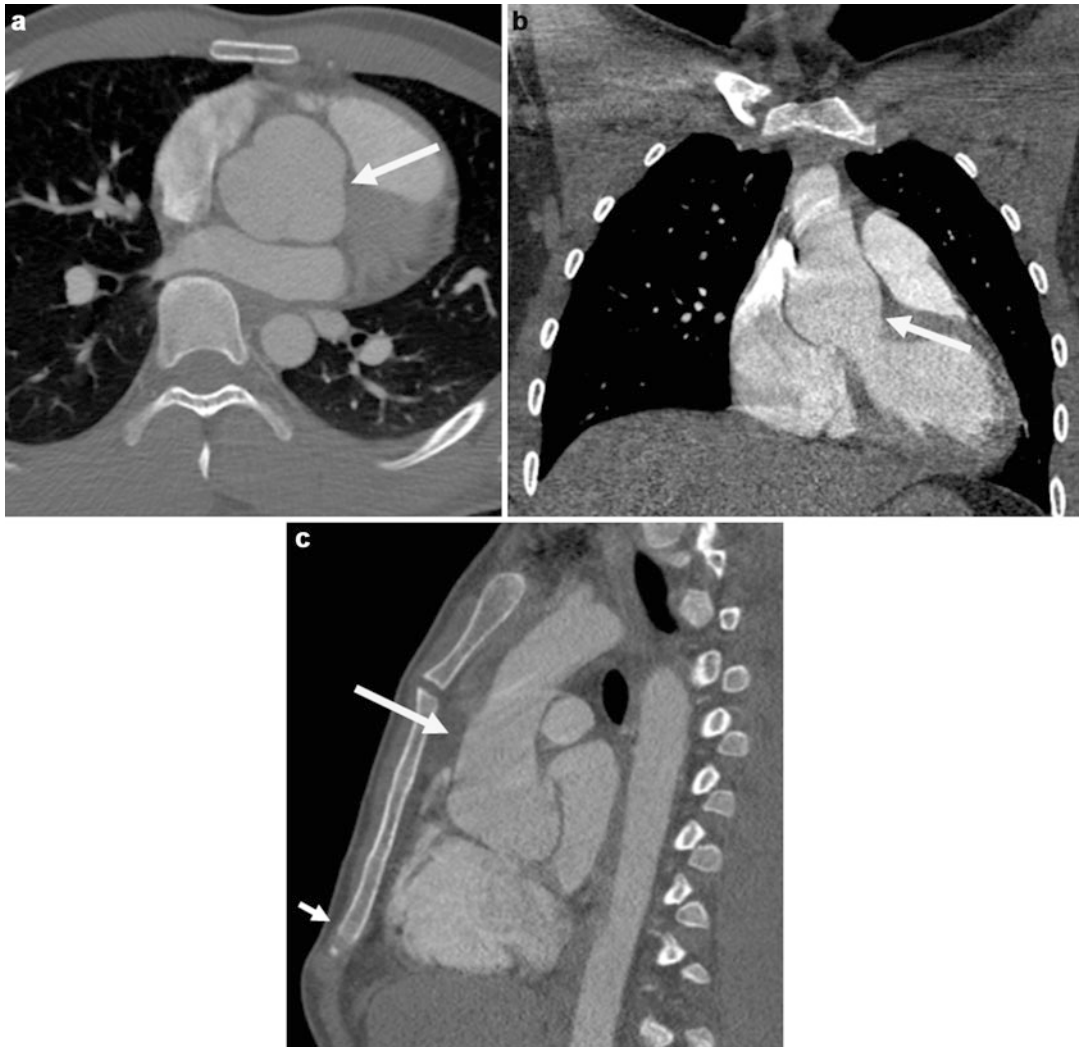


Fig. 17 (**a**–**c**) A 17-year-old male was evaluated because of a history of Marfan syndrome with complaints of headache and tearing back pain. He was noted to have pectus carinatum since birth. Since 12 years of age, he was noted to have flat feet and hyperextensible joints. He wore glasses and was told that he did not have lens dislocation (no ophthalmologic record was available). Previous echocardiogram (not shown) confirmed a markedly dilated aortic root of 3.8 cm (a Z-score of approximately +5.5). There was clover-leafing, also suggesting dilated aortic root. There was mild ascending aorta dilation and trivial mitral valve prolapse. Chest radiographs (not shown) showed a good expansion of left aortic arch and a prominent aortic knob. CT images (**a–c**) showed moderate dilation of the aortic root (*large arrows*) which measured 4.8 × 5 cm in AP and transverse dimensions. No evidence of aortic dissection or pulmonary embolism was noted. Sagittal image (**c**) showed mild pectus carinatum (*small arrow*). He was diagnosed with Marfan Syndrome at 12 years of age. His diagnosis was based on aortic root dilation, skeletal features, and FBN1 mutation (C.2695GG insertion resulting in a frameshift mutation and abnormal mRNA processing). He is now status post valve sparing aortic root replacement. (Courtesy of Dr. Grace Guo)

McCune-Albright Syndrome

Contents

McCune in 1936 described a 9-year-old female with precocious puberty, hyperpigmentation of the skin, and hyperthyroidism (McCune and Bruch 1936). In 1937, Albright published a case series of five females with bone disease, areas of hyperpigmentation, and precocious puberty (Albright et al. 1937). McCune-Albright syndrome (MAS) consists of polyostotic fibrous dysplasia, precocious puberty, café au lait spots, and other endocrinopathies secondary to hyperactivity of various endocrine glands. It is a rare disease with an estimated prevalence between 1/100,000 and 1/1,000,000.

Synonyms and Related Disorders

Albright syndrome; Mazabraud syndrome; Polyostotic fibrous dysplasia

Genetics/Basic Defects

1. Inheritance
    1. A sporadic condition
    2. Lack of genetic transmission in this syndrome
2. Molecular basis (Akintoye et al. 2002)
    1. Caused by a noninherited postzygotic somatic mutations in the guanine nucleotide-binding protein alpha subunit (*GNAS1*) gene coding for the alpha subunit of the stimulatory G protein ($G_s\alpha$) (Spiegel 1997).
    2. Mutations in *GNAS1* result in the constitutive activation of adenyl cyclase, which stimulates the synthesis of cAMP from ATP within cells.
    3. Diseases resulting from constitutive Gsα activity (Turan and Bastepe 2015).
        1. McCune-Albright syndrome
        2. Endocrine and nonendocrine tumors
    4. G proteins.
        1. Central in cell originating pathway leads to the generation of intracellular second messenger, cAMP/protein kinase A signaling (Anitha et al. 2015).
        2. Involved in transmitting hormone signals intracellularly by coupling cell surface receptors to intracellular signaling cascades.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_152

3. Constitutively activated Gs protein stimulates autonomous cell proliferation in skin and bones and hormonal hypersecretion of gonads, hypophysis, thyroid, and adrenal glands.
4. Constitutive activation of these intracellular signaling cascades is caused by the specific mutations in the absence of hormone stimulation.

5. Vast majority of $G_s\alpha$ mutations.
   1. Point mutations at the Arg201 position: associated with severe endocrine and nonendocrine manifestations (Shenker et al. 1993).
   2. Most being Arg201His or Cys
6. Potential mechanism for the development of fibrous dysplasia as a result of $G_s\alpha$ mutation in cells of the osteogenic lineage (Riminucci et al. 1997).
7. An activating $G_s\alpha$ mutation is present in fibrous dysplasia of bone in MAS (Shenker et al. 1994).
8. The term *gsp* oncogene was assigned to these mutations due to their association with certain neoplasms.
9. Presence of somatic mosaicism is reflected by the identification of normal and mutated cells throughout the body (Tinschert et al. 1999).
10. Timing of mutations.
    1. Early in embryogenesis: widespread involvement of the tissue and is likely lethal (accounts for the lack of autosomal dominant transmission of this disorder)
    2. Late in embryogenesis: milder phenotype
    3. Very late in tissue development after differentiation into a specific cell line
       1. Development of a single adenoma
       2. $G_s\alpha$-activating mutations reported in isolated hyperfunctioning thyroid nodules and in somatotroph adenomas

Clinical Features

1. Clinical features (Lee et al. 1986; Boston 2010)
   1. Extremely variable among affected individuals
   2. Consistent with a postzygotic somatic mutational event resulting in a mosaic distribution of the mutation (Weinstein et al. 1991)
   3. Clinical triad (de Sanctis et al. 1999)
      1. Polyostotic fibrous dysplasia
      2. Patchy cutaneous pigmentation (café au lait)
      3. Gonadotropin-independent sexual precocity (Bareille et al. 1999)
2. Endocrine abnormalities (Benedict 1962)
   1. Precocious puberty
      1. The most common endocrine feature and a central hallmark of MAS.
      2. Resulting from gonadotropin-independent autonomous ovarian or testicular function.
      3. Far more commonly observed in girls than boys (>50% of affected girls, only 15% of affected boys).
      4. The signs of puberty (development of breasts, testes, and pubic and axillary hair, body odor, menstrual bleeding, and increased growth rate) may appear before the age of 8 years in girls and 9 1/2 years in boys.
      5. Affected girls.
         1. Breast development or vaginal bleeding as early as 4 months of age
         2. Premature development of secondary sex characteristics (Foster et al. 1986)
         3. Excessive estrogen production, independent of gonadotropin activities, with development of ovarian cysts, sexual precocity, increased growth velocity, and markedly advanced skeletal maturity
      6. Affected boys.
         1. Premature testicular enlargement
         2. Premature spermatogenesis
         3. Premature development of secondary sex characteristics
         4. Macroorchidism (Coutant et al. 2001)
   2. Hyperthyroidism (30%)
      1. The second most commonly associated endocrinopathy
      2. Typically occurring in later childhood but occasionally within the first year of life

3. Primarily due to multinodular toxic goiter
4. Clinical effects
    1. Severe failure to thrive in infants and young children
    2. Decreased attention span
    3. Osteoporosis
    4. Tachycardia

3. Acromegaly/gigantism
    1. Resulting from excess growth hormone secreted by somatotroph adenomas in the pituitary (Bhansali et al. 2003)
    2. Characteristic stigmata
        1. Coarsening of facial features, such as frontal bossing and prognathism
        2. Enlargement of hands and feet
        3. Arthritis
    3. Complications
        1. Glucose intolerance
        2. Hypertriglyceridemia
        3. Hypertension
        4. Mild myopathy
4. Cushing syndrome (Danon et al. 1975)
    1. Adrenocorticotropic hormone (ACTH) independent
    2. Caused by adrenal enlargement and excessive secretion of the adrenal hormone cortisol
    3. Described mostly in infants (Bareille et al. 1999) and children
    4. Clinical signs
        1. Cessation of growth
        2. Poor muscle tone
        3. Obesity of the face and trunk
        4. Weight gain
        5. Skin fragility
        6. Hypertension in infancy
        7. Death possible in long-term untreated hypercortisolism
5. Clinical manifestations related to activating Gsα mutations (Chapurlat and Orcel 2008)
    1. Fibrous dysplasia of bone
    2. Café au lait spots
    3. Endocrine tumors and hypersecretion
        1. Gonadotropin-independent precocious puberty
        2. Testicular tumors
        3. Thyroid nodules and hyperthyroidism
        4. Pituitary tumors (acromegaly, corticotroph adenoma, non-secreting tumors)
        5. Adrenal cortical hyperplasia
        6. Adrenal adenomas with hypercortisolism
        7. Hyperparathyroidism
        8. Isolated premature thelarche
    4. Intramuscular myxomas
    5. Cardiomyopathy, sudden death
    6. Cholestatic liver disease
    7. Thymic hyperplasia
    8. Myelofibrosis
    9. Gastointestinal polyps
3. Nonendocrine abnormalities
    1. Skin pigmentation (café au lait spots)
        1. Flat brown patches of pigmentation with irregular contour (coast of Maine) of varying size.
        2. Frequently evident at birth.
        3. Involved area may be extensive.
    2. Fibrous dysplasia (HD) (Singer 1997)
        1. The invariable component of the syndrome
        2. Bone lesions usually evident by age of 10 years, often presenting with a limp, leg pain, or fractures
        3. Polyostotic in nature
            1. Affecting any bones
            2. Most commonly involving the femur, tibia, pelvis, phalanges, ribs, and the base of the skull
        4. Size and extent of involvement: ranging from small asymptomatic areas to markedly disfiguring lesions resulting in limping deformities
            1. Leg length discrepancy
            2. Coxa vara
            3. Shepherd's crook deformity of the femur (a characteristic sign of the disease)
            4. Bowing of the tibia
            5. Harrison's groove
            6. Protrusio acetabuli
            7. Frequent pathologic fractures
            8. Impingement on vital nerves

5. Craniofacial form
    1. Involvement of mandible (Gurler et al. 1998)
    2. Involvement of orbital and periorbital bones resulting in hypertelorism, cranial asymmetry, facial deformity such as leontiasis ossea, visual impairment, exophthalmos, and blindness
    3. Involvement of the sphenoid wing and temporal bones resulting in vestibular dysfunction, tinnitus, and hearing loss
    4. Involvement of cribriform plate resulting in hyposmia or anosmia
6. Low risk of malignant degeneration (0.4%) (Gross and Montgomery 1967)
7. Sarcoma may develop after radiation of the fibrous dysplasia lesion (Harris et al. 1962)
8. Fibrous dysplasia associated with single or multiple intramuscular or juxtamuscular myxomas (Mazabraud syndrome) (Cabral et al. 1998)

3. Hypophosphatemia
    1. Resulting from decreased reabsorption of phosphate in the renal tubule
    2. Causing rickets and short stature
    3. Normal parathyroid hormone levels
4. Chronic liver disease
    1. Mild cases: mild elevation of hepatic transaminases
    2. Severe cases: neonatal jaundice and chronic cholestasis
5. Persistent tachycardia: rare sudden death presumably due to cardiac arrhythmias
6. Associated malignancies (rare)
    1. Osteosarcomas (most common)
    2. Chondrosarcomas
    3. Fibrosarcomas
    4. Liposarcomas
    5. Breast cancer
    6. Thyroid cancer

4. Differential diagnosis of polyostotic fibrous dysplasia (Muthusamy et al. 2014)
    1. Multiple enchondromatosis (Ollier disease and Maffucci syndrome)
    2. Multiple hereditary exostosis (diaphyseal aclasis)
    3. Paget disease of bone (osteitis deformans)
    4. Skeletal metastases

Diagnostic Investigations

1. Elevated estradiol levels and suppressed or undetectable gonadotropins: diagnostic of gonadotropin-independent precocious puberty (Boston 2010).
2. Suppressed or undetectable levels of LH and FSH after administration of luteinizing hormone-releasing hormone: consistent with the diagnosis.
3. Elevated liver enzymes or hyperbilirubinemia even after normalization of cortisol or thyroxine levels suggests presence of $G_s\alpha$ activating mutations in the liver.
4. Hypophosphatemia (rickets and osteomalacia) results from increased urinary phosphate excretion.
5. Elevated thyroxine levels and suppressed TSH levels: consistent with hyperthyroidism.
6. Generally suppressed ACTH levels despite elevated cortisol levels since the glucocorticoid secretion is ACTH independent.
7. Elevated cortisol levels after dexamethasone suppression test: suggestive of Cushing syndrome.
8. Elevated 24-h urine-free cortisol levels: suggestive of Cushing syndrome.
9. Elevated serum growth hormone and insulin-like growth factor 1 levels in individuals with somatotroph adenomas due to $G_s\alpha$ activating mutations.
10. Biopsy of fibrous dysplasia lesions: can confirm the diagnosis if doubt remains after review of the radiographs.
11. Histology.
    1. Fibrous dysplasia:
        1. Caused by hyperproliferation of preosteoblastic cells
        2. Replacement of normal bones by irregular masses of fibroblasts
    2. Ovarian cyst: generally large, unilateral, and follicular in nature

3. Thyroid nodules: ranging from multinodular hyperplasia to colloid goiter
4. Adrenal hyperplasia
5. Somatotroph adenoma
6. Liver: ranging from normal hepatocytes with some fatty infiltration to focal nodular hyperplasia with fibrosis and chronic cholestasis

12. Pelvic ultrasound to detect ovarian cysts.
13. Isotopic bone scan.
    1. The most sensitive tool for detecting the presence of fibrous dysplasia lesions
    2. To detect asymptomatic fibrous dysplasia sites
    3. Often useful, especially at the initial evaluation, for determining the extent of the disease and predicting functional outcome
14. Skeletal survey (Anand 2011).
    1. Plain radiographs (Dumitrescu and Collins 2008)
        1. Often sufficient to make the diagnosis of fibrous dysplasia.
        2. Plain radiographs, demonstrating the classic ground-glass appearance, are usually sufficient for the diagnosis of fibrous dysplasia in the axial and appendicular skeleton. (The axial skeleton is comprised of bones of the skull, hyoid bone, vertebra, sternum, and ribs; the appendicular skeleton includes the hip, pelvic bone, and the shoulder girdle (clavicle and scapula)).
    2. Advanced skeletal maturation
    3. Premature closure of growth plates resulting in short stature
    4. Polyostotic fibrous dysplasia
        1. Often unilateral
        2. More frequently involved sites
            1. Lower extremities: femur (91%), tibia (81%)
            2. Pelvis (78%)
            3. Skull and facial bones (50%)
            4. Ribs
            5. Upper extremities
            6. Spine
            7. Shoulder girdle
    5. Pathological fractures (up to 85%)
        1. X-rays are often unable to detect new, small microfractures.
        2. When new focal pain develops in a fibrous dysplasia lesion and no fracture is evident on plain radiograph, CT and/or MRI can be useful for detecting subtle fractures.
        3. The classic lesion of the proximal femur in FD, the shepherd's crook deformity, is common.
    6. Long and short tubular bones
        1. Lucent lesions in the diaphysis or metaphysis
            1. With endosteal scalloping
            2. With or without bone expansion
            3. Absence of periosteal reaction
            4. Usually smooth and relatively homogeneous matrix of the lucency, described as a ground-glass appearance
            5. Presence of irregular areas of sclerosis with or without calcification
            6. The ring sign (a lucent lesion with a thick sclerotic border)
        2. Extension of lesions into the epiphysis observed only after fusion
            1. Premature fusion of the ossification centers resulting in adult dwarfism
            2. Dysplastic bone undergoing calcification and endochondral bone formation
    7. Skull and facial bones
        1. Sclerotic skull base. Diffuse sclerosis of the base of the skull often involves the sphenoid, sella turcica, roof of the orbit, thickening of the occiput, and obliteration of the paranasal sinuses.
        2. Mixed radiolucent and radiopaque pattern of maxillary and mandibular bones.
            1. Displacement of the teeth
            2. Distortion of the nasal cavities
    8. Pelvis and ribs
        1. Common cystic lesions characterized by a diffuse ground-glass appearance and ring lesions
        2. Protrusio acetabuli

9. Spine
    1. Well-defined, expansile, and radiolucent lesions with multiple internal septa or striations involving the vertebral body and, occasionally, the pedicles and arches
    2. Kyphotic deformity
    3. Spinal cord compression
    4. Rare paraspinal soft tissue extension and vertebral collapse
10. Radiographic features suggestive of malignant degeneration
    1. A rapid increase in the size of the lesion
    2. A change from a previously mineralized bony lesion to a lytic lesion

15. Radiologic features of fibrous dysplasia (Bousson et al. 2014)
    1. Bones
        1. No bone exempt
        2. Ribs, tubular bones, pelvis, spine
            1. Most frequent benign lesion of the rib
            2. Frequent benign lesion of the proximal femur
        3. Skull base, sphenoid, ethmoid, and frontal and mandibular bones
    2. Distribution
        1. Infrequent solitary involvement of the ilium (affected concomitantly with femur)
        2. Infrequent solitary involvement of the phalanges
        3. Several fibrous dysplasia foci separated by normal osseous tissue within the same bone
        4. Unilateral or predominantly unilateral involvement of a limb; involvement of vertebra and rib in the same metamere
    3. Location in long bones
        1. Diaphysis, metaphysis (femoral neck). Epiphyses usually spared
        2. Central (intramedullary) rather than peripheral
    4. Shape and size
        1. Elongated lesion along the long axis of the bone
        2. Spindle-shaped enlargement of tubular bones and ribs
        3. Curvature of the long bones: humerus, femur. "Shepherd's crook" deformity
        4. Calvarial deformity. Exophthalmos
    5. Margin
        1. Sharp with a well-defined border of sclerotic bone
        2. Expansile: the shell is thick, thin, or very thin with small perforations. No expansion if the lesion is smaller than the internal diameter of the bone
    6. Matrix
        1. Variable aspect, depending on the degree of ossification of the fibrous stroma. All aspects from radio transparent to opaque
        2. Characteristic ground-glass appearance
        3. Pure osteoblastic patterns are rare
        4. Few internal trabeculations
        5. Islands of cartilage occur in 10%
        6. Doughnut-shaped aspect in the cranial vault
        7. Increased uptake by bone scan and FDG PET
    7. Mandatory signs
        1. No soft tissue mass
        2. No lamellar, spiculated, or triangular periosteal reaction
16. Bone scintigraphy: valuable in early detection of the bone lesions (Anitha et al. 2015).
17. CT scan.
    1. CT scan of the skull: the most useful test for diagnosis of craniofacial fibrous dysplasia
    2. CT scan of the abdomen to demonstrate bilateral enlargement of the adrenal glands in infantile Cushing syndrome
18. Whole-body MRI can be used for evaluation and follow-up of polyostotic fibrous dysplasia (Ferreira et al. 2010).
19. Mutation detection (Akintoye et al. 2002).
    1. Standard PCR-based amplification
    2. Followed by sequencing of the appropriate region of the *GNAS1* gene
    3. Targeted sequence analysis of exons 8 and 9 of the GNAS gene: to detect p.Arg201His and p.Arg201Cys (Boyce and Collins 2015)

Genetic Counseling

1. Recurrent risk.
    1. Patient's sib: not increased since MAS is due to a somatic mutation
    2. Patient's offspring: not increased since a germ line-activating mutation in the $G_s\alpha$ gene might be lethal
2. Prenatal diagnosis: As FD/MAS is mosaic and not inherited, prenatal testing is not indicated (Boyce and Collins 2015).
3. Management (Boston 2010).
    1. Precocious puberty
        1. Medical care
            1. Difficulty to treat precocious puberty.
            2. The biosynthetic forms of gonadotropin-releasing hormone such as deslorelin, histrelin, and Lupron which suppress LH and FSH are not effective in most girls with MAS.
            3. Provera, a progesterone-like hormone, for cessation of vaginal bleeding but not effective in slowing the rapid rates of growth and bone development and may have unwanted effects on adrenal functioning.
            4. Ketoconazole, aimed at interrupting adrenal steroid biosynthesis, for cessation of vaginal bleeding.
            5. Testolactone and fadrozole (aromatase inhibitors, to block the conversion of testosterone to estradiol, thus lowering circulating estrogen levels) for halting pubertal progression.
            6. A multicenter trial of tamoxifen (an estrogen agonist/antagonist) treatment of precocious puberty in girls, resulting in a reduction of vaginal bleeding and significant improvements in growth velocity and rate of skeletal maturation (Eugster et al. 2003)
        2. Surgical care: ovarian cystectomy or oophorectomy not typically warranted because of the likelihood of cyst recurrence in residual ovarian tissue
    2. Hyperthyroidism
        1. Medical care: propylthiouracil or methimazole, drugs which block thyroid hormone synthesis, for patients with excessively high thyroid hormone levels
        2. Surgical care: thyroidectomy or hemithyroidectomy for hyperthyroidism associated with a goiter
    3. Infantile Cushing syndrome
        1. Medical care
            1. Treat with drugs that block cortisol synthesis
            2. Adequate adrenal steroid (hydrocortisone, Florinef) replacement after bilateral adrenalectomy
        2. Surgical care: surgical removal of the affected adrenal glands
    4. Acromegaly/gigantism
        1. Medical care: treat with synthetic analogs of the hormone somatostatin to suppress growth hormone secretion (Bhansali et al. 2003)
        2. Surgical care: surgical removal of the area of the pituitary which is secreting the pituitary growth hormone
    5. Early detection and treatment of patients with excess growth hormone to prevent morbidity related to the craniofacial form of the fibrous dysplasia (50% of polyostotic form)
        1. Morbidity
            1. Hearing loss
            2. Blindness
        2. Therapy
            1. Cabergoline
            2. Long-acting octreotide therapy
    6. Hypophosphatemic rickets: treat with oral phosphates, supplement with vitamin D
    7. Fibrous dysplasia
        1. Medical care (Isaia et al. 2002)
            1. Monitor vision and hearing closely if lesions are located near or around the orbits.
            2. Avoid contact sports to minimize the risk of pathologic fractures.
            3. Bisphosphonates used to inhibit bone absorption by osteoclast activity

through apoptosis induction and protein prenylation inhibition.

4. Pamidronate, a second-generation aminobisphosphonate for reduction in bone pain and markers of bone turnover.

2. Surgical care: grafting, pinning, and casting to surgically correct fractures and deformities

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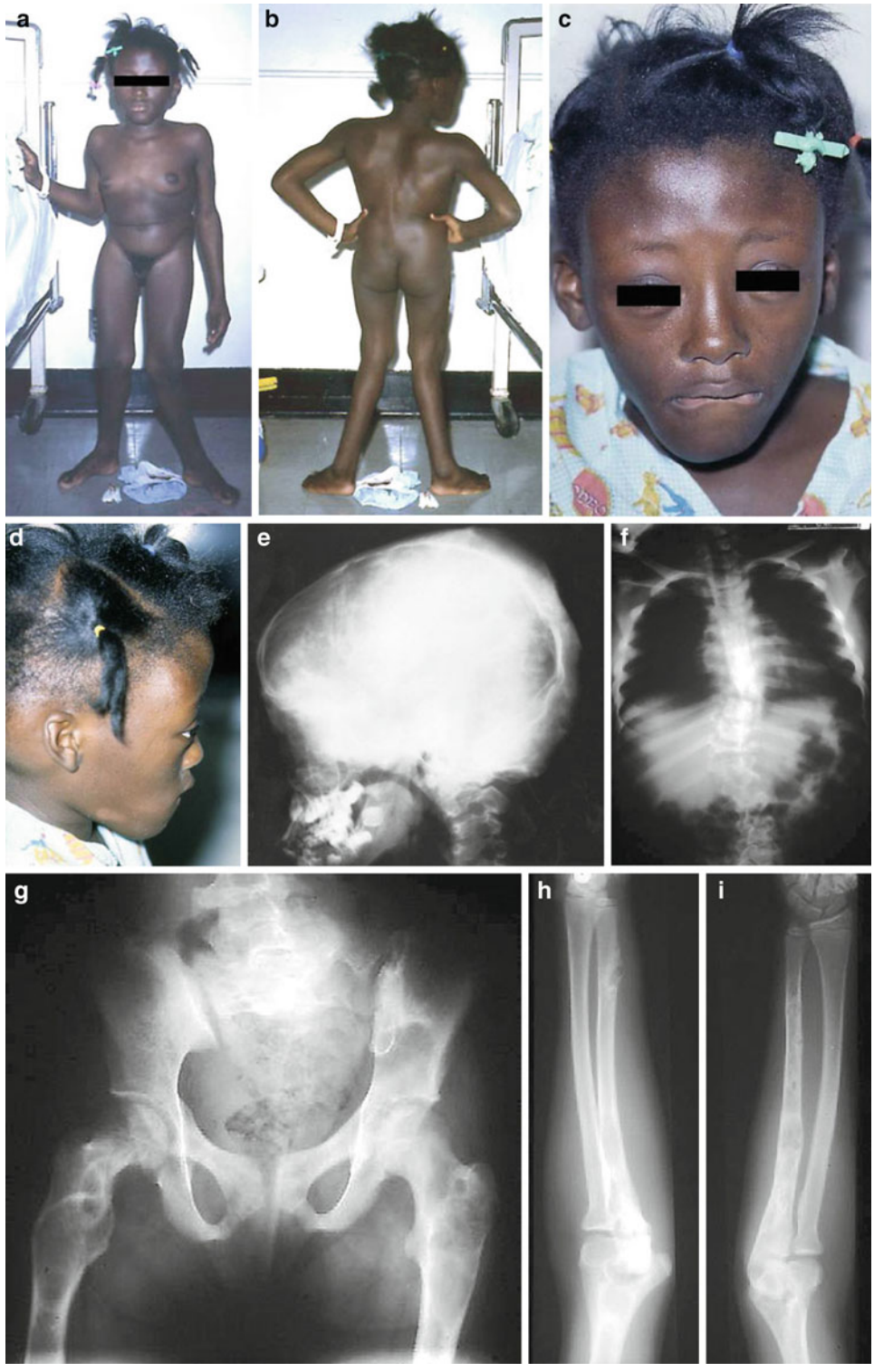

Fig. 1 (**a**–**i**) A girl with McCune-Albright syndrome showing precocious puberty, hyperpigmentation, and fibrous dysplasia affecting many bones shown by radiographs

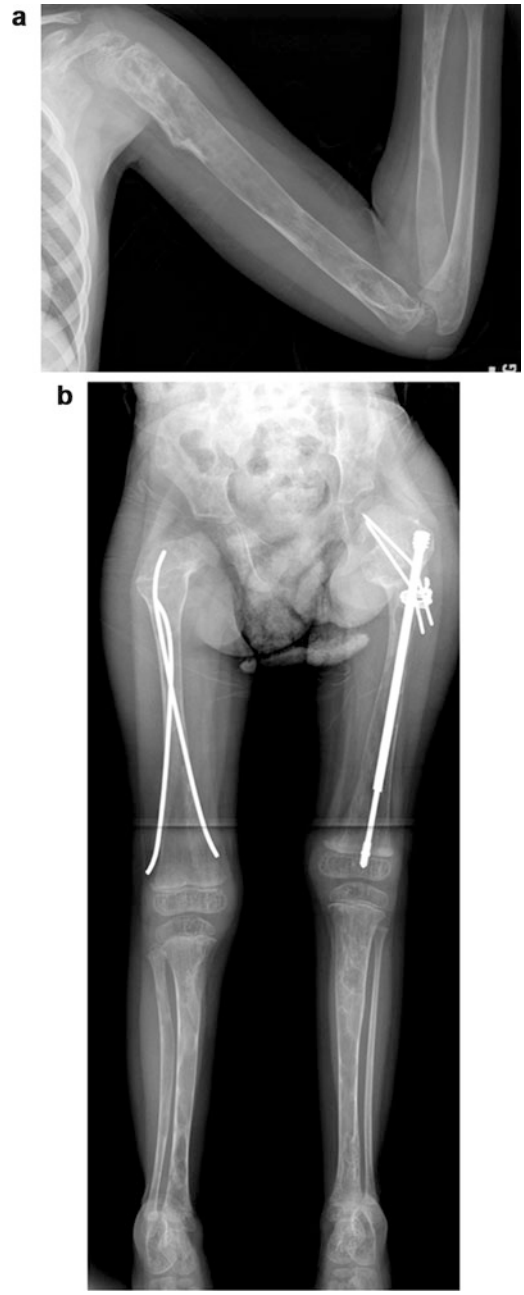

Fig. 2 (**a**, **b**) A 3-year-old female with patchy cutaneous pigmentation (café au lait spots) mainly on her right lower extremity was seen for McCune-Albright syndrome. The radiographs of upper extremities showed both humeri with ground-glass opacities (only left upper extremity is shown here) (**a**). The proximal and mid-humeral shafts were expanded and the cortices were markedly thinned. There was a small area of cortical irregularity with overlying periosteal reaction best appreciated on the second view which suggested a remote fracture. The radiographs of both lower extremities (**b**) showed two intramedullary rods within the right femur and a single intramedullary variable rod within the left femur. Two pins were seen through the left femoral neck. There was extensive expansion of the intertrochanteric region on the left side and slight varus configuration on the right side with mild expansion of the intertrochanteric region. There was diffuse osteopenia. Ground-glass density was present in both tibiae and fibula bilaterally, consistent with patient's history of polyostotic fibrous dysplasia (Courtesy of Dr. Grace Guo)

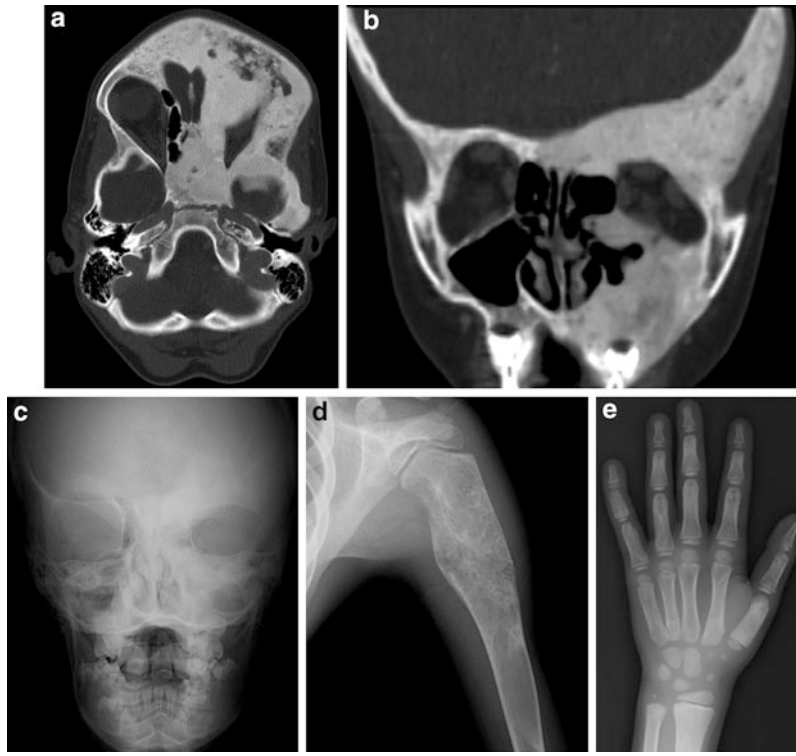

Fig. 3 (a-e) A boy has a diagnosis of McCune–Albright syndrome with polyostotic fibrous dysplasia and multiple cafe au lait spots with jagged borders and freckling. At age 6, head CT images (a, b) showed diffuse ground glass density, expansile bone lesion present in the high left parietal and left frontotemporal region. It involved the entire left the sphenoid bone, maxillary bone, superior bilateral nasal bones. It also extended into the anterior aspect of bilateral ethmoid sinuses as well as bilateral sphenoid sinuses. Posterior portion of the left orbital space was decreased due to surrounding bone lesion. At age 8, skeletal bone survey showed diffuse calvarial thickening in the left parietal bone. There was also marked thickening with ground glass density involving the left frontal bone and the skull base on the left. Involvement extended into the ethmoid sinuses (c). Expansile ground glass lesion involves the proximal half of the left humerus (d), and metacarpals and multiple phalanges (e) (Courtesy of Dr. Grace Guo)

Meckel-Gruber Syndrome

Contents

Meckel-Gruber syndrome (MKS) is a rare, lethal, and autosomal recessive disorder, characterized by occipital encephalocele, cystic dysplastic kidneys, and postaxial polydactyly. The incidence is estimated to be 1/13,250 (in USA) and 1/149,000 (in Great Britain) live births. The incidence in North African and Finnish populations is much higher at 1/3,500 and 1/9,000 (Salonen and Norio 1984), respectively. Meckel-Gruber syndrome is considered the most frequent syndromic cause of neural tube defects (Paetau et al. 1985; Morgan et al. 2002).

Synonyms and Related Disorders

Ciliopathies (Nephronophthisis, Jubert syndrome); Dysencephalia splanchnocystica; Gruber syndrome; Meckel syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Hsia et al. 1971)
2. Genetic (locus) heterogeneity (Paavola et al. 1997; Morgan et al. 2002; Jayakar et al. 2011; Szymanska et al. 2012; Barisic et al. 2014)
    1. *MKS1* locus to 17q21-24 in Finnish kindreds (Paavola et al. 1995; Roume et al. 1997; Salonen and Paavola 1998)
    2. *MKS2* locus to 11q13 in North African-Middle Eastern cohorts (Roume et al. 1998)
    3. *MKS3* to 8q21.3-q22.1 in Indian subcontinent cohorts: *MKS3* mutation also causes Jubert syndrome (Baala et al. 2007)
    4. *MKS4* to 12q21.31-q21.33 in a Kosovar Albanian family with two affected male fetuses
    5. *MKS5* to 16q12.2
    6. *MKS6* to 4p15.3 in 11 Finnish families
    7. *MKS7* to 3q21 (*NPHP3* gene)
    8. *MKS8* to 12q24.31 (*TCTN2* gene)
    9. *MKS9* to 17p11.2 (*B9D1* gene)
    10. *MKS10* (*B9D2* gene)
    11. *MKS11* (TMEM231 gene)
    12. Known MKS loci account for the overwhelming majority of MKS cases but additional loci exist including MKS13

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_153

caused by TMEM107 mutation (Shaheen et al. 2015)
13. Report of the first MKS patients with TMEM231 mutations, combined with the recent identification of TMEM231 mutations in Joubert syndrome, confirms the designation of TMEM231 as a ciliopathy gene with variable phenotypic consequences (Shaheen et al. 2013)

3. The ciliopathies (Barker et al. 2014)
   1. Ciliopathies share many clinical features, with renal, retinal, and hepatic involvement frequently observed alongside skeletal malformations and central nervous system developmental defects. The most severe are lethal in the early gestation or neonatal periods (Adams et al. 2008).
   2. While many genes are associated with a single ciliopathy, mutation in others can give rise to a number of clinically different outcomes. For example, there is substantial overlap in the underlying genetic basis of the kidney disorder nephronophthisis (NPHP), the neurodevelopmental disorder Joubert syndrome (JBTS), and the lethal malformation disorder Meckel-Gruber syndrome (MKS) even though the clinical presentation of the three diseases varies considerably and genotype-phenotype correlations are frequently unclear (Coppieters et al. 2010).

Clinical Features

1. Phenotypic variability (Seller 1981; Farag et al. 1990; Wright et al. 1994)
2. Major clinical features (Alexiev et al. 2006)
   1. Clinical triad (Nyberg et al. 1990)
      1. Occipital encephalocele (85%)
         1. Extrusion of rhombic roof elements (cerebellar vermis, caudal third ventricle, distended fourth ventricle) through a widened posterior fontanelle
         2. Protruding CNS structures covered by a dural sac
         3. Medial occipital cortex occasionally included in the sac formed by the dilated caudal third ventricle
      2. Dysplastic cystic kidneys (100%)
         1. Result in oligohydramnios
         2. Lead to fetal pulmonary hypoplasia
      3. Postaxial polydactyly (55%)
   2. Microcephaly
   3. Oral clefts
      1. Cleft lip
      2. Cleft palate
   4. Liver fibrosis (Salonen 1984)
   5. Ambiguous genitalia
3. Other clinical features
   1. CNS abnormalities
      1. Absent olfactory lobe
      2. Absent pituitary gland (hypopituitarism)
      3. Hydrocephalus
      4. Dandy-Walker malformation
   2. Craniofacial features
      1. Sloping forehead
      2. Microphthalmia/anophthalmia
      3. Micrognathia
      4. Malformed tongue
      5. Abnormal ears
   3. Short neck
   4. Hypoplastic thyroid
   5. Congenital heart defect
   6. Gastrointestinal abnormalities
      1. Omphalocele
      2. Malrotated bowel
      3. Fibrotic or cystic liver
   7. Absent or small adrenals
   8. Accessory spleen
   9. Urinary tract anomalies
   10. Short limbs
   11. Abnormal palmar creases
   12. Club feet
   13. Syndactyly
4. Lethal outcome
   1. Abortions
   2. Stillborns
   3. Neonatal deaths
   4. Rare survivals till 2 years of age

Diagnostic Investigations

1. Ultrasonography
    1. CNS anomalies
    2. Cystic dysplastic kidneys
2. MRI of the brain for CNS anomalies
3. Echocardiography for congenital heart defect
4. Radiography (Seppänen and Herva 1983; Kjaer et al. 1999)
    1. Microcephaly with an occipital bone defect and encephalocele or hydrocephaly
    2. Malformations of the cranial base (basilar part of the occipital bone or the postsphenoid bone)
    3. Short upper extremities
    4. Bell-shaped thorax with abdominal distension
    5. Cleft vertebral bodies in the lumbar region of the spine
    6. Postaxial polydactyly in the hands and feet
5. Necropsy
    1. Renal anomalies
        1. Cystic dysplastic kidneys
        2. Hypoplastic kidneys/ureters/bladder
        3. Rectovesical fistula
    2. Triad of CNS malformations (Herman and Siegel 1996)
        1. Prosencephalic dysgenesis (Ahdab-Barmada and Claassen 1990)
            1. Agenesis of olfactory bulbs and tracts (arhinencephaly)
            2. Complete holoprosencephaly
            3. Hypoplasia of optic nerves and chiasm
            4. Microphthalmia
            5. Agenesis of the corpus callosum
            6. Fused thalami
            7. Hypoplasia of the third ventricle
            8. Small or absent pituitary gland
            9. Microcephaly
            10. Cleft/high arched palate
            11. Micrognathia
        2. Occipital encephalocele
            1. Displacement of rhombic roof elements including caudal third ventricle, cerebellar vermis, and fourth ventricle
            2. Extruded through an enlarged posterior fontanelle rather than through an occipital cranium bifidum
            3. Often associated with a variant of Dandy-Walker cyst with Chiari malformation
        3. Rhombic roof dysgenesis
            1. Absent brain stem tectum
            2. Agenesis/dysgenesis cerebellar vermis
            3. Elongated brain stem
            4. Aqueduct stenosis
    3. Histologic features of the CNS (Paetau et al. 1985)
        1. Polymicrogyria
        2. Heterotopias
        3. Characteristic neuroepithelial rosettes
    4. Hepatic dysgenesis (Blankenberg et al. 1987)
        1. Consistent features
        2. Arrested development of the intrahepatic biliary system
            1. Reactive biliary bile duct proliferation
            2. Bile duct dilatation
            3. Portal fibrovascular proliferation
    5. Lung hypoplasia
    6. Gastrointestinal anomalies
        1. Pancreatic cyst
        2. Malrotated bowel
        3. Anal atresia
    7. Genital anomalies
        1. Hypoplastic genitalia
        2. Bicornuate uterus
        3. Persistent urogenital sinus
6. Next-generation sequencing (Jones et al. 2014): detected mutations in *CC2D2A* (*MKS6*) (known to cause MKS and Joubert syndrome)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25%

2. Patient's offspring: not surviving to reproductive age

2. Prenatal diagnosis
   1. Ultrasonography (Friedrich et al. 1979; Braithwaite and Economides 1995): diagnosis more difficult in the second trimester because of oligohydramnios secondary to poor renal output impairing visualization. However, 1st trimester diagnosis has been made (Jones et al. 2014).
      1. Occipital encephalocele
      2. Renal anomalies (large cystic kidneys, renal agenesis, renal hypoplasia, and ureteral duplication)
      3. Postaxial polydactyly
      4. Oligohydramnios
      5. Dandy-Walker malformation
      6. Cerebellar hypoplasia
   2. MRI, a valuable complement to ultrasonography in assessing fetal anomalies in the presence of severe oligohydramnios
   3. Elevated serum α-fetoprotein
   4. Amniocentesis
      1. Elevated amniotic fluid α-fetoprotein (Nevin et al. 1979; Johnson and Holzwarth 1984)
      2. Normal karyotype
   5. Preimplantation genetic diagnosis reported in a Chinese family with autosomal recessive Meckel-Gruber syndrome type 3 (MKS3) (Lu et al. 2013)

3. Management
   1. No specific treatment
   2. Supportive care for lethal cases
   3. Operative excision of a small encephalocele
   4. Ventriculoperitoneal shunt for hydrocephalus

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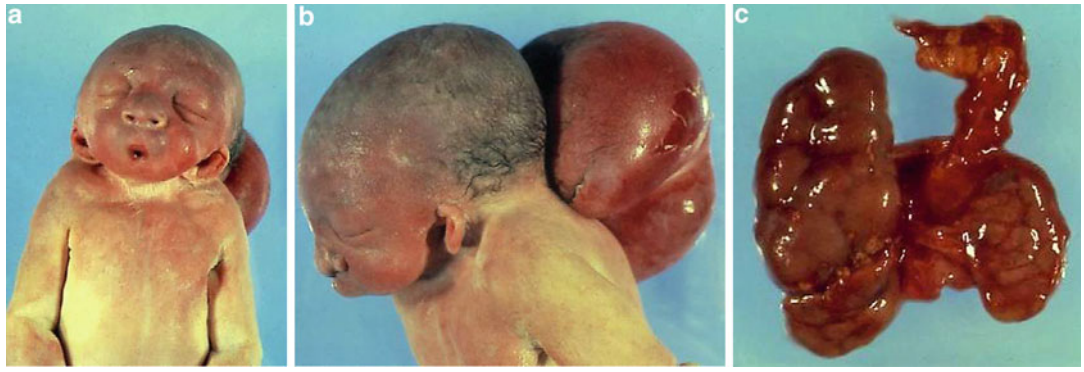

Fig. 1 (**a**–**c**) A neonate with Meckel-Gruber syndrome showing a large occipital encephalocele, microcephaly, sloping forehead, micrognathia/retrognathia, low-set malformed ears, and short neck (**a**, **b**). The infant also had post-axial polydactylies. Necropsy showed unilateral renal dysgenesis. Contralateral renal cystic dysplasia was present (**c**)

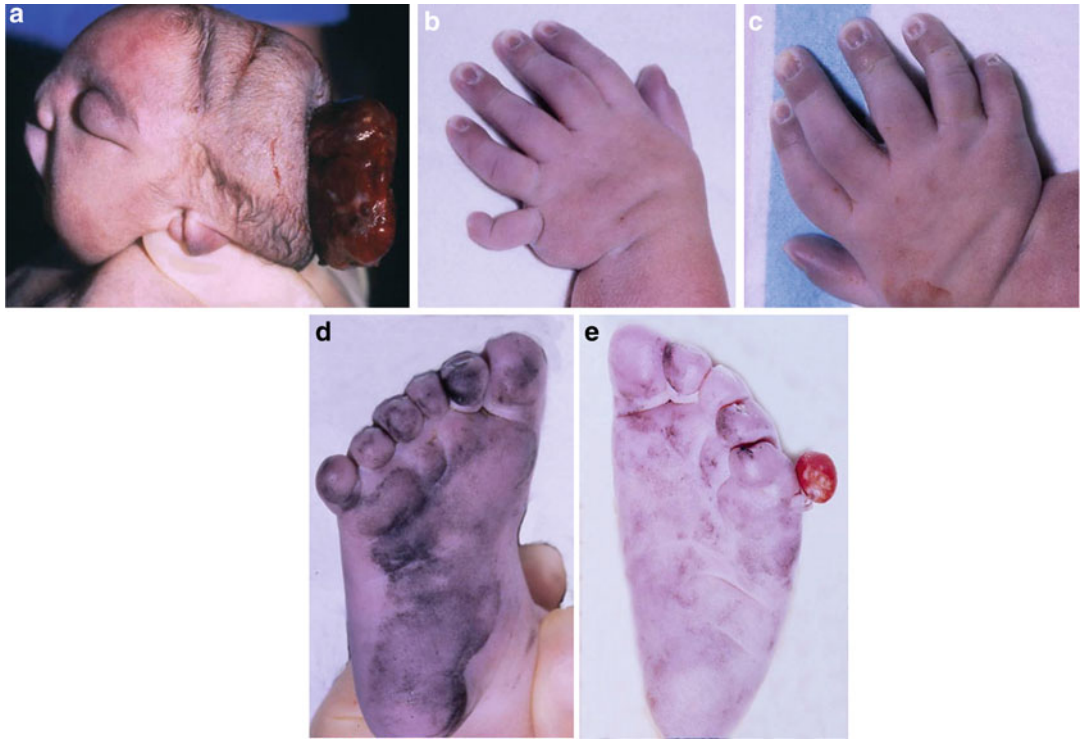

Fig. 2 (**a**–**e**) Another neonate with Meckel-Gruber syndrome showing a large occipital encephalocele, microcephaly, sloping forehead, micrognathia/retrognathia, low-set malformed ears, short neck, (**a**) and post-axial polydactylies (**b**–**e**)

Megalencephalic Leukoencephalopathy with Subcortical Cysts

Contents

In 1995, van der Knaap et al. (1995) described a syndrome of cerebral leukoencephalopathy and megalencephaly with infantile onset in eight children, including two siblings. These children had normal or near-normal neurologic status despite evidence of severe white matter disease. The syndrome is currently termed megalencephalic leukoencephalopathy with subcortical cysts (MLC).

Synonyms and Related Disorders

Vacuolating megalencephalic leukoencephalopathy with subcortical cysts; Van der Knaap disease/leukoencephalopathy

Genetics/Basic Defects

1. A heterogeneous neurodegenerative leukodystrophy (Arnedo et al. 2014):
    1. About 75% of MLC patients have an autosomal recessive inheritance with mutations in the *MLC1* gene (MLC1) that encodes a putative membrane protein, expressed mainly in the brain at distal astrocyte junctions, nearby the cerebrospinal fluid–brain barrier and the glial limiting membrane.
    2. Only, recently, a second gene, *HEPACAM* (*GLIALCAM*, hepatic and glial cell adhesion molecule), was discovered through a combination of proteomics and genetic approaches and found to be responsible for the disease, confirming genetic heterogeneity, not only in terms of an additional gene but also in terms of inheritance.
    3. Patients with recessive mutations in *GLIALCAM* gene (MLC2A) presented a classical MLC phenotype, overlapping with the clinical presentation of *MLC1* gene-mutated patients.
    4. Patients with dominant mutations in the *GLIALCAM* gene (MLC2B) are always preceded by signs of MLC and, thereafter, are associated with various degrees of phenotypic expression, ranging from benign familial macrocephaly to macrocephaly–mental retardation with or without autism.
2. An autosomal recessive disorder suggested by parental consanguinity and affected siblings (Goutieres et al. 1996).
3. Caused by mutation in the *MLC1* gene which is expressed predominantly in astrocytes, located

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on 22 qt13.33, encoding a putative membrane protein with eight predicted transmembrane domains (Leegwater et al. 2001).
4. Megalencephalic leukoencephalopathy with subcortical cysts protein-1 regulates epidermal growth factor receptor signaling in astrocytes (Lanciotti et al. 2016).
5. Genetically determined homozygous or compound heterozygous cases have been documented in almost all racial groups throughout the world and in both sexes equally.
6. Although the disease is considered rare, a higher frequency is observed in populations where consanguinity remains a common cultural practice:
    1. Indian Agarwal megalencephalic leukodystrophy with cysts is caused by a common MLC1 mutation (320insC) (Gorospe et al. 2004).
    2. Among the Agarwals of India, almost all documented cases test positive for a homozygous insertional mutation (135insC) owing to founder effect (Singhal et al. 2003).
    3. G59E mutation appears to be common among Libyan Jews (Ben-Zeev et al. 2002).
    4. S93L mutation appears to be somewhat among the Japanese (Saijo et al. 2003; Tsujino et al. 2003).
    5. MLC is relatively common in Iranian population, as expected for rare diseases with high inbreeding, with a surprisingly high frequency of novel mutations (Karimineja d et al. 2015).
    6. Autosomal recessive inheritance pattern and clinical variability of MLC in Egyptian patients (Mahmoud et al. 2014).
7. Marked clinical intrafamilial and interfamilial variability in mutation-proven cases and genetic heterogeneity (Blattner et al. 2003; Patrono et al. 2003).
8. A broad spectrum of pathogenetic mutations (missense, splice site, insertion, and deletions) identified in the *MLC1* gene, enlarging the spectrum of allelic variants without a straightforward genotype–phenotype correlation.

Clinical Features

1. Clinical findings of 122 patients reviewed by Riel-Romero et al. (2005):
    1. Clinical presentation:
        1. Accelerated head growth beginning in the first year of life, resulting in extreme macrocephaly (48%)
        2. Mild developmental delay (25%)
    2. Gradually increasing spasticity (pyramidal findings) (86%) and ataxia (78%)
    3. Seizures (66%) (Van der Knaap et al. 1995)
    4. Loss of ambulation (38%)
    5. Dysarthria (15%)
    6. Hypotonia (11%)
    7. Dysmetria (9%)
    8. Tremor (7%)
    9. Dystonia (5%)
    10. Dysphagia (5%)
    11. Choreoathetosis (3%)
2. Clinical course: although progressive in its nature, MLC is characterized by a relatively mild clinical course (discrepantly mild cognitive impairment) compared with the severity of the neuroradiological findings (Van der Knaap et al. 1995).
3. Differential diagnosis (Van der Knaap and Scheper 2011; Koç et al. 2015): infantile megalencephalic leukoencephalopathies (neurologic disorders characterized by progressive deterioration and severe impairment of neurological function resulting in marked disability and a shortened lifespan, leukodystrophic changes on neuroimaging, and megalencephaly):
    1. Alexander disease:
        1. A rare neurological disorder that follows a progressive and usually fatal course
        2. Does not share the relatively benign course of MLC
        3. The most common infantile form: characterized by loss of developmental milestones, inexorable psychomotor retardation, megalencephaly, spasticity, seizures, ataxia, hyperreflexia, and

pyramidal signs, with a lifespan of a few months to early childhood
4. Considered a leukodystrophy because myelin changes are invariably observed while sparing the axons
5. *GFAP* as the causative gene for Alexander disease
6. Magnetic resonance imaging (MRI) findings:
1. Abnormal enhancement of caudate nuclei, anterior columns of the fornices, and periventricular areas
2. Frequent hydrocephalus
3. Cavitations in the frontal deep white matter

2. Canavan disease:
1. Does not share the relatively benign course of MLC.
2. MRI findings: frequent involvement of the globus pallidus and thalami which are not involved in MLC.
3. The white matter may be cystic in Canavan disease, but the typical subcortical cysts seen in MLC are lacking.
4. *N*-Acetylaspartate is elevated in urine and blood.
5. Deficiency of the enzyme aspartoacylase can be demonstrated in cultured fibroblasts.

3. Glutaric aciduria I: the presence of biochemical abnormalities (glutaric acid, 3-OH-glutaric acid in the urine, glutarylcarnitine in the blood)
4. Laminin alpha-2 deficiency:
1. Most closely resembles that observed in MLC.
2. However, the typical subcortical cysts are generally lacking (van der Knaap et al. 1997). In addition, individuals with laminin alpha-2 deficiency have prominent weakness and hypotonia, not shared by individuals with MLC. The diagnosis can be confirmed with molecular genetic testing.

4. Other differential diagnosis (Van der Knaap and Scheper 2011):
1. Merosin-deficient congenital muscular dystrophy:
1. Typical subcortical cysts are generally lacking, although the white matter disease most clearly resembles that observed in MLC.
2. Prominent weakness and hypotonia in affected individuals, not shared by individuals with MLC.
3. Diagnosis: confirmed using muscle biopsy and staining for merosin.

2. Infantile GM gangliosidosis:
1. Infantile GM1 gangliosidosis:
1. MRI features in infantile GM1 gangliosidosis: very similar to those of GM2 gangliosidosis.
2. Demonstration of deficiency of beta-galactosidase activity in leukocytes or cultured fibroblasts confirms the diagnosis.

2. Infantile GM2 gangliosidosis:
1. MRI: characterized by prominent involvement of the basal ganglia and thalami in addition to the white matter abnormalities
2. Definitive diagnosis: established by assaying hexosaminidase A and B in serum, leukocytes, or cultured skin fibroblasts

Diagnostic Investigations

1. Brain imaging (CT, MRI) (Mejaski-Bosnjak et al. 1997):
1. Diffusely abnormal and swollen white matter of the cerebral hemispheres
2. The presence of subcortical cysts in the anterior temporal and frontoparietal region with preservation of gray matter structures

2. Brain MRI (Leegwater et al. 2002; Zukić et al. 2016):
1. "Swollen white matter" and diffuse supratentorial symmetrical white matter changes in the cerebral hemispheres, with relative sparing of central white matter structures, such as the corpus callosum, internal capsule, and the brain stem.

2. Subcortical cysts are almost always present in the anterior temporal region and are also frequently noted in the frontoparietal region.
3. The white matter swelling gradually decreases and cerebral atrophy may ensue.
4. The subcortical cysts may increase in size and number (Rajagopal et al. 2006).

3. Quantitative proton MRS (MR spectroscopy) (Brockmann et al. 2003):
   1. Underlines the MRI evidence of a white matter disorder without cortical involvement.
   2. Quantitative localized proton MR spectroscopy of white matter revealed marked reduction of *N*-acetylaspartate, creatine, and choline with normal values for myoinositol, consistent with axonal loss and astrocytic proliferation.
4. Technetium-99 m ethyl cysteinate dimer SPECT (Kiriyama et al. 2007):
   1. Hypoperfusion in the cerebral white matter (shown high signal intensity on magnetic resonance imaging (MRI) T2 images).
   2. Hypoperfusion found unexpectedly in the frontal cortices (corresponded clinically to a low score on the frontal assessment battery), which showed no abnormalities on MRI.
   3. Decreased GABA receptor density as suggested by ^{123}I-iomazenil SPECT provided further evidence of cortical neuron dysfunction.
   4. Findings suggest that SPECT can be used to noninvasively monitor in vivo cortical function in this disease.
5. Histopathology:
   1. Splitting of the outer most lamellae of the myelin sheaths consistent with an edematous process, with sparing of the axons
   2. Cavitating spongiform leukoencephalopathy with vacuoles in the outermost lamellae of myelin sheaths
   3. Intense fibrillary astrogliosis of subcortical white matter with well-preserved myelinated axons
   4. Normal cortical neuronal structure
6. Molecular genetic testing:
   1. *MLC1* gene mutation determination clinically available.
   2. Sequence analysis of *MLC1* gene mutations detects approximately 70% of cases whose MRI and clinical picture are consistent with the diagnosis of MLC, implying that at least one other gene may be responsible for the remaining 30% of cases.

Genetic Counseling

1. Recurrence risk for autosomal recessive inheritance:
   1. Patient's sib:
      1. Twenty-five percent chance of inheriting both mutation alleles and being affected
      2. Two thirds chance of being carriers in unaffected sibs
   2. Patient's offspring: recurrence risk not increased unless the spouse is a carrier, in which case 50% of offspring will be affected; otherwise, all offspring of the affected parent will be carriers who will be asymptomatic.
2. Prenatal diagnosis for pregnancies at increased risk and carrier testing for relatives at risk: possible if both *MLC1* disease-causing alleles have been identified in the family:
   1. Prenatal diagnosis of MLC in two families of Agarwal community in India in whom the affected children were positive for this common mutation (c.135 136insC) by restriction fragment length polymorphism using chorionic villi (CV) sample at 12 weeks of gestation (Shukla et al. 2008).
   2. After molecular confirmation of the disease, molecular prenatal diagnosis in the 11th week of pregnancy on DNA extracted from CVS: the fetus was heterozygous and also a carrier for the novel deletion in the *MLC1* gene (Shariati et al. 2015).
3. Management: largely supportive
   1. Antiepileptic drugs for seizure control
   2. Physical therapy to improve motor function
   3. Occupational therapy

4. Speech therapy as needed
5. Special education
6. Antibiotic treatment for infections
7. Attention to general care and nutritional requirements
8. Prevention of head trauma: protective helmet suggested

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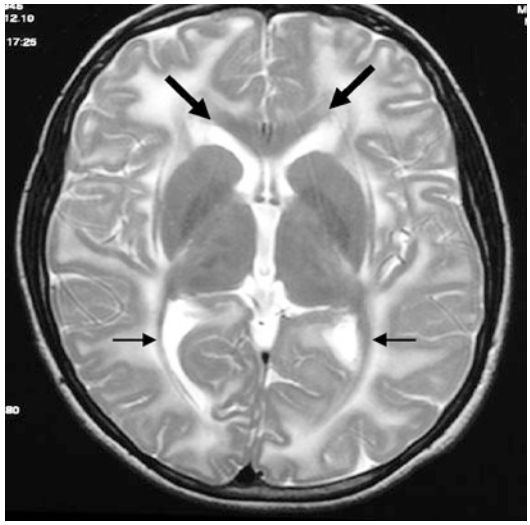

Fig. 1 A 15-year-old Caucasian female was evaluated for megalencephaly and possible leukodystrophy. Early developmental status was normal except for the presence of macrocephaly. She had a bicycle accident with trauma to her head, followed by a generalized tonic–clonic seizure 7 months later. At 15 years of age, she had striking macrocephaly (head circumference of 65 cm), receiving special education, and was found to have mild bilateral clonus axial T1-weighted scan that demonstrates hyperintensity throughout cerebral white matter with sparing of the genu of the corpus callosum (*large arrowheads*), middle portion of the internal capsule, and the geniculocalcarine tracts (*small arrows*). Sequence analysis of the *MLC1* gene revealed two novel mutations. One mutation was inherited from the mother and was characterized by the substitution of adenine for guanine at nucleotide position 366 in exon 3. This mutation resulted in a change in the corresponding amino acid from arginine to histidine at amino acid position 84 (R84H). The other mutation was inherited from her father; it is in the canonical splicing site following exon 5 (538 + 1 g → a) and is expected to cause the transcription of a variant messenger ribonucleic acid (RNA) that can be translated into an altered protein. A 12-year-old brother was noted to have macrocephaly, seizures, significant learning difficulty, behavioral problems, increasing difficulty in ambulation, hyperreflexia, spasticity with positive Babinski reflexes, sustained clonus, and difficulty with tandem gait. His MRI showed a markedly increased T2-weighted signal throughout the supratentorial white matter with cysts in both temporal lobes in a pattern virtually identical to his sister's. Sequencing of the MLC1 gene revealed the same mutations identical to his older sister (Courtesy of Dr. DMS Riel-Romero)

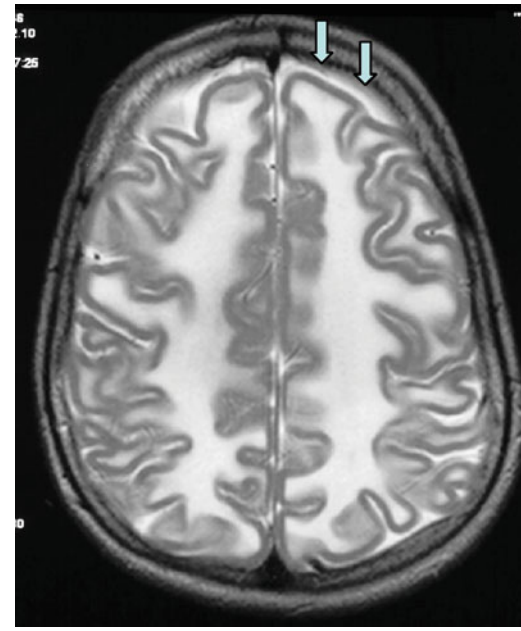

Fig. 2 Axial T-weighted scan at a more rostral level shows that the cortical U fibers are also hyperintense and therefore not spared (*arrows*)

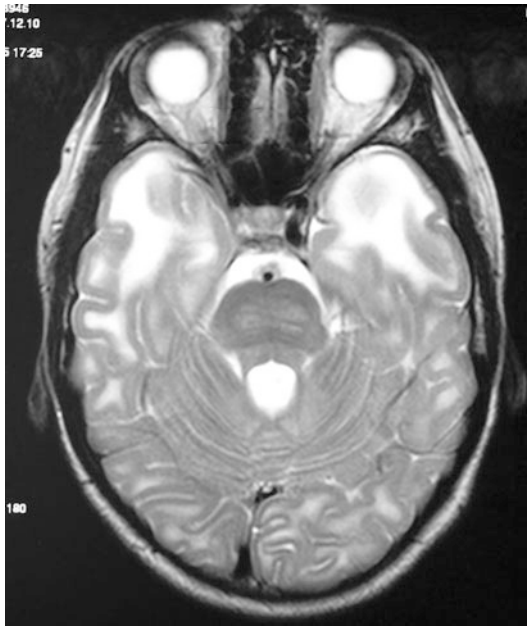

Fig. 3 Anterior temporal regions show homogeneous white matter hyperintensity within the cysts, which expand and smooth the convolutions of the temporal poles – typical findings in megalencephalic leukoencephalopathy with subcortical cysts

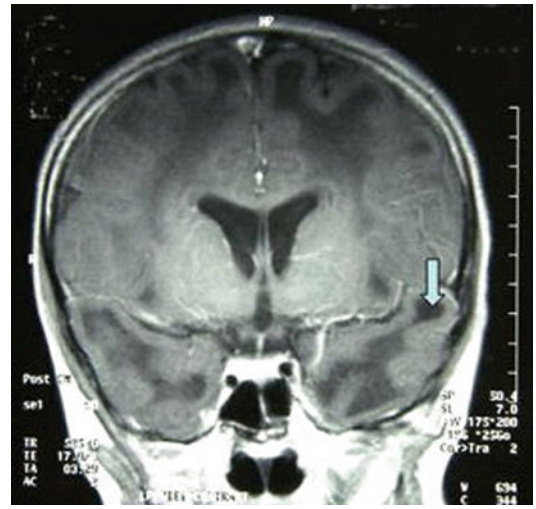

Fig. 4 Gadolinium-enhanced T-weighted coronal slice through the anterior temporal lobes demonstrates the absence of abnormal enhancement in the white matter or elsewhere and hypointensity within a subcortical cyst (*arrowhead*)

Menkes Disease

Contents

Menkes and colleagues described Menkes disease in 1962 that reported five male infants in a family affected with a distinctive syndrome of neurologic degeneration, peculiar hair, and failure to thrive. Menkes disease is also called "kinky or steely hair disease." The incidence of MK was originally estimated to be 1/35,000 (Danks et al. 1972), but more recent estimates have shown it to be a very rare disorder with 1/300,000 live-born babies affected (Tönnesen et al. 1991, 1992).

Synonyms and Related Disorders

ATP7A-related copper transport disorders; ATP-related distal motor neuropathy; Kinky hair disease (Menkes 1972); Occipital horn syndrome

Genetics/Basic Defects

1. Inheritance:
    1. An X-linked recessive disorder of copper metabolism (Tümor 1998):
        1. Recognized to segregate as an X-linked recessive trait (Menkes et al. 1962)
        2. Observation of two different cell populations (normal fibroblasts and mutant cells with increased copper accumulation) in cultured fibroblasts of female Menkes carriers, suggesting that the Menkes disease gene was subject to random X-inactivation and also confirming the X-linked recessive inheritance of the disease
    2. New mutations in one third of cases
2. Menkes gene mapped to chromosome Xq13.3:
    1. Physical evidence of the location of the Menkes disease gene (*ATP7A*, *MNK*) suggested by observation of a female patient with a de novo balanced X:2 translocation (X breakpoint at Xq13) and a male patient with X chromosome rearrangements with a breakpoint at Xq13.3 (Kodama and Murata 1999).
    2. The Xq13.3 breakpoint subsequently shown to be at the *MNK* locus by fluorescence in situ hybridization (FISH) analyses.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_155

3. MNK belongs to a large family of cation-transporting P-type ATPases.
4. Studies on a male patient with an intrachromosomal insertion, resulting in 46,Y,ins(X)(p11.4q13.3q21)mat, detected during a systematic screening of 180 unrelated MK patients, helped in the localization and cloning of the gene (Tommerup et al. 1993; Tümor et al. 1992).

3. Cause: Mutations in *ATP7A* gene (Gu et al. 2001), which encodes a transmembrane copper-transporting P-type adenosine triphosphatase (ATPase) protein, leading to deficiencies of copper absorption in intestinal absorption and in intracellular processing of copper in the central nervous system and connective tissues, whereby enzymes requiring copper as a cofactor no longer function properly.
4. The genes for two copper-transporting ATPases, ATP7A and ATP7B, are defective in the heritable disorders of copper imbalance, Menkes disease (MNK) and Wilson disease (WND), respectively (Menkes 1999; His and Cox 2004).
5. Mutation spectrum:
   1. Cytogenetic abnormalities (Tümor 1998):
      1. Visible cytogenetic abnormalities comprising about 1% of the underlying genetic defect in Menkes disease
      2. Four female patients reported to have balanced X-autosomal translocations (Abusaad et al. 1999):
         1. The first patient with a de novo t (X;2) (Kapur et al. 1987) with a breakpoint at Xq13.3 (Verga et al. 1991) provided the first convincing physical evidence of the location of the Menkes disease gene (MNK) and proved to be a starting point for the identification of the gene by three groups (Chelly et al. 1993; Mercer et al. 1993; Vulpe et al. 1993).
         2. The second female, with an X;1 translocation, reinforced the cytogenetic evidence that the Menkes gene is located at Xq13.3 (Beck et al. 1994).
      3. In both of these X;autosome translocation carriers, and in the third female with an X;21 reciprocal translocation [t(X;21)(q13.3;p11.1)] (Sugio et al. 1998), a de novo translocation disrupting the disease gene, the breakpoints were subsequently shown to be at the MNK locus by fluorescence in situ hybridization (FISH) analyses (Beck et al. 1994; Tümer et al. 1992).
      4. A girl with classic Menkes disease, carrying a de novo balanced translocation 46,X,t(X;13)(q13.3;q14.3), was reported (Abusaad et al. 1999). The translocation breakpoints at Xq13.3 and 13q14.3 coincide with the Menkes disease and Wilson disease loci, respectively.
   3. Other affected females with Menkes disease and variant phenotypes (Smpokou et al. 2015):
      1. 46,X,t(X;16)(q13.3;p11.2) (Sirleto et al. 2009).
      2. A 22-month-old girl: ATP7A gene analysis showed a heterozygous, frameshift mutation in exon 17 (c.3445delC), predicted to be pathogenic.
      3. A 4-year-old girl: ATP7A gene analysis showed a heterozygous deletion of exons 8–12, predicted to be pathogenic as well as 2 polymorphisms (c.2299G > C, IVS13-290A).
      4. A 7-year-old girl: ATP7A gene analysis showed the same two heterozygous polymorphisms (c.2299G > C, IVS13-29C > A) as in the 4-year-old patient but no pathogenic mutations or deletions detected.
   4. A male patient reported to have a unique rearrangement of the X chromosome where the long arm segment Xq13.3-q21.2 was inserted into the short arm

2. Gross deletion mutations (20%)
3. Point mutations (remaining genetic defects):
    1. Splice site (23%)
    2. Nonsense (20.7%)
    3. Missense (17.2%)
    4. Small insertions/deletions (39.1%)
    5. Partial gene deletions (Poulsen et al. 2002a, b):
        1. About 15% of the mutations causing Menkes disease are partial gene deletions.
        2. Only spanning of the deletion can be applied for carrier detection.
        3. In addition to spanning of the deletion on genomic DNA, carrier detection based on the use of a previously unrecognized polymorphism in intron 13 of ATP7A in combination with previously identified intragenic polymorphic markers, which can be used for carrier detection.
6. Genetic defect/pathogenesis:
    1. Failure of copper transport to the affected fetus resulting in copper deficiency in utero, compounded by impairment of copper absorption and ineffective copper transport into the central nervous system after birth
    2. Decreased copper transport across cellular compartments, particularly the gut
    3. Decreased availability of copper for cuproenzymes
    4. Dysfunction of numerous copper-dependent enzyme systems (decreased enzyme activities):
        1. Dopamine β-hydroxylase:
            1. Severe neurodegeneration
            2. Hypothermia
            3. Abnormalities in serum catecholamines
        2. Ascorbate oxidase: skeletal deformities
        3. Cytochrome c oxidase:
            1. Hypothermia
            2. Severe neurodegeneration
            3. Impaired myelination
            4. Muscle weakness
            5. Mitochondrial abnormalities
        4. Lysyl oxidase (decreased strength of collagen and elastin):
            1. Frayed/split internal elastic layer of arteries
            2. Bladder diverticula
            3. Loose skin and joints
        5. Monamide oxidase:
            1. Kinky hair
            2. Reduced pigmentation of hair and skin
            3. Severe neurodegeneration
        6. Tyrosinase:
            1. Depigmentation of hair
            2. Skin pallor
        7. Sulfhydryl oxidase: pili torti (Kodama and Murata 1999)
        8. Ceruloplasmin: decreased levels of circulating copper
        9. Copper–zinc superoxide dismutase:
            1. Failure of free radical detoxification, contributing to profound Purkinje cell loss
            2. Cytotoxic effects
    7. Loss of function of specific cuproenzymes resulting in the clinical features of Menkes disease:
        1. Abnormal hair and pigmentation
        2. Laxity of the skin
        3. Metaphyseal dysplasia
        4. Cerebellar degeneration
        5. Failure to thrive
    8. Favorably skewed X-inactivation accounts for neurological sparing in female carriers of Menkes disease (Desai et al. 2011)
    9. Allelic heterogeneity resulting in milder forms of the disease, occipital horn syndrome, also known as X-linked cutis laxa or Ehlers–Danlos syndrome type IX (Peltonen et al. 1983; Kaler 1998; Tümor 1998; Kodama et al. 1999):
        1. Clinical resemblances to Menkes disease with milder manifestations
        2. Biochemical resemblances to Menkes disease:
            1. Patients typically have between 20% and 35% residual copper transport function and far less severe neurodevelopmental abnormalities, even in the

absence of early diagnosis and treatment (Kaler et al. 1994).
2. Low serum copper and ceruloplasmin.
3. Increased copper accumulation and markedly low lysyl oxidase activity.
4. Impairment of *MNK* in patients with occipital horn syndrome (base pair substitution mutations affecting the normal mRNA splicing) giving a direct molecular evidence for the allelic relationship between the two diseases.

10. *ATP7A*-related distal motor neuropathy:
    1. Another allelic variant of Menkes disease.
    2. Caused by mutations in the copper-transporting P-type ATPase gene, *ATP7A*.
    3. Males with *ATP7A* mutations have even greater quantity of residual copper transport activity and manifest a late-onset syndrome restricted to progressive distal motor neuropathy, without overt signs of systemic copper deficiency (Kennerson et al. 2010).

Clinical Features

1. Phenotype: considerable variability in the severity of clinical expression encompassing the severe classical form (90–95% of patients) to the mild occipital horn syndrome.
2. Distinctive clinical features present by 3 months of age, often manifested by:
    1. Loss of early developmental milestones
    2. Poor weight gain (failure to thrive)
3. Neonatal hypothermia.
4. Neonatal hypoglycemia.
5. Hyperbilirubinemia.
6. Poor feeding.
7. Impaired weight gain (failure to thrive).
8. CNS abnormalities:
    1. Profound (truncal) hypotonia
    2. Abnormal head control
    3. Hyperactive reflexes
    4. Generalized seizures:
        1. Myoclonic
        2. Occasional tonic–clonic
    5. Developmental delay
    6. Severe mental retardation
9. Abnormal and characteristic hair, responsible for the synonyms of "kinky hair disease" or "steely hair disease" in the past (Bankier 1995):
    1. Depigmented, short, sparse, coarse, and twisted scalp hair: a striking and pathognomonic feature
    2. Fragile, frequently broken hair
    3. Twisted strands reminiscent of steel wool cleaning pads
    4. Eyebrows:
        1. Unusual appearance
        2. Scant
    5. White or gray hair lacking pigment secondary to absence of tyrosinase activity
10. Characteristic face:
    1. "Jowly," "pudgy," or "cherubic" face
    2. Sagging cheeks
    3. Large-appearing ears
    4. High-arched palate
    5. Delayed tooth eruption
11. Ocular abnormalities:
    1. Retinal hypopigmentation
    2. Retinal vessel tortuosity
    3. Macular dystrophy
    4. Congenital cataracts
    5. Partial optic nerve atrophy
    6. Decreased retinal ganglion cells
    7. Microcysts in the pigment epithelium of the iris
12. Connective tissue abnormalities (Menkes 1988) secondary to loss of lysyl oxidase activity:
    1. Loose skin (cutis laxa)
    2. Pectus excavatum
    3. Umbilical and/or inguinal hernias
    4. Diverticula of the bladder, uterus, and other organs
    5. Vascular complications including aortic aneurysms commonly present
    6. Tortuosity of the intracranial blood vessels by neuroimaging techniques
    7. Radiographic evidence:
        1. Wormian skull bones
        2. Osteoporosis

3. Metaphyseal dysplasia including anterior flaring and fracture of the ribs
4. Resembling scurvy

13. Progressive neurologic deterioration:
    1. Usually death by 3 years of age
    2. Rare survival beyond childhood in some children with profound neurologic deficits
    3. Long survival, especially with copper therapy, to teens and people in their twenties
14. Patients with milder or atypical manifestations than "classical" Menkes disease:
    1. Milder phenotype:
        1. Mild intellectual delay
        2. Ataxia
    2. Later onset of symptoms
    3. Less severe clinical course
    4. A longer life span
15. Clinical expression of Menkes disease in a girl with X;13 translocation (Abusaad et al. 1999):
    1. Onset: 4 months.
    2. Hypotonia.
    3. Delayed milestones.
    4. Seizures (Verrotti et al. 2014) are usually characterized by 3 stages:
        1. An early stage with focal clonic seizures and status epilepticus
        2. An intermediate stage with infantile spasms
        3. A late stage with multifocal, myoclonic, and tonic seizures
    5. Hair: dry, sparse, lusterless.
    6. Alopecia: pili torti.
    7. Dysmorphic facies:
        1. A high forehead and bitemporal narrowing
        2. Somewhat asymmetrical face with a prominent right ear, broad cheeks, downturned mouth corners, and sparse eyelashes and eyebrows
    8. Dry scaly skin.
    9. Hyperextensible joints.
    10. Tapering fingers.
    11. Puffy hands and feet.
    12. Decreased serum Cu.
    13. Decreased serum ceruloplasmin.
    14. Increased Cu uptake.
    15. Death at 3 years.
16. Occipital horn disease is a very mild allelic form of Menkes disease:
    1. A connective tissue disorder caused by a secondary deficiency of the cuproenzyme, lysyl oxidase.
    2. Milder phenotypic manifestations.
    3. Connective tissue abnormalities:
        1. Hyperelastic and easily bruisable skin
        2. Bladder diverticula
        3. Varicosities
        4. Hypermobile joints
    4. Skeletal abnormalities:
        1. Short broad clavicles
        2. Fused carpal bones
        3. Thoracic malformations
        4. Bony exostosis of the occiput (occipital horn) secondary to calcifications of the muscle at the insertion sites
    5. Occasional mild neurologic impairment.
    6. Any male infant with connective tissue abnormalities and mental retardation should be evaluated for the possibility of Menkes disease for biochemical evidence of defective copper transport because of somewhat atypical presentation of these milder phenotypes (Proud et al. 1996).

Diagnostic Investigations

1. Biochemical phenotype:
    1. Low levels of copper in the serum, liver, and brain resulting from impaired intestinal absorption (Kaler 2010).
    2. Low serum ceruloplasmin levels.
    3. Diagnosis of Menkes disease is confirmed by decreased serum copper and ceruloplasmin. Interpretation of these values is difficult in the first months of life. In such cases, the following analysis may be helpful in confirming the diagnosis:
        1. Copper accumulation in the placenta or chorionic villi
        2. Copper accumulation in the cultured skin fibroblasts
    4. Low activities of numerous copper-dependent enzymes (Kaler 2010):

1. Dopamine β-hydroxylase:
   1. Temperature instability
   2. Hypoglycemia
   3. Eyelid ptosis
   4. Pupillary constriction
2. Peptidylglycine α-amidating monooxygenase (reduced bioactivity of many neuroendocrine peptides)
3. Cytochrome c oxidase (impaired myelination, muscle weakness)
4. Copper–zinc superoxide dismutase (diminished protection against O_2 free radicals, possible motor neuron damage)
5. Tyrosinase (reduced pigmentation of hair and skin)
6. Diamine oxidase (reduced histamine degradation)
7. Lysyl oxidase (decreased strength of collagen and elastin)
8. Ceruloplasmin (decreased circulating copper levels)

5. Paradoxical accumulation of copper in certain tissues, such as the duodenum, kidney, spleen, pancreas, skeletal muscle, and placenta

2. Light microscopy of hair (Chang 2014):
   1. Pathognomonic pili torti (180° twisting of the hair shaft)
   2. Trichoclasis (transverse fracture of the hair shaft)
   3. Trichoptilosis (longitudinal splitting of the shaft)
   4. Trichorrhexis nodosa (small, beaded swelling with fractures at regular intervals)
   5. Monilethrix elliptica (swelling with intervening tapered constrictions)
3. MRI/MRA of the brain:
   1. White matter abnormalities reflecting impaired myelination
   2. Progressive degeneration of gray matter
   3. Cortical encephalomalacia
   4. Diffuse cerebral atrophy
   5. Cerebellar atrophy
   6. Ventriculomegaly
   7. Tortuosity (corkscrew appearance) of cerebral blood vessels
   8. Subdural hematoma (common in infants)
   9. Cerebrovascular accidents in older patients
4. Cerebral angiogram for tortuous winding vessels.
5. Variable electroencephalogram (normal, moderately to severely abnormal):
   1. Hypsarrhythmia after 5 months of age
   2. Low amplitude or absent evoked potentials
6. Echocardiography:
   1. Dysplastic coronary vessels
   2. Vascular complications including aortic aneurysms
7. Pelvic ultrasound to detect diverticula of the urinary bladder.
8. Renal ultrasound:
   1. Hydronephrosis
   2. Hydroureter
   3. Bladder diverticula
9. Radiography:
   1. Skull radiograph:
      1. Wormian bones in the lambdoidal and posterior sagittal sutures
      2. “Occipital horn”
   2. Metaphyseal spurring of long bones
   3. Diaphyseal periosteal reaction
   4. Anterior flaring or multiple fractures of ribs
   5. Scalloping of the posterior aspects of the vertebral bodies
   6. Osteoporosis seen after 6 months of age
10. Histologic examination of tortuous cerebral blood vessels:
    1. Thinning of the connective tissue
    2. Disruption of the elastic lamina
11. Ultrastructural cutaneous alterations of the elastic fibers (Martins et al. 1997): The reticular dermis showed marked changes in the elastic fibers with a paucity of the central amorphous component while retaining normal microfibrillary material.
12. Cytogenetic studies using traditional chromosome banding techniques verified by FISH using yeast artificial chromosomes spanning the gene:
    1. Mainly carried out in affected females for identification of possible X:autosome translocation at Xq13.3

2. Rare chromosome abnormality in male patients

13. Molecular diagnosis:
    1. Molecular diagnosis of Menkes disease: complicated by the heterogeneity at this locus.
    2. Almost all mutations detected in the Menkes disease gene are unique to an affected family.
    3. About 20% of these mutations involve rearrangements or partial gene deletions that can be identified by Southern blot analysis.
    4. Molecular diagnosis (superior to biochemical information) when the mutation in a given family is known, especially in cases of prenatal diagnosis.
    5. Carrier diagnosis is best done with mutation analysis and is readily accomplished when the specific mutation is known. In families where the mutation has not been identified, polymorphic markers and intragenic repeats have been used to facilitate carrier diagnosis.
14. Female carrier determination:
    1. Measurement of copper (^{64}Cu) accumulation in fibroblasts: difficult to interpret negative results because of random X-inactivation of one of the X chromosomes. Normal results do not completely exclude carrier status (Tümor 1998).
    2. Presence of pili torti in the hair: a positive clinical indicator, but its absence does not eliminate the possibility.
    3. Heterozygote detection by mutation detection in a given family with a known mutation (Kaler 2010):
        1. Allele-specific PCR
        2. Restriction enzyme analysis
        3. Heteroduplex analysis
        4. SSCP followed by DNA sequencing
        5. Southern blot analysis
    4. Linkage studies using intragenic polymorphic markers helpful in carrier detection, prenatal diagnosis, and genetic counseling where the mutation has not been identified (Tümor 1998).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib:
        1. Carrier mother: 50% of brothers affected, 50% of brothers normal; 50% of sisters carriers, 50% of sisters normal
        2. Noncarrier mother: instances of recurrence reported due to gonadal mosaicism
    2. Patient's offspring: not surviving to reproduction
2. Prenatal diagnosis:
    1. First trimester (Tonnesen et al. 1989):
        1. Measurement of total copper content in chorionic villus (CV) samples.
        2. Maternal deciduum contamination of a CV sample could cause a false-positive diagnosis.
        3. First trimester prenatal diagnosis by DNA analysis (Tümor et al. 1994)
    2. Second trimester: copper (^{64}Cu) accumulation and kinetic studies in cultured amniotic fluid cells (Gu et al. 2002) and chorionic villus cells (Tonnesen and Horn 1989).
    3. Nine female fetuses: identified as carriers on the basis of the tissue culture studies or raised placenta copper values (Horn 1981).
    4. Mutation detection in a given family with a known mutation (Das et al. 1995; Kaler and Tümer 1998).
    5. Almost every affected family shows a different alteration, ranging from cytogenetic abnormalities to single base pair changes (Tümer and Horn 1997). Thus, although the gene has been cloned, molecular testing for prenatal diagnosis is quite challenging, and confirmation by biochemical diagnosis is still required. DNA-based analysis is used in families where the mutation has been identified and for carrier detection where negative results are not reliable owing to random X chromosome inactivation.
3. Prenatal diagnosis/preimplantation genetic diagnosis may be an option for some families in which the pathogenic variant has been identified (Kaler 2015).

4. Management:
    1. No definitive therapeutic options currently available.
    2. Oral copper treatment: not effective.
    3. Early parenteral administrations of cupric acetate:
        1. Normalizes serum copper and ceruloplasmin levels but not CNS copper levels
        2. Improves seizure control
        3. Will not interrupt the progression of neurologic manifestations
    4. Early subcutaneous injections of copper–histidine with encouraging results (Kreuder et al. 1993; Sarkar et al. 1993; Sarkar 1997; Christodoulou et al. 1998; Gu et al. 2002; Tümer and Møller 2010; Tümer 2013):
        1. Normalizes serum copper, ceruloplasmin, dopamine, and norepinephrine levels after 3 months of treatment.
        2. May be able to cross the blood–brain barrier and thus disrupt the progression of neurological symptoms including decreased seizures.
        3. Prolong survival, especially if treatment started within 1 month of life.
        4. Does not prevent the connective tissue complications because lysyl oxidase may not incorporate copper–histidine well.
        5. Certain Menkes disease mutations that inhibit copper-induced trafficking of an otherwise functional copper transporter may be particularly responsive to copper replacement therapy (Kim et al. 2003).
        6. Importance of diagnosis with molecular analysis in the neonatal period so that early treatment with parenteral copper–histidine can be initiated (Costa et al. 2015).
    5. Prenatally initiated copper replacement is inadequate to correct Menkes disease caused by severe loss-of-function mutations and that postnatal ATP7A gene addition represents a rational approach in such circumstances (Haddad et al. 2012).

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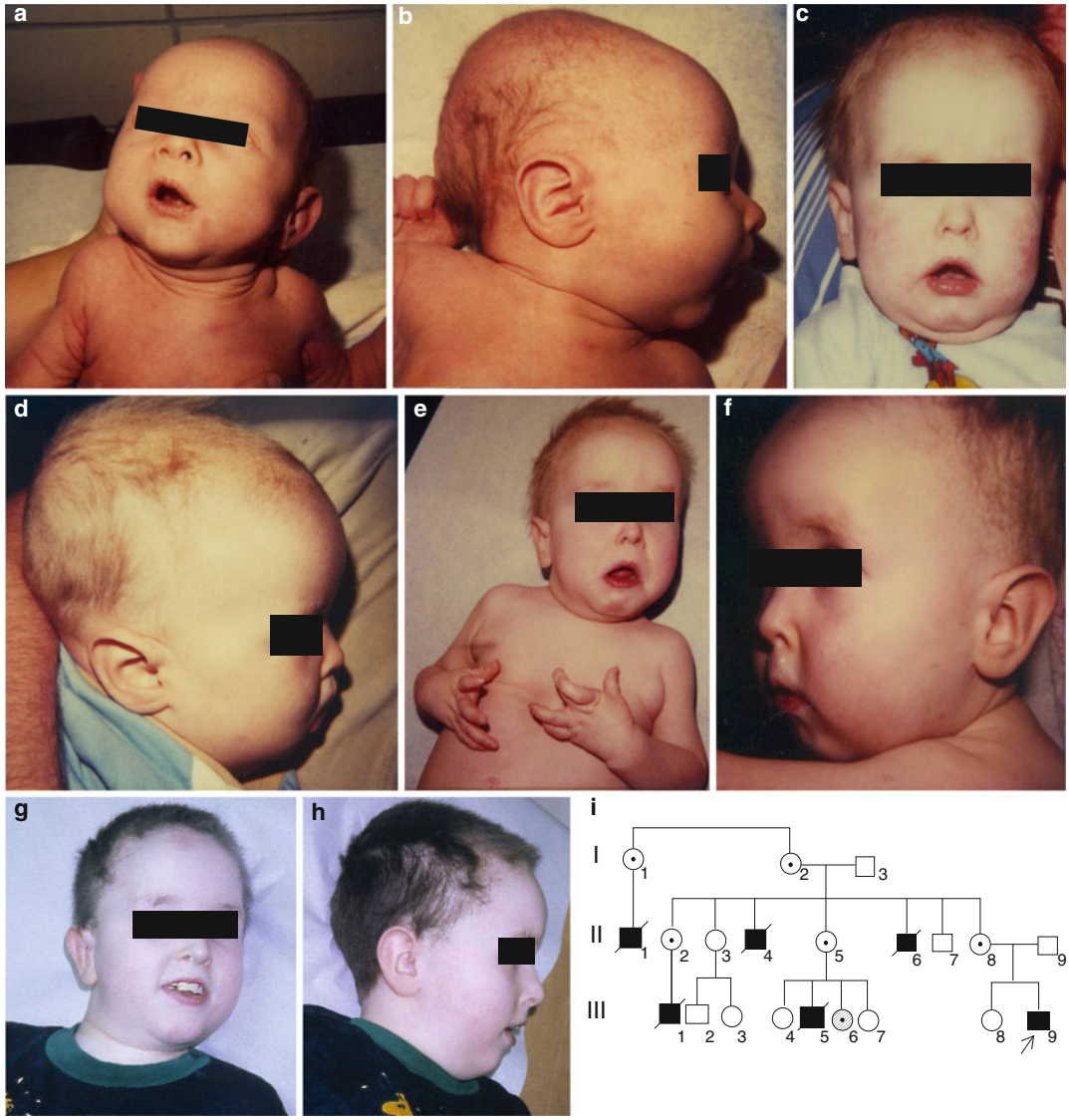

Fig. 1 (**a**–**i**) A boy with Menkes disease at 1 month (a, b), 9 months (c), 1 year (d), 27 months (e, f), and 9 years (g, h) showing sparse, coarse, twisted hair, sagging cheeks, large-appearing ears, and pectus excavatum. The boy was treated with cuprous sulfate and survived to his twenties. The pedigree is shown here illustrating X-linked recessive mode of inheritance

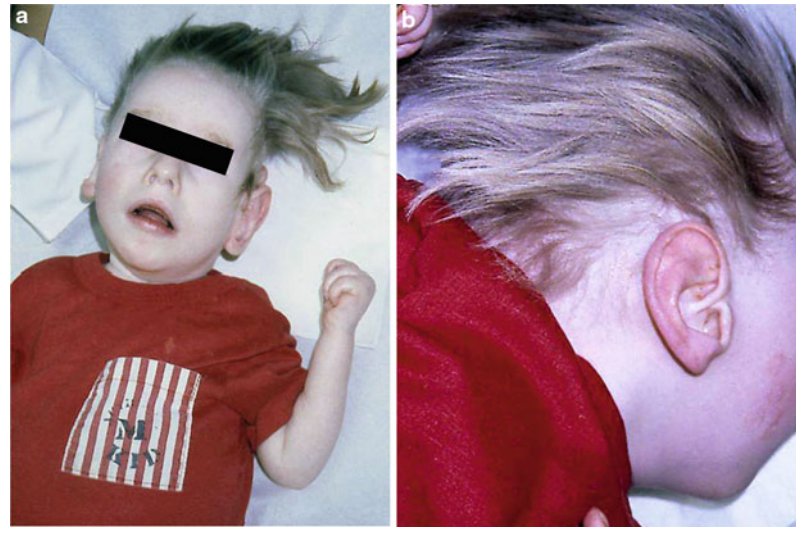

Fig. 2 (**a**–**b**) A cousin of the previous child with Menkes disease at 3 years of age showing coarse/twisting hair, sagging cheeks, and large-appearing ears

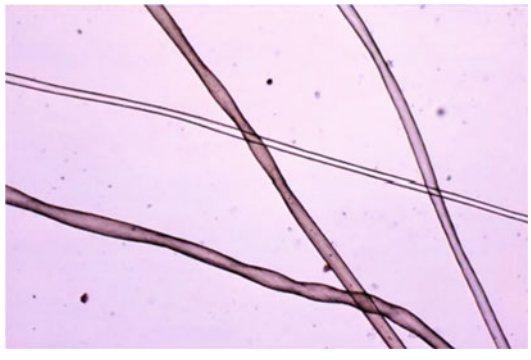

Fig. 3 Hairs showing pili torti (moderate variation in diameters; two hair shafts are twisted) in an 8-month-old male infant affected with Menkes disease

Metachromatic Leukodystrophy

Contents

Metachromatic leukodystrophy (MLD) is a lysosomal storage disease resulting from the deficient arylsulfatase A activity and the accumulation of sulfatides. The incidence among Caucasians is estimated to be about 1 in 40,000 births (Gustavson and Hagberg 1971). The name of MLD originated from the metachromatic staining of the stored substance in histological sections.

Synonyms and Related Disorders

Arylsulfatase A deficiency; Cerebroside sulfatase deficiency; Metachromatic leukoencephalopathy

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Genetic heterogeneity (Kihara 1982)
3. Caused by deficiency of arylsulfatase A (ASA) activity:
    1. Resulting in accumulation of the enzyme substrate sulfatide (cerebroside sulfuric ester) in:
        1. Oligodendrocytes (Gieselmann et al. 1994a) and Schwann cells
        2. Visceral organs such as the kidneys (sulfatide excreted in high amounts in the urine)
    2. Leading to severe myelin breakdown:
        1. Resulting in demyelination of the white matter of the brain, spinal cord, and peripheral nerves
        2. Providing the pathophysiologic basis for the deterioration and eventual premature demise
4. Arylsulfatase (*ARSA*) gene:
    1. Mapped to 22q13.31
    2. MLD caused by *ARSA* mutations (Gieselmann 2008): more than 11 different mutations have been identified in the *ASA* gene (missense mutations are by far the most frequent type of defect found):
        1. Two most common mutations observed in Europe are (Berger et al. 1997) as follows:
            1. 459 + 1G > A
            2. A missense mutation causing a Pro426Leu substitution (accounts for about 25% of all alleles among European patients) (Polten et al. 1991)
        2. A missense mutation causing an Ile179Ser substitution (accounts for

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about 12% of all defective alleles) (Berger et al. 1997).
   3. All other mutant alleles have only been found in a few or single patients (Schestag et al. 2002).
   4. Patients homozygous for alleles, which do not allow for the synthesis of functional ASA, always suffer from the severe form of the disease, whereas alleles allowing the expression of residual enzyme activity are associated with the later-onset juvenile or adult forms of metachromatic leukodystrophy (Gieselmann 2008).
3. ASA pseudodeficiency (ASA-PD) caused by *ARSA* mutation:
   1. Originally described in healthy individuals.
   2. Low ASA activity.
   3. Normal urinary sulfatide levels.
   4. The pseudodeficiency, in most cases, is caused by homozygosity for the arylsulfatase A pseudodeficiency (ASA-PD) allele (Polten et al. 1991).
   5. MLD mutations are also known to occur within this allele: 1–2% of PD alleles are estimated to have a disease-causing mutation (Rafi et al. 2003).
   6. Characterization of the mutations causing pseudodeficiency has allowed the detection of the pseudodeficiency allele in the DNA of probands and has thus improved the diagnosis and genetic counseling for metachromatic leukodystrophy (Gieselmann et al. 1994b).
4. Chromosomal deletion unmasking a recessive disease such as 22q13 deletion syndrome and metachromatic leukodystrophy (Bisgaard et al. 2009):
   1. One patient had a pathogenic mutation in the *ARSA* gene and succumbed to MLD.
   2. Another patient had a pseudoallele which did not lead to MLD.
5. Pathophysiology (Ikeda et al. 2010):
   1. Inability to degrade sulfated glycolipids, especially the galactosyl-3-sulfate ceramides, characterizes metachromatic leukodystrophy.
   2. A deficiency in the lysosomal enzyme sulfatide sulfatase (arylsulfatase A) is present in metachromatic leukodystrophy.
   3. Some patients with clinical metachromatic leukodystrophy have normal arylsulfatase A activity but lack an activator protein that is involved in sulfatide degradation.
   4. Both defects result in the accumulation of sulfatide compounds in neural and in nonneural tissue, such as the kidneys and gallbladder.
   5. These defects may result from a number of different mutations, and many new causative mutations have been identified (Anlar et al. 2006; von Figura et al. 2001).
5. Prosaposin (PSAP) gene including rare variants (Cesani et al. 2016):
   1. Codes for the activator protein saposin B.
   2. Mutation update, an extensive review of all the ARSA- and PSAP-causative variants published in the literature to date, accounts for a total of 200 ARSA and 10 PSAP allele types.

Clinical Features

1. Three main clinical forms based on the age of onset of the disease (Barth et al. 1994):
   1. Late-infantile form (50–60% of cases)
   2. Juvenile form (20–30% of cases)
   3. Adult form (15–20% of cases)
2. Late-infantile form (Clark et al. 1979):
   1. The most common form
   2. Onset of the disease: between the ages of 15 months and 2 years
   3. Clinical symptoms:
      1. Loss of acquired motor skills
      2. Flaccid weakness and hypotonia
      3. Ataxic gait with absent tendon reflexes
   4. Progression of the disease:
      1. Quadriplegia.
      2. Speech disturbances:
         1. Dysarthria
         2. Aphasia

3. Speech deterioration leading to loss of speech
3. Difficulty in feeding (dysphagia) with bulbar and pseudobulbar palsies.
4. Irritability.
5. Muscle wasting.
6. Peripheral neuropathy.
7. Ataxia.
8. Ophthalmic features:
   1. Nystagmus
   2. A cherry-red spot in the macula in some patients (Crumrine 2001)
   3. Optic atrophy leading to blindness
9. Epileptic seizures usually occur at advanced stages of the disease.
10. Mental deterioration progresses with the disease until the patients are no longer able to establish any contact with their surroundings.
11. Death generally occurs 1–7 years after onset.

3. Juvenile form (Haltia et al. 1980):
   1. Clinical symptoms usually develop between the ages of 4 and 12 years.
   2. Progression of the illness similar to that of the infantile form.
   3. Clinical characteristics:
      1. Loss of developmental milestones by the end of the first decade
      2. Gross motor:
         1. Incoordination
         2. Clumsiness
         3. Ataxia with progressive gait disturbance leading to loss of ambulation
         4. Progressive hypertonia with tremor, postural abnormalities, and/or leg scissoring
         5. Diminished deep tendon reflexes
      3. Speech and language:
         1. Slurred speech
         2. Speech deterioration
      4. Cognitive and behavioral changes:
         1. Abnormal and bizarre behavior
         2. Daydreaming
         3. Difficulty in following directions
         4. Emotional difficulties
         5. Intellectual decline
         6. Mental deterioration
      5. Ophthalmologic features: optic atrophy leading to blindness
      6. Other CNS manifestations:
         1. Pseudobulbar palsy.
         2. Epileptic seizures usually occur at advanced stages of the disease.
         3. Mental illness with features of psychosis, dementia, and emotional disorders in older children.
         4. Progressive neurological problems but less severe than in the late-infantile form.
   4. Prognosis:
      1. Fatal in majority of cases.
      2. Course of disease may last more than 20 years in a few cases.
4. Adult form (Baumann et al. 1991):
   1. Wide range of onset: from 19 to 46 years
   2. Very rare occurrence
   3. Slow progression of the disease
   4. Survival of 5–10 years common
   5. Cognitive and behavioral changes (the first symptoms in many cases):
      1. Personality changes:
         1. Anxiety
         2. Apathy
         3. Bewilderment
         4. Emotional instability
         5. Psychosis
      2. Poor school or job performance:
         1. Decreased mental alertness
         2. Defective visual-spatial discrimination
         3. Disorganized thinking
         4. Poor memory
   6. Mental deterioration:
      1. Often the first symptom
      2. Loss of professional abilities leading to total incapacity
      3. Progressive deterioration eventually leading to dementia
   7. Rare epileptic seizures
   8. Ophthalmologic features:
      1. Horizontal nystagmus
      2. Optic atrophy leading to blindness
   9. Final stages:
      1. Loss of speech
      2. Immobility
      3. Incontinence

5. Arylsulfatase pseudodeficiency:
   1. Low arylsulfatase activity in healthy individuals
   2. Allelic variant metachromatic leukodystrophy
6. Nonallelic variants of MLD (Fluharty 2008):
   1. Multiple sulfatase deficiency (Austin variant of MLD):
      1. Caused by a defect in processing of an active site cysteine to formylglycine (alanine-semialdehyde), a proenzyme activation step common to most sulfatases (Dierks et al. 2005; Zafeiriou et al. 2008).
      2. Findings suggesting a diagnosis of multiple sulfatase deficiency include:
         1. Reduced activity of other sulfatases including arylsulfatase B, arylsulfatase C, and iduronate sulfatase (the enzyme that is deficient in Hunter syndrome and heparan-N-sulfamidase in leukocytes or cultured cells)
         2. Presence of mucopolysaccharides (glycosaminoglycans) as well as sulfatides in the urine
      3. Although clinical variability of multiple sulfatase deficiency is great, features of both MLD and a mucopolysaccharidosis (MPS) may be present (Macaulay et al. 1998).
      4. More severe forms of multiple sulfatase deficiency resemble late-infantile MLD. In other cases, MPS-like features such as coarse facial features and skeletal abnormalities may be evident in infancy and early childhood, with MLD-like symptoms becoming evident in later childhood.
      5. Eventually, the disease course resembles MLD with demyelination dominating the clinical picture (von Figura et al. 2001). Ichthyosis, common to arylsulfatase C deficiency, is also often present.
      6. A defect in the formylglycine-generating enzyme (FGE) is causative (Dierks et al. 2005) and is responsible for the activation of most sulfatases, and a variable degree of arylsulfatase A deficiency occurs in many tissues in its absence.
   2. Sphingolipid activator protein B-deficient MLD (saposin B deficiency):
      1. A defect in the glycolipid-binding protein saposin B, which is needed to solubilize sulfatides before they can be hydrolyzed by arylsulfatase A, causes an MLD-like disorder.
      2. While a number of other glycolipid degradative processes are disrupted in saposin B deficiency, it is the failure in sulfatide catabolism that dominates the clinical picture.
      3. Age of onset is variable, with too few cases having been reported to delineate a typical clinical picture.
      4. An MLD-like clinical presentation, leukodystrophy on MRI, normal arylsulfatase A enzyme activity, and evidence of excess urinary sulfatide excretion and/or sulfatide storage suggest activator deficiency.
      5. Diagnosis depends on depressed sulfatide degradation by cultured cells, immunochemical assessment of saposin B levels, or sequence analysis of the gene encoding prosaposin (Sandhoff et al. 2001).

Diagnostic Investigations

1. Diagnosis suspected in individuals with progressive neurologic dysfunction and MRI evidence of a leukodystrophy.
2. Demonstration of decreased (<10% of normal controls) or absence ASA enzyme in the urine, leukocytes, or cultured skin fibroblasts (Gieselmann 1991; Gieselmann et al. 1991a):
   1. Low ASA activity also observed in:
      1. Individuals with multiple sulfatase deficiency
      2. Individuals with copies of pseudodeficiency (PD) allele

2. Low ASA activity is seen in individuals without MLD due to the high frequency of the common PD allele in the general population.
3. Differentiation of ASA pseudodeficiency from MLD:
    1. Inability to reliably distinguish MLD and ASA pseudodeficiency, based solely on enzyme activity determinations
    2. Cerebroside sulfate loading test:
        1. Exposure of the cells to radioactively labeled cerebroside sulfate, the natural substrate of arylsulfatase A.
        2. Cultured cells from pseudodeficient individuals will degrade this substrate at normal rates, whereas those from MLD patients do not.
        3. Disadvantages: require experienced investigator, noncommercially available substrate, and tissue culture facilities.
    3. PD allele mutations studies using allele specific amplification
3. Urinalysis showing metachromatic granules in the urine sediment.
4. Urine chemistry showing markedly increased sulfatide levels.
5. Sulfatide analysis by mass spectrometry for screening of metachromatic leukodystrophy in dried blood and urine samples (Spacil et al. 2016).
6. Ultra-performance liquid chromatography/tandem mass spectrometry for determination of sulfatides in dried blood spots from patients with metachromatic leukodystrophy: This method provides a fast and effective screening and monitoring tool for the diagnosis and treatment of MLD (Han et al. 2014).
7. Sulfatide loading of fibroblast cultures and subsequent measurement of hydrolysis of added substrate: The differences in hydrolysis of added sulfatide provide a functional test that separates late-infantile, juvenile, and adult forms (Krivit et al. 1995).
8. Absence of gallbladder function on a cholecystography (Crumrine 2001).
9. Screening for gallbladder abnormalities by ultrasound in order to prevent early death (van Rappard et al. 2016b):
    1. Gallbladder involvement is the rule rather than the exception in MLD.
    2. The high prevalence of hyperplastic polyps, a known precancerous condition, and one death from gallbladder carcinoma at a young age suggest that MLD predisposes to neoplastic gallbladder abnormalities.
10. Abnormal brain stem auditory, visual, and somatosensory evoked potentials.
11. Elevated CSF levels of protein and cytokines (Thibert et al. 2016).
12. Brain imaging shows progressive loss of white matter due to demyelination (Faerber et al. 1999):
    1. Symmetric diffuse high-intensity signal on proton density and T2-weighted images throughout the white matter consistent with demyelination
    2. Hypointense signal abnormalities in the white matter of the centrum semiovale with the following two distinct appearances (Liaw et al. 2015):
        1. A radiating pattern ("tigroid" appearance) of linear tubular structures or horizontal linear hypodensity indicative of spared perivascular white matter
        2. Areas of relatively normal-appearing white matter: a punctate appearance to the linear structures ("leopard skin" appearance) within the demyelinated centrum semiovale
    3. Cerebral atrophy with ventricular enlargement
13. Volumetric MRI data correlate to disease severity in metachromatic leukodystrophy (Tillema et al. 2015):
    1. Significant cerebral cortical gray matter volume (GMV) loss is already present in early stages of MLD.
    2. IQ correlates with cerebral white matter (WM) severity scores and lesion volume, but not with volumetric measures.
    3. In adult presentations, there is more pronounced global atrophy with GMV and

WM volume loss and accelerated cortical thinning, most prominently in the cingulate gyrus and frontal lobes.

14. Nerve conduction studies show decreased nerve conduction velocities and demyelinating polyneuropathy (Liaw et al. 2015).
15. Nerve biopsies show metachromasia of Schwann cells.
16. Molecular studies of ASA mutations (Fluharty 2008):
    1. Targeted mutation:
        1. *ARSA*-mild alleles
        2. *ARSA*-PD alleles
    2. Sequence analysis/mutation scanning
    3. Deletion/duplication analyses
17. Diagnosis of the presymptomatic siblings of the index case: Only combination of gene sequencing with thorough biochemical analysis allowed the correct diagnosis of the sibling, who was promptly directed to treatment (Lorioli et al. 2014).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib:
        1. Recurrence risk: 25%
        2. Younger siblings in the same family with an older sibling who is clinically affected by MLD (Krivit et al. 1995):
            1. Require appropriate and rapid evaluation.
            2. May be affected but clinically presymptomatic.
            3. Therapy with bone marrow transplantation in affected but asymptomatic sibling may be curative.
            4. Sibling with very low levels of white blood cell arylsulfatase A may not indicate the presence of disease because of the combination of the pseudodeficient gene with a metachromatic leukodystrophy gene.
    2. Patient's offspring:
        1. Do not survive into reproductive age in late-infantile and juvenile forms
        2. Not increased in adult form unless the spouse is a carrier
2. Carrier detection (Gieselmann 1991a, b):
    1. Individuals with about 50% of arylsulfatase A:
        1. Suspected to be carriers of an MLD allele and have genetic risk for MLD
        2. Likely to be carriers of a pseudodeficiency allele and have no genetic risk for MLD
    2. Enzyme activity determination: impossible to distinguish heterozygotes of a pseudodeficiency allele from heterozygous of an MLD allele
    3. Mutation detection of the pseudodeficiency allele in the DNA to facilitate the differential diagnosis of MLD and pseudodeficiency
3. Prenatal diagnosis for couples at risk:
    1. Demonstration of the absence of arylsulfatase A in cultured chorionic villi or amniocytes (van der Hagen et al. 1973; Eto et al. 1982).
    2. A combination of biochemical and molecular tests performed on chorionic villus samples or cultured amniotic fluid cells.
    3. Demonstration of the disease-causing mutation previously identified in the proband on fetal DNA obtained from amniocentesis or CVS.
    4. Preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.
4. Management:
    1. Primarily supportive:
        1. Currently, no available treatment can reverse the fatal outcome of the devastating MLD.
        2. Nasogastric or G-tube feeding for dysphagia of bulbar and pseudobulbar palsies
        3. Multidisciplinary approach
    2. Replacement of ASA might degrade the accumulated cerebroside sulfate and thereby be an effective treatment: both

intravenous and intrathecal infusion of ASA in a patient with the late-infantile form of metachromatic leukodystrophy (Greene et al. 1969).

3. Kidney transplantation from a deceased donor with MLD: The excellent clinical result after kidney allograft, and the ability to continue dialysis if acute rejection intervenes, suggests that renal transplantation from MLD patients is safe and effective (Sondheimer et al. 2014).
4. Bone marrow transplantation:
    1. For individuals who are presymptomatic or have only mild neurologic manifestations
    2. Significant risks associated with this procedure
    3. Highly dependent on the availability of adequately matched donors
    4. Long-term stabilization after bone marrow transplantation in juvenile metachromatic leukodystrophy (Kidd et al. 1998)
    5. Appears to slow the progression of the disease and improve the quality of life
    6. Bone marrow transplantation: an effective treatment of patients with lysosomal and peroxisomal storage diseases, including metachromatic leukodystrophy (Krivit et al. 1999)
    7. Successful treatment of metachromatic leukodystrophy using bone marrow transplantation of HoxB4 overexpressing cells in the mouse model (Miyake et al. 2010)
5. Developing treatment options for metachromatic leukodystrophy (Batzios and Zafeiriou 2012):
    1. Correction of ASA deficiency by a recombinant adenovirus that potentially could be used to transfer the gene to the brain, and gene therapy for MLD based on gene transfer of the ASA gene to mutant cells will be feasible because the overexpression of ASA in cells does not lead to profound deficiency of other sulfatases or result in a new phenotype (Ohashi et al. 1996).
    2. Hematopoietic stem cell transplantation (HSCT) (Solders et al. 2014; van Rappard et al. 2016a):
        1. In comparison with the untreated siblings, HSCT halted the progression of the disease in treated patients.
        2. Effectiveness is overshadowed by serious limitations.
        3. As the best moment for hematopoietic cell transplantation (HCT) is as early as possible and before clinical disease onset, it is of utmost importance to test all siblings of an index case, including older ones.
        4. For more advanced and late-infantile patients, results are discouraging.
        5. For the majority of patients evaluated, HCT was no longer an option neither did they qualify for treatment trials, emphasizing the need of earlier diagnosis and better treatment strategies.
    3. Umbilical cord blood transplantation: may be greatly beneficial even to late-infantile MLD patients or minimally symptomatic juvenile MLD (Martin et al. 2013), since it has important advantages, such as quick availability and low risk of morbidity and mortality in relation to HSCT.
    4. Mesenchymal stem cell (MSC) transplantation: Initial results show that MLD patients might benefit from this treatment option, since MSCs have significant advantages, such as great transdifferentiation capability, widespread distribution throughout the body, and easy accessibility.
    5. Intracerebral gene therapy with oligodendroglial, neural progenitor, embryonic, and microencapsulated recombinant cells represents add-on treatment options still on experimental level.

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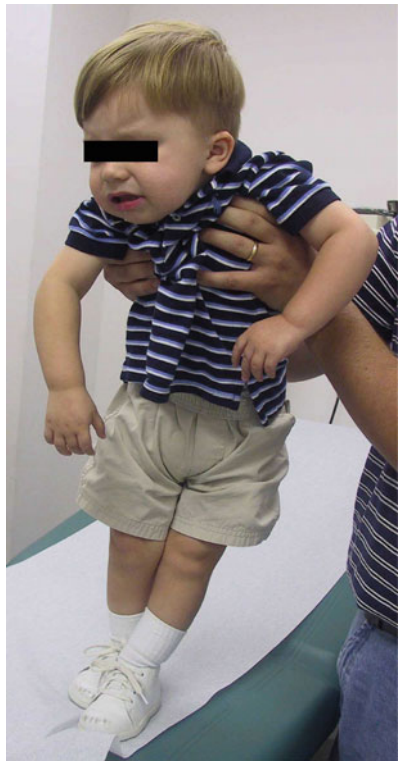

Fig. 1 A 28-month-old boy with late-infantile form metachromatic leukodystrophy showing extreme hypotonia. At about 15 months of age, he stopped talking and showed muscle weakness. MRI of the brain demonstrated demyelination. Arylsulfatase A activity was absent in the cultured fibroblasts. Urinary excretion of excess sulfatides confirmed the diagnosis of metachromatic leukodystrophy. DNA analysis shows no copies of the pseudodeficiency allele or the common late-infantile mutation. Mutation screening of the entire coding sequence of the arylsulfatase A gene revealed the mutation E253K which was inherited from the mother and the second mutation P192R which was inherited from the father. The E253K mutation has been described as a disease-causing mutation in the literature. The second mutation P192R most likely is a disease-causing mutation

Fig. 2 A 3-year-old girl presented with progressive muscle weakness in the lower limbs for 2–4 months. The low leukocyte arylsulfatase A at 0.4 (control: $\geq$2.5) was consistent with diagnosis of metachromatic leukodystrophy

Miller-Dieker Syndrome

Contents

In *1963*, Miller reported two siblings with a specific pattern of malformations in which lissencephaly was a key feature. Later in *1969*, Dieker et al. described a similar condition. Jones et al. in *1980* further characterized the phenotype and suggested the designation Miller-Dieker syndrome to distinguish it from other lissencephaly syndromes. At present, Miller-Dieker syndrome is known to be a contiguous gene disorder caused by haploinsufficiency of a gene or genes having a major role in the development of the brain and the face (Alvarado et al. 1993).

Synonyms and Related Disorders

Chromosome 17p13.3 deletion syndrome; Miller-Dieker lissencephaly syndrome

Genetics/Basic Defects

1. Genetics: a contiguous gene deletion syndrome involving chromosome 17p13.3 (Miny et al. 1993; Chitayat et al. 1997)
    1. Association of Miller-Dieker syndrome and del(17)(p13) (Stratton et al. 1984)
        1. First reported by Dobyns et al. in *1983*
        2. Deletions of the lissencephaly critical region in 17p13.3 including LIS1 (Ledbetter et al. 1992; Dobyns et al. 1993)
        3. Familial cases reported by Miller (1963) with affected members being carriers of an unbalanced rearrangement from t (15;17)(q26.1;p13.3)
        4. Family reported by Dieker et al. (1969) with affected members being carriers of an unbalanced rearrangement from t (12;17)(q24.31;p13.3)
    2. A microdeletion in a critical 350-kb region of chromosome 17p13.3 observed in familial and sporadic cases, detected by high-resolution banding
    3. Southern blot analysis of restriction fragment length polymorphism with several different DNA markers in 17p13.3 and later FISH analysis using different DNA probes of this segment
        1. Observed in >90% of patients with Miller-Dieker syndrome
        2. Observed in 38% of patients with isolated lissencephaly

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Mutations and large deletions of the lissencephaly gene (*LIS1*)
   1. Deletions involving *LIS1*: more common than mutations
   2. *LIS1* deleted in Miller-Dieker syndrome
   3. *LIS1* mutations observed in patients with isolated lissencephaly sequence
      1. Missense mutations
      2. Nonsense mutations
      3. Small deletions or insertions
      4. Splice site mutations
      5. Partial deletions
   4. Phenotype-genotype correlations (Cardoso et al. 2002)
      1. Most severe LIS phenotypes observed in patients with large deletions of 17p13.3
      2. Milder phenotypes observed in patients with intragenic mutations
      3. Mildest phenotypes observed in patients with missense mutations
3. Classification of lissencephaly (Dobyns et al. 1984; Pilz and Quarrell 1996; Spalice et al. 2009)
   1. Lissencephaly type I (classical) (de Rijk-van Andel et al. 1990)
      1. Isolated lissencephaly sequence (Dobyns et al. 1992)
      2. Miller-Dieker syndrome
      3. Subcortical band heterotopia
      4. Nonclassified forms
   2. Lissencephaly type II (cobblestone)
      1. Walker-Warburg syndrome
      2. Fukuyama congenital muscular dystrophy
      3. Muscle-eye-brain disease
      4. Non-unclassified forms
   3. Rare forms
      1. Neu-Laxova syndrome
      2. Cerebrocerebellar syndrome
4. Cytogenetic mechanisms in Miller-Dieker syndrome (Dobyns et al. 1991)
   1. De novo abnormalities (44%)
      1. Deletion (terminal or interstitial) (36%)
      2. Dicentric translocation (4%)
      3. Ring chromosome (4%)
   2. Familial rearrangement (12%)
      1. Reciprocal translocation (8%)
      2. Pericentric inversions (4%)
   3. Normal karyotype (44%)
      1. Submicroscopic deletion (36%)
      2. No deletion detected (8%)
5. Molecular explanation for Miller-Dieker syndrome (Toyo-oka et al. 2003)
   1. Heterozygous deletions of 17p13.3 result in the human neuronal migration disorders.
      1. Isolated lissencephaly sequence
      2. More severe Miller-Dieker syndrome
   2. Mutations in *PAFAH1B1* (the gene encoding LIS1): responsible for isolated lissencephaly sequence and contributing to Miller-Dieker syndrome.
   3. The gene encoding 14-3-3ε (YWHAE), one of a family of ubiquitous phosphoserine/threonine-binding proteins: always deleted in individuals with Miller-Dieker syndrome, providing a molecular explanation for the differences in severity of human neuronal migration defects with 17p13.3 deletions.
   4. *CRK*: may be involved in the facial phenotype of the 17p13.3 microdeletion syndrome, and that CRK, and not YWHAE, seems to be involved in limb malformations (Østergaard et al. 2012).

Clinical Features

1. Prenatal and neonatal history
   1. Polyhydramnios
   2. Prenatal growth deficiency
   3. Neonatal resuscitation
   4. Neonatal jaundice
   5. Postnatal growth deficiency
2. CNS anomalies
   1. Type I (classical) lissencephaly: can occur either in association with the Miller-Dieker syndrome or as an isolated finding, termed “isolated lissencephaly sequence.”
      1. Agyria (absent gyration of the cerebral cortex)
      2. Pachygyria (unusually thick convolutions of the cerebral cortex)

2. Absent or hypoplastic corpus callosum
3. Cavum septi pellucidi
4. Midline calcification
5. Ventricular dilatation
6. Abnormal positioning of the olivary nuclei in the midbrain
7. Occasional mild cerebellar vermis hypoplasia
8. Microcephaly
9. Seizures usually by age 9 weeks
10. Cerebral palsy
11. Profound mental retardation

3. Craniofacial features
   1. High, prominent, and wrinkled forehead
   2. Bitemporal narrowing
   3. Furrowed brow
   4. Epicanthal folds
   5. Broad nasal bridge
   6. Short and pointed nose with anteverted nostrils
   7. Long prominent upper lip with thin upper vermilion border
   8. Micrognathia
   9. High-arched palate
   10. Low-set and malformed ears
4. Congenital heart defects
5. Omphalocele (Chitayat et al. 1997)
6. Hands and fingers
   1. Clinodactyly
   2. Camptodactyly
   3. Transverse palm crease
7. Sacral dimple
8. Cryptorchidism
9. Prognosis: often die within the first few months of life
10. Differential diagnosis
    1. Isolated lissencephaly sequence (Dobyns et al. 1984, 1992)
       1. Brain abnormalities
          1. Lissencephaly (type I)
          2. Numerous heterotopias
          3. Failure of opercularization
          4. Enlarged ventricles (usually colpocephaly)
          5. Probable hypoplasia of the corpus callosum
       2. Neurological abnormalities
          1. Profound mental retardation
          2. Decreased spontaneous activity
          3. Early hypotonia
          4. Subsequent hypertonia
          5. Poor feeding
          6. Seizures
       3. Craniofacial features
          1. Microcephaly
          2. Bitemporal hollowing
          3. Prominent occiput
          4. Micrognathia
       4. Occasional abnormalities
          1. Prenatal polyhydramnios, decreased fetal movement
          2. Postnatal: may require resuscitation at birth
          3. Neurological: infantile spasms
       5. Chromosome studies
          1. Normal chromosomes by conventional studies
          2. Submicroscopic deletions by FISH observed in increasing numbers
    2. Norman-Roberts syndrome (Dobyns et al. 1984)
       1. Probably an autosomal recessive disorder
       2. Brain abnormalities
          1. Lissencephaly (type I)
          2. Numerous heterotopias
          3. Failure of opercularization
          4. Slightly enlarged ventricles (probable colpocephaly)
          5. Probable hypoplasia of the corpus callosum
       3. Neurological abnormalities
          1. Profound mental retardation
          2. Decreased spontaneous activity
          3. Poor feeding
          4. Seizures
       4. Cranial abnormalities
          1. Microcephaly
          2. Bitemporal hollowing
          3. Slightly prominent occiput
          4. Low, sloping forehead
       5. Facial features
          1. Widely set eyes
          2. Broad, prominent nasal bridge
          3. Micrognathia
          4. Absence of upturned nares
          5. Normal eyes

6. Other features
    1. Clinodactyly
    2. Chordee
    3. Low birth weight
7. Normal chromosomes

3. Walker-Warburg syndrome (Dobyns et al. 1989)
    1. Most commonly seen in the United Kingdom
    2. An autosomal recessive disorder
    3. Type II lissencephaly
    4. Hydrocephalus
    5. Cerebellar malformation (vermian hypoplasia)
    6. Eye abnormalities
        1. Retinal dysplasia
        2. Microphthalmia
        3. Colobomata
        4. Cataracts
        5. Glaucoma
        6. Corneal clouding commonly due to Peters' anomaly
        7. Congenital muscular dystrophy in all patients
        8. Elevated CK
        9. Abnormal EMG
        10. Pathological changes on muscular histology
    7. Other abnormalities
        1. Cleft lip/palate
        2. Genital anomalies in males: cryptorchidism, small penis
        3. Occasional contractures
4. Muscle-eye-brain disease (Santavuori et al. 1989)
    1. Mainly reported in Finnish population
    2. An autosomal recessive disorder
    3. Type II lissencephaly
    4. Hydrocephalus
    5. Eye abnormalities
        1. Primarily myopia
        2. Occasional glaucoma, retinal dystrophy, and cataracts
    6. Congenital muscular dystrophy: a constant feature
    7. Elevated CK levels
    8. Hypotonia
    9. Feeding difficulties
    10. Severe mental retardation
    11. Seizures common
5. Fukuyama congenital muscular dystrophy (Fukuyama et al. 1981)
    1. Mainly reported in the Japanese population
    2. An autosomal recessive disorder
    3. Cobblestone lissencephaly (type II)
    4. Eye abnormalities
        1. Myopia
        2. Optic atrophy in some patients
    5. Muscular dystrophy in all patients
    6. CK levels ranging from 10 to 50 times normal
    7. Hypotonia
    8. Marked mental retardation

Diagnostic Investigations

1. Chromosome analysis to detect microdeletion at 17p13.3
    1. High-resolution analysis indicated for all patients with type I or atypical lissencephaly
    2. Molecular cytogenetic technology using FISH (Pilz et al. 1998) to detect a submicroscopic deletion when chromosome analysis is normal and Miller-Dieker syndrome is suspected based on clinical evaluation
    3. Parental studies in case of positive findings (van Zelderen-Bhola et al. 1997)
2. MRI of the newborn brain
    1. Smooth brain
    2. Bilateral primitive Sylvian fissure giving rise to a "figure 8" appearance of the brain
    3. Persistent fetal configuration of the posterior horns of the ventricular system (colpocephaly)
3. DNA mutation analysis of *LIS1* available clinically (Dobyns and Das 2009)
    1. Direct sequencing
    2. Deletion/duplication analysis to identify deletions/duplications not detectable by sequence analysis
    3. Array comparative genomic hybridization (aCGH)

4. Multiplex ligation-dependent probe amplification (MLPA) analysis

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: based on the specific cytogenetic mechanism involved
        1. Very low recurrence risk in most patients (80% of individuals with MDS) whose abnormalities occur de novo
        2. Very high recurrence risk in families (20% of individuals with MDS) where one parent is the carrier of a balanced chromosome rearrangement involving 17p13
        3. Proband with an intragenic mutation in *LIS1*: risk to sibs negligible if neither parent has mosaicism for the mutation present in the proband
    2. Patient's offspring: patients not surviving to reproductive age
    3. A high risk for abnormal phenotypes for an individual carrying a balanced translocation with a breakpoint in 17p13 ascertained because of a relative with Miller-Dieker syndrome or dup(17p)
        1. Approximately 26% risk in all recognized pregnancies
        2. Thirty-three percent risk in pregnancies which remain viable in the second trimester or after
        3. Frequency of spontaneous miscarriages and stillbirths not appearing to be unduly elevated in these families
2. Prenatal diagnosis (Chen et al. 2013)
    1. To date, at least 28 cases of chromosome 17p13.3 deletion syndrome with prenatal findings and diagnosis reported
    2. Ultrasonography for pregnancy at risk (Sultzman et al. 1991)
        1. Polyhydramnios
        2. IUGR
        3. Lissencephaly
        4. Microcephaly
        5. Ventriculomegaly
        6. Absence of corpus callosum
        7. Congenital heart defects
        8. Omphalocele
        9. Renal abnormalities
    3. Fetal MRI of the brain
    4. Prenatal diagnosis by amniocentesis or CVS
        1. Indications
            1. Carrier parents with balanced chromosome rearrangements involving 17p13 (Pollin et al. 1999)
            2. Probably parents of all Miller-Dieker syndrome patients because of the small possibility of gonadal mosaicism in apparently de novo cases
            3. Normal relatives of unknown karyotype
        2. Cytogenetic analysis
            1. High-resolution analysis of chromosome 17
            2. Molecular cytogenetic studies (FISH)
        3. Analysis of fetal DNA: aCGH
        4. Preimplantation genetic diagnosis: available for families in which the disease-causing mutation has been identified
3. Management
    1. Supportive care
    2. Early infant intervention
    3. Anticonvulsants for seizures

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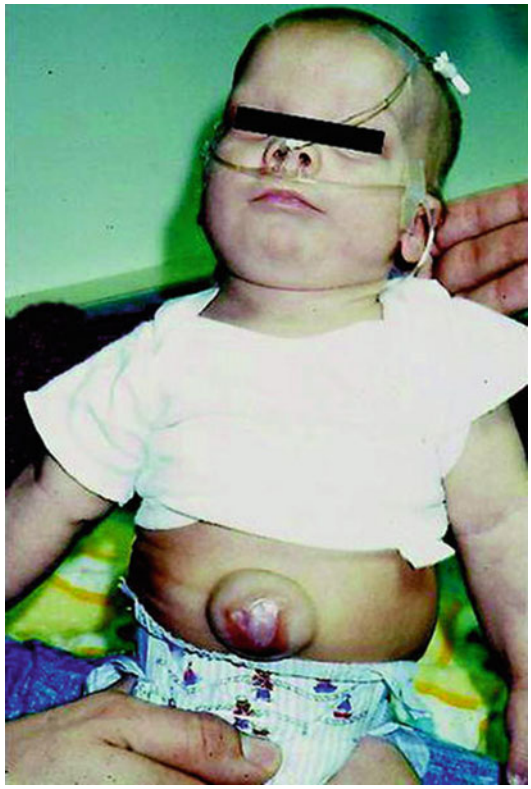

Fig. 1 A child with Miller-Dieker syndrome showing high forehead, frontal bossing, bilateral temporal narrowing, small nose with anteverted nares, prominent upper lip, micrognathia, and a surgically repaired omphalocele

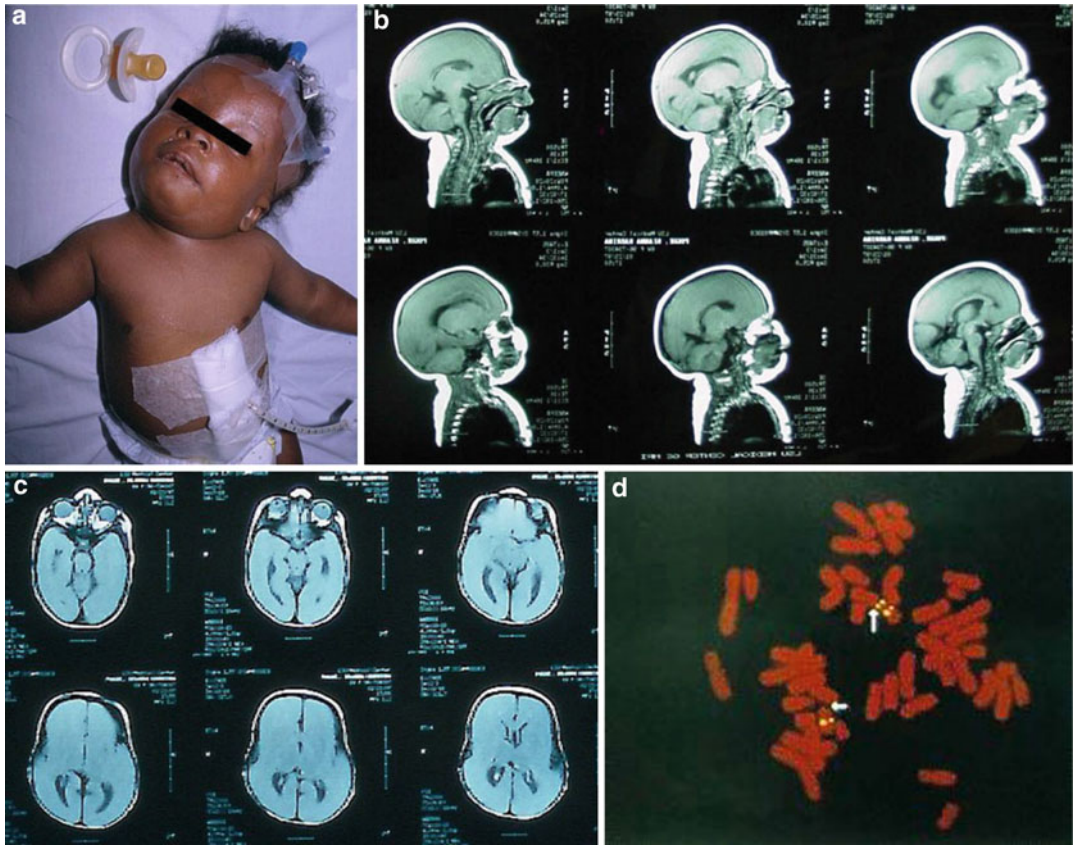

Fig. 2 (**a**–**d**) A child with Miller-Dieker syndrome showing characteristic facial traits like the previous child. The MRI of the brain showed diffuse and complete type I lissencephaly. FISH revealed one chromosome 17 lacked a signal at 17p13 indicating the presence of a deletion

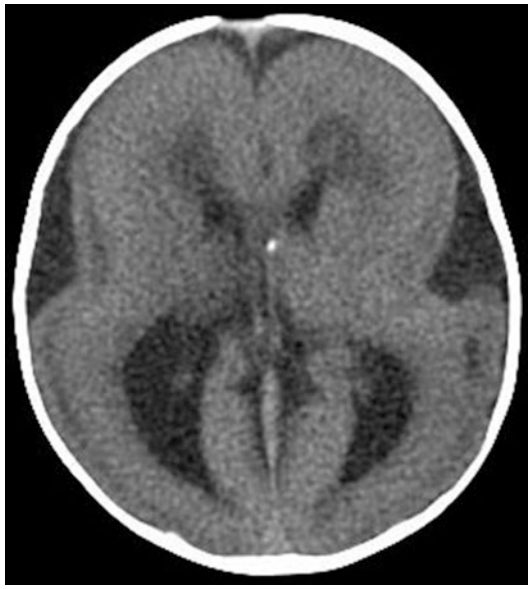

Fig. 3 This 7-week-old baby boy was evaluated for symmetrical intrauterine growth retardation with lissencephaly, hypostasis, undescended testicles, camptodactyly of digits 3 and 4 bilaterally on the hands, and craniofacial dysmorphism consisting of hypertelorism, downslanting palpebral fissures, and retrognathia. CT of the brain without contrast showed pachygyria and figure-8-shaped lissencephaly, consistent with Miller-Dieker syndrome. MRI of the brain showed remarkable abnormality consistent of lack of cortical gyri. There is a smooth cortical surface with lack of cortical sulci and a layer of subcortical heterotopic gray matter (band heteropia), consistent with lissencephaly, pachygyria, heterotopic gray matter. These findings are most consistent with a Miller-Dieker syndrome

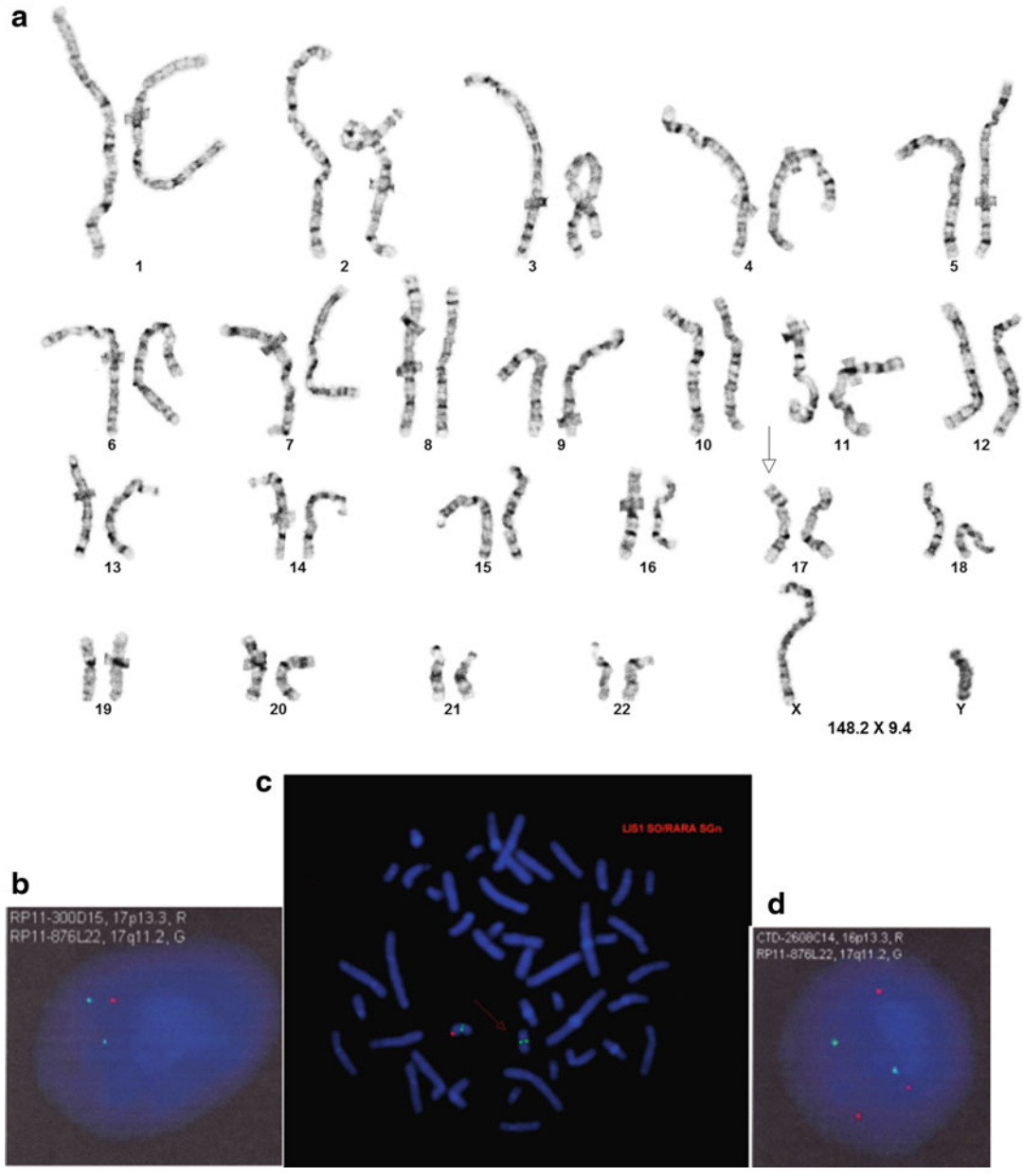

Fig. 4 (**a**–**d**) Results of high-resolution karyotype (**a**) (Courtesy of Dr. Leonard Prouty) and metaphase (**c**) and interphase (**b**, **d**) FISH analysis were consistent with cells exhibiting an unbalanced derivative chromosome 17, arising from the translocation of genetic material from the terminal short arm of chromosome 16 at band 16p13.3 to the terminal short arm of chromosome 17 at band 17p13.3 in all analyzed cells, resulting in a net gain of the terminal 16p arm and a net loss of the terminal 17p arm [ish der(17) t(16;17)(p13.3;p13.3)(CTD-2608C14+;RP11-300D15-)] (Courtesy of CombiMATRIX Diagnostics). The mother's metaphase and interphase FISH analysis exhibited an apparently balanced translocation between the terminal short arms of chromosomes 16 and 17 at bands 16p13.3 and 17p13.3 based on the unbalanced derivative chromosome seen in her offspring (Figures not shown)

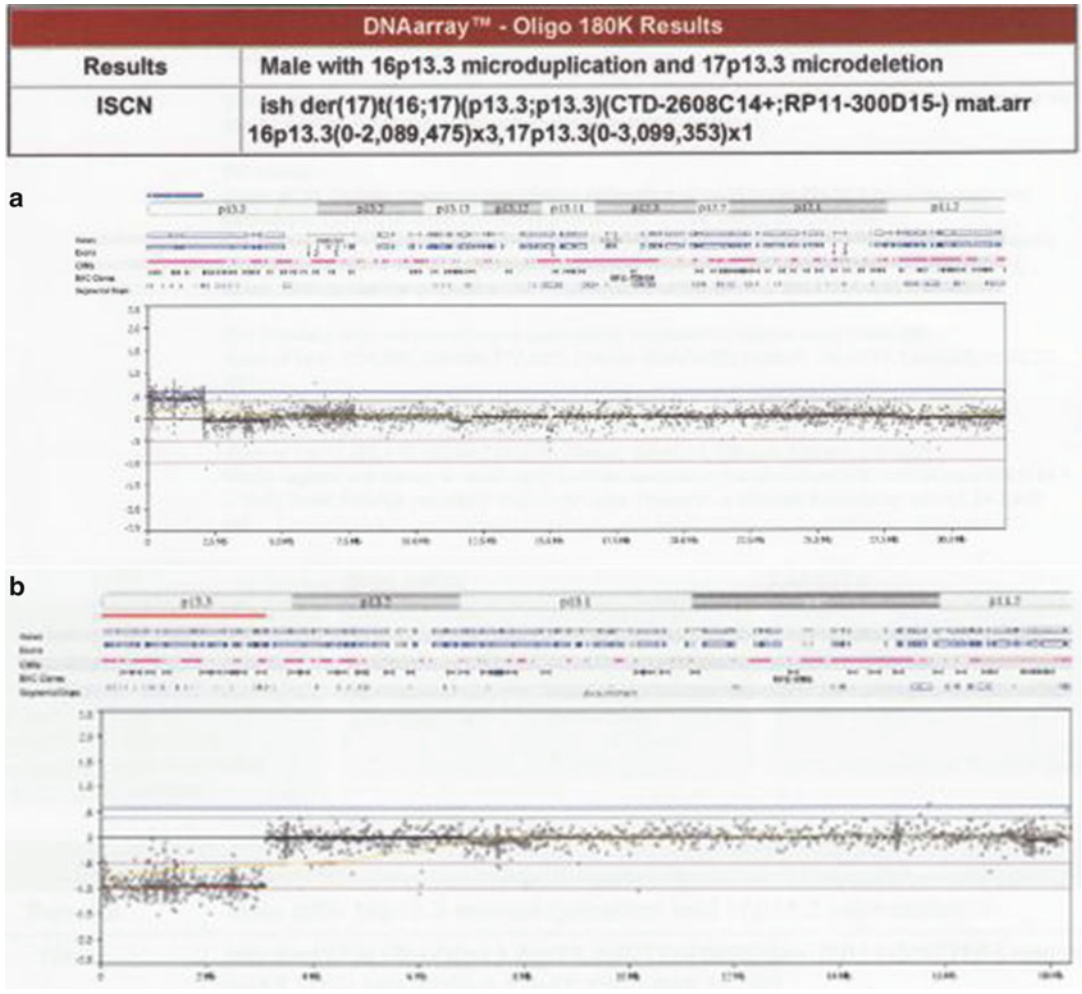

Fig. 5 (**a**, **b**) A chromosomal microarray was done and the baby found to have a 2.0 Mb microduplication of 16p13.3 (**a**) and a 3.0 Mb microdeletion of 17p13.3 (**b**) (Courtesy of CombiMATRIX Diagnostics). The deleted segment of 17p included the *LIS1* (PAFAH1B1) gene and is consistent with Miller-Dieker syndrome or lissencephaly/subcortical band heterotopia. The mother had FISH analysis results consistent with an apparently balanced translocation between the terminal short arms of chromosomes 16 and 17 at bands 16p13.3 and 17p13.3

Mitochondrial Leber Hereditary Optic Neuropathy

Contents

Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. They can be caused by mutation of genes encoded by either nuclear DNA or mitochondrial DNA (mtDNA) (Chinnery 2014). Mitochondrial disorders are a major cause of chronic human disease with an estimated prevalence of 1 in 10,000 in the United Kingdom, and 1 in 200 individuals is at-risk mutational carrier (Elliott et al. 2008; Schaefer et al. 2008). Ocular involvement, especially optic nerve dysfunction, is a prominent feature in this group of disorders, suggesting the underlying mitochondrial etiology. Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA) (Kjer-type optic atrophy) are the two most common inherited optic neuropathies, resulting from mitochondrial dysfunction.

In 1871, the German ophthalmologist Theodore Leber (1871) first described the distinctive clinical entity of LHON with a characteristic pattern of visual loss among members of four families, subsequently confirmed in pedigrees from different populations (Bell 1931; Imai and Moriwaki 1936; Lundsgaard 1944). These early studies highlighted the salient features of LHON, including the maternal transmission of the disease, the predilection of males to lose vision, and the almost exclusive involvement of the optic nerve.

Autosomal dominant optic atrophy is the most common primary hereditary optic neuropathy (Yoshida et al. 2006). It is characterized by optic nerve pallor and reduced visual acuity (Eliott et al. 1993; Votruba et al. 1998a, b). It was first described clinically by Batten (1896) and later by Kjer (1959) and typically presents in childhood with bilateral visual loss that is usually symmetrical, temporal optic nerve pallor, centrocecal visual field scotoma, and color vision deficit (Caldwell et al. 1971; Smith 1972; Hoyt 1980; Jaeger 1988).

Synonyms and Related Disorders

Autosomal dominant optic atrophy (DOA) (Kjer-type optic atrophy); Hereditary optic neuropathies; Leber hereditary optic neuropathy (LHON); Leber optic atrophy; Leber optic neuropathy

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Genetics/Basic Defects

1. LHON (Yu-Wai-Man et al. 2009):
    1. Caused by primary mitochondrial DNA (mtDNA) mutations affecting the respiratory chain complexes:
        1. Over 95% of LHON pedigrees are now known to harbor one of the three mitochondrial DNA (mtDNA) point mutations: m.3460G > A, m.11778G > A (a point mutation within the mitochondrial genome known to cause the first human disease, LHON) (Wallace et al. 1988; Newman et al. 1991), and m.14484T > C, which all involve genes encoding complex I subunits of the mitochondrial respiratory chain (Mackey et al. 1996).
        2. New MT-ND1 pathologic mutations for Leber hereditary optic neuropathy (Martinez-Romero et al. 2014): this mutation expands the spectrum of deleterious changes in mitochondrial DNA-encoded complex I polypeptides associated with this pathology and highlights the difficulties in assigning pathogenicity to new homoplasmic mutations that show incomplete penetrance in sporadic Leber hereditary optic neuropathy patients.
    2. Mitochondrial genetic factors:
        1. Homoplasmy: in most LHON pedigrees, the primary mutation is homoplasmic (every mtDNA molecule harbors the mutant allele, i.e., only one type of mtDNA exists within an individual).
        2. Heteroplasmy (both mutant and wild-type mtDNA coexist within an individual):
            1. Cells can contain anywhere between 100 and 10,000 mitochondria depending on their metabolic demands. With 2–10 mtDNA molecules in each mitochondrion, this results in a very high copy number per cell.
            2. Ten to fifteen percentage of LHON carriers are thought to be heteroplasmic (one mtDNA subpopulation carrying the wild-type allele) (Smith et al. 1993; Harding et al. 1995; Man et al. 2003).
            3. Available data suggest that heteroplasmy contributes to incomplete penetrance, with the risk of blindness being minimal if the mutational load is <60% (Chinnery et al. 2001).
        3. MtDNA haplogroups:
            1. MtDNA accumulates mutations about ten times faster than nuclear genome, resulting in a high degree of polymorphism (Brown et al. 1979).
            2. Because human mtDNA is strictly maternally inherited and does not recombine, polymorphisms have accumulated sequentially along radiating female lineages as women migrated out of Africa into the different continents about 150,000 years ago (Wallace et al. 1999).
            3. Reflecting its evolution, a number of stable polymorphic variants cluster together in specific combinations referred to as haplogroups, with individuals of European ancestry belonging to one of nine haplogroups: H, I, J, K, T, U, V, W, and X (Torroni et al. 1996; Hofmann et al. 1997).
            4. Comprehensive studies of almost 95% of a 328-living-member pedigree with LHON 11778/J haplogroup indicate the strong influence of environmental risk factors (Sadun et al. 2003).
            5. A recent meta-analysis of 159 - European LHON pedigrees indicated that the risk of visual loss for the three primary LHON mutations is influenced by the mtDNA background (Hudson et al. 2007).
    3. Nuclear genetic factors:
        1. The predominance of affected males in LHON cannot be explained by mitochondrial inheritance, and segregation

analysis suggests the existence of a recessive X-linked susceptibility gene acting in synergy with the mtDNA mutation to precipitate the optic neuropathy (Bu and Rotter 1991, 1992; Nakamura et al. 1993).
2. LHON has been suggested to involve both mitochondrial and X-chromosome-linked loci: a proportion of affected females are likely heterozygous at the X-linked locus and affected due to unfortunate X-chromosome inactivation (Bu and Rotter 1992).
3. Although the actual causative gene in this region of interest has not yet been identified, a high-risk haplotype (DXS8090-DXS1068) at Xp21 was defined which increased the risk of visual failure >35-fold for the m.11778G > A and m.14484 T > C mutations but not for m.3460G > A (Hudson et al. 2005).
4. The possibility of other autosomal nuclear modifier genes in LHON has not been excluded, and the genetic etiology of LHON might prove even more complex, with epistatic interaction of these multiple nuclear susceptibility loci and genetic heterogeneity.

4. Environmental factors:
   1. The existence of discordant monozygotic twins strongly suggests that environmental factors also contribute to penetrance.
   2. Anecdotal reports of nutritional deprivation, exposure to industrial toxins, antiretroviral drugs, psychological stress, or acute illness precipitating the onset of blindness in LHON (Mackey et al. 2003; Sanchez et al. 2006; Carelli et al. 2007).
   3. The role of environmental triggers in LHON remains largely unanswered, and more robust epidemiological data are needed, which will necessitate a multicenter collaborative effort in order to collect sufficient number of subjects for analysis.

2. DOA (Allen et al. 2015):
   1. Caused by mutations in the *OPA1* gene, a gene encoding for a dynamin-like mitochondrial GTPase, an inner mitochondrial membrane protein critical for mtDNA maintenance and oxidative phosphorylation, in the majority of DOA families.
   2. These mutations are maternally inherited and can have an asymmetric presentation.
   3. The mitochondrial DNA haplogroup appears to contribute to disease pathogenicity with haplogroup J of particular importance (Howell et al. 2003; Sadun et al. 2003).
   4. Rarely, mutations in OPA3 cause recessive optic atrophy that is commonly associated with cataracts and other neurological abnormalities (Ferré et al. 2009).
3. Pathology for both LHON and DOA: limited in the majority of cases to the retinal ganglion cells (RGCs), a highly specialized group of cells within the eye
4. Expanding phenotype associated with LHON and DOA: providing important insights into possible disease pathways leading to optic nerve degeneration and visual failure

Clinical Features

1. LHON (Yu-Wai-Man et al. 2009; Milea et al. 2010):
   1. Affected individuals are usually entirely asymptomatic – blurring and clouding of vision affecting the central visual field are usually the first symptoms of LHON (Piotrowska et al. 2015).
   2. Presymptomatic phase:
      1. Fundal abnormalities such as telangiectatic vessels around the optic disks and variable degrees of retinal nerve fiber layer edema:
         1. Documented in some asymptomatic carriers
         2. Can fluctuate with time
      2. Thickening of the temporal retinal nerve fiber layer found in a proportion of

unaffected carriers by using optical coherence tomography imaging: provides further evidence that the papillomacular bundle is particularly vulnerable in this disorder (Savini et al. 2005; Quiros et al. 2006)
3. Subtle impairment of optic nerve function in some individuals on detailed psychophysical testing (Sadun et al. 2006):
    1. Loss of color vision affecting mostly the red-green system
    2. Reduced contrast sensitivity
    3. Subnormal visual electrophysiological parameters
3. Acute phase:
    1. Experiencing blurring or clouding of vision in one eye
    2. Subacute presentation in the vast majority of an early age of onset (<20 years) with slow progression of the visual deficits and large optic nerve head surface area (Nikoskelainen et al. 1996; Barboni et al. 2006)
    3. Devastating, with the majority of patients showing no functional improvement and remaining as legally blind
4. Interval between involvement between both eyes (Ohden et al. 2016):
    1. The vision of the fellow eye may remain unaffected for months to years after initial presentation.
    2. Involvement of the fellow eye may occur at any time after initial presentation – even after decades of stable unilateral vision loss.
    3. With advancements in therapeutics for LHON, it is important to note that any delay in involvement of the fellow eye may represent the natural disease course, rather than an effect of therapy.
5. Associated features:
    1. Cardiac arrhythmias.
    2. Neurological abnormalities: rarely clinically significant, but a small number of LHON pedigrees have severe neurological deficits such as spastic dystonia, ataxia, and juvenile onset encephalopathy in addition to the optic neuropathy ("LHON plus" syndromes) (Bower et al. 1992; Nikoskelainen et al. 1994, 1995; Meire et al. 1995; Mashima et al. 1996)
        1. Postural tremor
        2. Peripheral neuropathy
        3. Nonspecific myopathy and movement disorders

2. DOA:
    1. Prevalence:
        1. A historical figure of 1 in 50,000 among Caucasians often quoted in the literature (Lyle 1990)
        2. Thought to be the most common inherited optic neuropathy in the Netherlands, with a population frequency of 1 in 12,000, a higher prevalence linked to a mutational founder event (Thiselton et al. 2001)
    2. Insidious onset of symptoms: 13–25% of patients with optic atrophy in premolecular case series were visually asymptomatic and were only identified through contact tracing via other affected family members (Kline and Glaser 1979; Hoyt 1980).
    3. Pronounced inter-/intrafamilial variability in the severity of visual symptoms:
        1. Makes genetic counseling difficult
        2. Visual decline: classically starts in the first two decades of life
        3. Visual acuity: ranges from 6/6 to the detection of hand movement only
        4. The rate of progression of visual loss: not easy to predict, with 19–50% of patients experiencing further, albeit slow, deterioration on long-term follow-up (Kjer 1959; Eliott et al. 1993; Votruba et al. 1998a, b; Puomila et al. 2005; Cohn et al. 2008).
    4. Pupil afferent deficits (Bremner et al. 2001):
        1. Pupil function appears less affected than visual function.
        2. The retinotectal fibers serving the pupil light reflex are less susceptible to damage from the *OPA1* genetic defect than the retinogeniculate fibers serving vision.

5. Better overall visual prognosis compared to LHON (Kjer et al. 1996; Votruba et al. 1998a, b; Cohn et al. 2007):
    1. A mean visual acuity of 6/24–6/36
    2. Results in significant visual impairment with about half of all affected individuals failing the driving standards and 13–46% registered as legally blind
6. Generalized dyschromatopsia: predominant color defect involving both the blue-yellow and red-green axes, with a minority of patients having pure tritanopia (<10%), which was once considered to be a pathognomonic feature of dominant optic atrophy (Berninger et al. 1991).
7. Central, centrocecal, and paracentral scotomas are the most common field abnormalities with sparing of the periphery, findings consistent with the primary involvement of the papillomacular bundle in this condition.
8. The optic disk pallor in DOA falls into two main categories (Kline and Glaser 1979; Hoyt 1980; Kjer 1959):
    1. Diffuse pallor involving the entire neuroretinal rim in about half of all cases
    2. A temporal wedge in the remainder of cases
9. Other common optic disk findings (Votruba et al. 1998a, b, 2003; Fournier et al. 2001):
    1. Saucerization (79%)
    2. Peripapillary atrophy (69%)
    3. A cup to disk ratio 0.5 (48%)
    4. A typical profile with bilateral symmetrical thinning around the optic disk, most pronounced in the temporal quadrant (circumpapillary retinal nerve fiber layer thickness using optical coherence tomography) (Ito et al. 2007; Kim and Hwang 2007)
10. Normal tension glaucoma: single nucleotide polymorphisms in intron 8 and exon 4 of the *OPA1* gene could increase the risk of normal (but not high) tension glaucoma in whites (Yu-Kai-Man et al. 2010b).
11. Extraocular findings: *OPA1* gene may be responsible for a continuum of phenotypes, ranging from mild visual loss to very variable, sometimes severe, multisystemic involvement of the disease (Amati-Bonneau et al. 2008; Hudson et al. 2008).
12. Optic atrophy associated with multiple sclerosis-like disease in a patient carrying a new missense *OPA1* mutation (p.S646L) in the highly conserved dynamin domain (Vemy et al. 2008), suggesting a relationship between mitochondrial dysfunction and the central nervous system defect.
13. Optic atrophy and deafness occurring in patients with a specific R445H mutation (Amati-Bonneau et al. 2005; Zeviani 2008) and other mutations.
14. Multisystemic disorders associated with optic atrophy 1 mutations (autosomal dominant optic atrophy "plus") (ADOA "plus syndrome"): an optic atrophy associated with early onset in childhood, followed by chronic progressive external ophthalmoplegia, ataxia, sensorineural deafness, sensorimotor neuropathy, and myopathy in adult life.

Diagnostic Investigations

1. LHON (Yu-Wai-Man et al. 2009):
    1. Tentative diagnosis of LHON usually be made on the following:
        1. Clinical grounds (especially if classical ophthalmological features are present).
        2. A clear maternal history is elicited.
    2. Ophthalmoscopic findings (Huoponen 2001):
        1. Presymptomatic stage:
            1. Peripapillary telangiectatic microangiopathy visible in the presymptomatic stage: the first sign of the disease (Nikoskelainen et al. 1982, 1983)

2. Increased hyperemia, swelling of the optic disk, and arteriolar dilation at the end of the presymptomatic stage
2. Acute stage:
   1. Visual loss.
   2. Severe hyperemia, arteriolar dilation, disk swelling, telangiectatic angiopathy, and a glistening, whitish, opaque nerve fiber layer: hallmarks of this stage of the disease.
   3. Decreased visual acuity and development of a relative centrocecal scotomas can be minimal or even absent.
3. End stage:
   1. Disappearance of microangiopathy
   2. Fading of retinal nerve fiber layer
   3. Large and absolute centrocecal scotoma

3. Molecular genetic testing on a blood DNA sample: remains the gold standard and will confirm that the patient harbors one of the three primary mtDNA LHON mutations, with implications for future genetic counseling:
   1. Targeted mutation analysis:
      1. Primary pathogenic LHON-causing mtDNA mutations
      2. Secondary LHON-causing mtDNA mutations
   2. Sequence analysis and mutation scanning
4. Biochemical findings associated with the primary mutations:
   1. Variable complex I defects: associated with all the primary mutations
   2. A defect in respiratory chain function in LHON: first demonstrated in platelet mitochondria from a family that was subsequently shown to harbor the ND1/3460 mutations (Parker et al. 1989)
   3. A marked reduction in the specific activity of complex I associated with the ND1/3460 mutation: further detected in lymphoblasts (Majander et al. 1991; Brown et al. 2000), leukocytes (Carelli et al. 1997), and fibroblasts (Cock et al. 1999)
   4. ND4/11778 mutation: less severe reduction in complex I function
   5. A reduction in respiration of NADH-linked substrates (Majander et al. 1991; Lodi et al. 2000)
   6. Alteration in the affinity of complex I for ubiquinone (Degli Esposti et al. 1994)
5. Electrophysiological studies, including pattern electroretinograms (PERGs) and visual evoked potentials (VEPs), if indicated, can be carried out to exclude retinal pathology and confirm optic nerve dysfunction (Sherman and Kleiner 1994).
6. An electrocardiogram is also recommended to exclude a preexcitation syndrome which has been documented in LHON, although such a finding is rare and does not require any intervention in the absence of cardiac symptoms (Nikoskelainen 1994; Riordan-Eva and Harding 1995).
7. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are usually normal in LHON.

2. DOA (Votruba et al. 1998a, b; Delettre-Cribaillet et al. 2009):
   1. Clinical diagnosis: the majority of patients present in early to mid-childhood and the clinical diagnosis are generally reliable from 6 years of age and above, except in rare cases.
   2. Visual acuity.
   3. Color vision.
   4. Visual fields.
   5. Assessment of extraocular muscles.
   6. Hearing evaluation.
   7. Electrophysiology:
      1. Visual evoked potentials (VEPs): typically absent or delayed, indicating a conduction defect in the optic nerve
      2. Pattern electroretinogram (PERG): an abnormal N95:P50 ratio with reduction in the amplitude of the N95 waveform (Holder et al. 1998), supporting a ganglion cell origin for the optic atrophy since the N95 component of the PERG is thought to be specific for the retinal ganglion cell

8. Muscle biopsy and histoenzymology (La Morgia et al. 2014):
    1. As for LHON, DOA also may present a "plus" phenotype, which includes deafness, chronic external ophthalmoplegia, peripheral neuropathy, cerebellar atrophy, and mitochondrial myopathy (Amati-Bonneau et al. 2008; Yu-Wai-Man et al. 2010a).
    2. In these cases, muscle biopsy histology and histoenzymology may disclose the hallmarks of mitochondrial myopathy with cytochrome *c* oxidase negative fibers, whereas molecular analysis will reveal the pathological accumulation of multiple mtDNA deletions (Yu-Wai-Man et al. 2010a).
9. Molecular genetic testing available clinically:
    1. Sequence analysis of all exons of *OPA1*
    2. Target mutation analysis for the Danish founder mutation
    3. Sequence analysis of RNA RT-PCR amplification on *OPA1*
    4. Deletion/duplication analysis
3. Diffusion tensor imaging mapping of brain white matter (Manners et al. 2015):
    1. Patients with Leber hereditary optic neuropathy had preferential involvement of the optic and acoustic radiations, consistent with transsynaptic degeneration.
    2. Whereas patients with optic atrophy gene 1-autosomal dominant optic atrophy presented with widespread involvement suggestive of a multisystemic, possibly a congenital/developmental, disorder.

Genetic Counseling

1. Recurrence risk (Yu-Wai-Man and Chinnery 2013; Yu-Wai-Man et al. 2009):
    1. LHON:
        1. Not possible to predict accurately whether or when LHON carriers will become affected
        2. Two main predictive factors for visual failure:
            1. Gender: males, a 50% lifetime risk of blindness, and females, only 10% lifetime risk of blindness.
            2. Age: most patients experience visual loss in their late teens and 20s. The probability of becoming affected decreases with age, being minimal once past the age of 50 years.
        3. Once a primary LHON mutation has been identified in a proband, other maternally related family members can be offered molecular genetic testing to exclude the possibility of a de novo mutation, which is rare.
        4. Since LHON shows strict maternal inheritance, male carriers can be reassured that none of their children will inherit the mtDNA mutation, whereas female carriers will transmit the pathogenic mutation to all of their offspring.
        5. Since most mothers are homoplasmic, their children will only harbor the mutant species, but the situation is more complex for a heteroplasmic mother as she could transmit a higher or a lower level of the mutation to a particular offspring, which will impact on the latter's risk of visual failure.
        6. Given the variability associated with the clinical manifestation of LHON, finding evidence of the 11778 mutation in the older man gave his young relative the advantage of a rapid diagnosis, avoiding unnecessary diagnostic procedures and providing him a small window of opportunity to prepare for his visual disability (Malouf et al. 2016).
        7. Although the mutant level can be determined and there is evidence that a mutational threshold of $>60\%$ in blood is necessary for disease expression, genetic counseling for these unaffected heteroplasmic carriers remains difficult.

8. For similar reasons, the prenatal genetic testing of heteroplasmic women with amniocentesis or chorionic villus sampling (CVS) would be difficult to interpret.
9. Patient's sib:
    1. The recurrent risk depends on the genetic status of the mother.
    2. All sibs at risk of inheriting the mutation if the mother has the mtDNA mutation.
10. Patient's offspring:
    1. An affected or unaffected male with a primary LHON-causing mtDNA mutation cannot transmit the mutation to any of his offspring.
    2. An affected or unaffected female with a primary LHON-causing mtDNA mutation transmits the mutation to all of her offspring.
    3. An affected female with heteroplasmy may transmit a low level of mutant mtDNA to her offspring, confirming a low disease risk (Chinnery et al. 2001).
11. Other family members:
    1. The recurrence risk depends on the genetic status of the proband's mother.
    2. If the proband's mother has an mtDNA mutation, her sibs and mother are also at risk.

2. DOA (Votruba et al. 1998a, b; Yoshida et al. 2006; Delettre-Cribaillet et al. 2009):
    1. Despite DOA being an autosomal dominant Mendelian disorder with high penetrance (0.98) (Eiberg et al. 1994), genetic counseling for mutational carriers is difficult because of the pronounced inter- and intrafamilial heterogeneity and variability in the visual phenotype.
    2. A multidisciplinary approach to the diagnosis and management of these patients is helpful, involving both clinical ophthalmologists and geneticists, electrodiagnostic services, low vision specialists, and educational advisors.
3. An apparently sporadic person who presents with nonprogressive optic atrophy and normal neuroimaging:
    1. Important to examine all family members fully, as relatives may be only mildly affected.
    2. Establish a disease pedigree and the mode of transmission.
4. A person uncertain of his clinical status from a family known to be affected by dominant optic atrophy: needs to include color vision and electrophysiology in the full clinical assessment of the patient in order to be able to make a diagnosis.
5. Patient with the absence of a mutation: genetic counseling relies on conventional risk assessment.
6. With the availability of molecular testing for *OPA1* becoming more accessible, an increasing number of individuals with pathogenic mutations are being identified who are otherwise visually unaffected.
7. Patient with *OPA1* mutation:
    1. Genetic counseling is difficult since clinical manifestation of the same mutation within a family can be remarkably variable.
    2. Dramatic psychological impact on the person involved with awareness of one's susceptibility to the disease without an actual possibility of intervention.
8. The clinical features of the primary optic neuropathies are sufficiently similar that clinical examination cannot reliably differentiate individuals with dominantly inherited disease caused by mutations in *OPA1*, maternally inherited disease caused by mitochondrial DNA mutations, or recessively inherited disease in patients with *OPA3* mutations. By identifying the disease-causing mutation, genetic testing can accurately define the inheritance pattern and subsequent disease risk for family members (Allen

et al. 2015). In addition, genetic testing can measure mitochondrial heteroplasmy, which is an important feature of mitochondrial disease pathogenicity (Wallace and Chalkia 2013).

9. Patient's sib:
    1. Risk depends on the genetic status of the parents.
    2. A 50% risk if a parent is affected.
    3. Apparently low risk when the parents are found to be clinically unaffected on the basis of visual acuity study, color vision evaluation, fundus examination, VET, and PERG.
    4. Possibilities of germ line mosaicism in a parent or a de novo mutation in the proband exist if a disease-causing mutation cannot be detected in the DNA of either parent.
10. Patient's offspring: a 50% risk of inheriting the mutation.

2. Prenatal diagnosis and preimplantation genetic diagnosis (Yu-Wai-Man and Chinnery 2013): once the mtDNA LHON-causing variant in the mother has been identified, prenatal diagnosis or preimplantation genetic diagnosis for a pregnancy at increased risk for LHON may be an option that a couple may wish to consider.
    1. LHON:
        1. Prenatal diagnosis for pregnancies at increased risk: possible by amniocentesis or CVS.
        2. MtDNA mutation in the mother must be identified before prenatal testing can be performed.
        3. Reasons for difficult accurate interpretation of a positive prenatal test:
            1. The mtDNA mutational load in amniocytes and chorionic villi is unlikely to correspond to that of other fetal or adult tissues because of mitotic segregation.
            2. The presence of the mtDNA mutation does not predict the occurrence, age of onset, severity, or rate of progression of this typically adult-onset disease.
    2. DOA:
        1. Prenatal diagnosis for pregnancies at an increased risk is possible by amniocentesis or CVS.
        2. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
3. Management:
    1. LHON:
        1. Mainly supportive:
            1. Provision of visual aids
            2. Registration with the relevant social services
        2. ECG may reveal a preexcitation syndrome in both affected and unaffected LHON carriers.
        3. Risk factors for additional vision loss, such as smoking and consuming alcohol (Meyerson et al. 2015).
        4. Currently, the most promising compounds are short-chain quinones that have been shown to protect the vision of LHON patients during the early stages of the disease (Gueven and Faldu 2013).
    2. DOA:
        1. Supportive.
        2. Treatment of decreased visual acuity.
        3. Patients are advised to avoid alcohol and tobacco consumption, as well as the use of medications that may interfere with mitochondrial metabolism (Lenaers et al. 2012).
    3. In vitro fertilization: in addition to neuroprotective strategies for rescuing retinal ganglion cells from irreversible cell death, innovative in vitro fertilization techniques are providing the tantalizing prospect of preventing the germ line transmission of pathogenic mtDNA mutations, eradicating in so doing the risk of disease in future generations (Yu-Wai-Man et al. 2014).
    4. Gene therapy for Leber hereditary optic neuropathy (Feuer et al. 2016):
        1. No serious safety problems were observed in the first five participants enrolled in this phase I trial of virus-

based gene transfer in this mitochondrial disorder.

2. Additional study follow-up of these and additional participants planned for the next 4 years are needed to confirm these preliminary observations.

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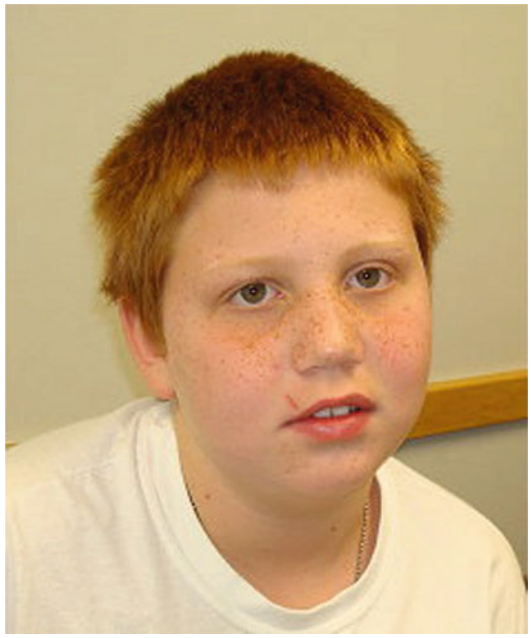

Fig. 1 A 10-year-old boy was relatively healthy until last year when he suddenly started having trouble seeing and complained constant headache. He was noted to have painless visual failure, optic nerve atrophy in his left eye, and exophthalmos. He has also experienced minor tremors, muscle weakness, nausea, and movement disorder. Family history revealed similarly affected males in two generations on the maternal side of the family. Molecular genetic analysis detected an apparently homoplasmic m.11778G > A mutation. This mutation in *ND4* gene is commonly associated with Leber hereditary optic neuropathy (LHON). The result confirms the carrier/affected status of this boy for a mitochondrial DNA disorder

Mitochondrial Myopathies

Contents

Mitochondrial myopathies here imply the disorders of the respiratory chain that exclusively or predominantly affect the skeletal muscle (DiMauro and Gurgel-Gianneti 2006). They frequently present with multisystem dysfunction and have a broad variety of phenotypes and genetic etiologies. They can be classified genetically into two major groups: those due to mutations in mitochondrial DNA (mtDNA) and those due to mutations in nuclear DNA (nDNA). The prevalence of mitochondrial disorders as a whole is approximately 1 in 10,000 (Schaefer et al. 2008), although the carrier frequency of mtDNA mutations is about 1 in 200 (Elliott et al. 2008).

Synonyms and Related Disorders

Ataxia neuropathy syndromes (ANS); Infantile myopathy with COX deficiency; Kearns-Sayre syndrome (KSS); Leber's hereditary optic neuropathy (LHON); Leigh syndrome; Mitochondrial DNA depletion syndrome; Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); Mitochondrial recessive ataxia syndrome (MIRAS); Myoclonus epilepsy and ragged-red fibers (MERRF); Myoclonic epilepsy myopathy sensory ataxia (MEMSA); Myopathy, neurogastrointestinal encephalopathy (MNGIE); Pearson syndrome; Progressive external ophthalmoplegia (PEO); Sensory ataxia neuropathy dysarthria ophthalmoplegia (SANDO); Spinocerebellar ataxia with epilepsy (SCAE)

Genetics/Basic Defects

1. Possible mechanisms for a mitochondrial disease to be confined to skeletal muscle (Dimauro 2006; DiMauro and Gurgel-Gianneti 2006):
   1. Occurrence of mutations in tissue-specific nuclear genes: although reasonable, this concept lacks verification.
   2. Somatic mtDNA mutation: these spontaneous, de novo mutations occur in the oocyte or the embryo, affect myoblasts after germ layer differentiation, and are best exemplified by myopathies due to mutations in mtDNA protein-encoding genes (Andreu et al. 1999).
   3. Skewed heteroplasmy: "garden-variety" pathogenic mutations in mtDNA are heteroplasmic and ubiquitous but have such a skewed predominance in the skeletal

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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muscle that they surpass a pathogenic threshold only in this tissue, resulting in myopathic phenotypes.

2. Disorders due to mutations in mtDNA:
   1. Impair mitochondrial protein synthesis in toto:
      1. mtDNA rearrangements (Pfeffer and Chinnery 2013):
         1. Deletions: single large-scale deletions are typically due to sporadic events and are usually not inherited, although inherited deletions have been described (Chinnery et al. 2004). The deletions can be associated with sporadic progressive external ophthalmoplegia (PEO), either alone or in the context of the multisystemic Kearns-Sayre syndrome (Hays et al. 2006).
         2. Depletion (loss of mtDNA) and multiple deletions are typically secondary effects of faulty mtDNA maintenance, from mutation of nDNA-encoded mitochondrial proteins.
         3. Duplications.
      2. Mutations in tRNA genes:
         1. A3243G mutation in $tRNA^{LEU(UUR)}$ in 50% of patients with MELARS (Karrpa et al. 2005)
         2. The 7472-insertion mutation in $tRNA^{Ser(UCN)}$ associated with a patient with MERRF and a patient with pure myopathy (Pulkes et al. 2005)
      3. Mutations in rRNA genes
   2. Impair specifically the activity of the respiratory chain complex whose subunit is mutated: mutations in protein-encoding genes:
      1. One protein-encoding gene that is rapidly attaining the status of "pathogenic hot spot" is *ND5*, which encodes subunit 5 of complex I (DiMauro and Davidzon 2005):
         1. Although none of the mutations in *ND5* causes a pure myopathy, the muscle is involved in multisystem disorders ranging from MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) to LHON (Leber's hereditary optic neuropathy), Leigh syndrome, and MERRF (myoclonus epilepsy and ragged-red fibers), often overlapping in individual patients.
         2. From the myopathological point of view, it is worth noting that muscle biopsies from these patients only occasionally exhibit ragged-red fibers (RRF), which are invariably cytochrome c oxidase (COX) positive.
      2. Mutations in *ND1* and in *ND*4 have been associated with pure myopathy (Hays et al. 2006).
      3. A mutation in *ND2* (G4810A) joins the list of mutations causing severe exercise intolerance (chronic fatigue syndrome) followed by mild ptosis and PEO (Pulkes et al. 2005).
3. Disorders due to mutations in nDNA affecting the mitochondrial respiratory chain directly fall into the following 3 major groups:
   1. "Direct hits" (mutations in respiratory chain subunits):
      1. Complexes I and II
      2. Coenzyme Q10 (CoQ10): variable presentation of CoQ10 deficiency (Lalani et al. 2005; Hirano et al. 2006; Horvath et al. 2006)
   2. "Indirect hits" (mutations in ancillary proteins that are needed for the correct assembly and function of respiratory chain complexes): complexes III, IV, and V.
   3. Defects in intergenomic signaling (mutations in nuclear genes that control the abundance and quality of mtDNA and result in multiple deletions of mtDNA or mtDNA depletion or both conditions at once): mutations in *POLG* gene cause autosomal dominant PEO (adPEO) and also autosomal recessive PEO (arPEO) (Spinazzola and Zeviani 2005).

Clinical Features

1. Onset (Pfeffer and Chinnery 2013):
   1. Occur at any age

2. More severe phenotypes typically present earlier in life, e.g., so-called deletion syndromes (caused by sporadic, large-scale deletions of mtDNA) (Pearson syndrome)
3. More moderate syndrome present in early childhood or adolescence, e.g., Kearns-Sayre syndrome.
4. Milder phenotype typically present later in life, e.g., progressive external ophthalmoplegia

2. Clinical course:
   1. Usually progressive conditions
   2. Can produce significant disability
   3. Premature death, in some instances, often due to non-muscle involvement such as cardiac conduction defects or seizures (Schapira 2006)
3. Clinical features by organ systems:
   1. Central nervous system:
      1. Neurologic central:
         1. Ataxia
         2. Movement disorder
         3. Spasticity
         4. Seizures
         5. Stroke-like episodes
         6. Migraine
         7. Encephalopathy
         8. Cognitive impairment
      2. Neuropsychiatric:
         1. Depression
         2. Fatigue
         3. Psychosis
   2. Ocular system:
      1. Myopathy: ophthalmoplegia and/or ptosis
      2. Optic nerve atrophy
      3. Pigmentary retinopathy
      4. Cataract
   3. Musculoskeletal system:
      1. Myopathy (skeletal muscle: ocular > axial/proximal > bulbar > distal muscles)
      2. Myalgia
   4. Cardiac system:
      1. Conduction abnormalities
      2. Cardiomyopathy: hypertrophic > dilated
   5. Endocrine system:
      1. Diabetes mellitus
      2. Hypothyroidism
      3. Hypoparathyroidism
      4. Gonadal failure
      5. Growth hormone deficiency
   6. Renal system:
      1. Renal tubular acidosis
      2. Toni-Fanconi-Debre syndrome
   7. Gastrointestinal system:
      1. Dysphagia
      2. Dysmotilty:
         1. Gastroparesis
         2. Diarrhea
         3. Constipation
         4. Pseudo-obstruction
   8. Neurologic peripheral:
      1. Axonal polyneuropathy
      2. Sensory ataxia
      3. Sensorineural hearing loss
      4. Autonomic dysfunction
   9. Others:
      1. Short stature
      2. Spontaneous abortion
4. Mitochondrial myopathy syndromes presenting with ocular myopathy:
   1. Progressive external ophthalmoplegia (PEO):
      1. Ptosis
      2. Ophthalmoplegia
      3. Proximal myopathy often present
      4. Other clinical features variably present
   2. Kearns-Sayre syndrome (KSS):
      1. PEO
      2. Ptosis
      3. Pigmentary retinopathy
      4. Cardiac conduction abnormality
      5. Ataxia
      6. CSF elevated protein
      7. Diabetes mellitus
      8. Sensorineural hearing loss
      9. Myopathy
   3. Ataxia neuropathy syndromes (ANS) including mitochondrial recessive ataxia syndrome (MIRAS), spinocerebellar ataxia with epilepsy (SCAE), sensory ataxia neuropathy dysarthria ophthalmoplegia

(SANDO), and myoclonic epilepsy myopathy sensory ataxia (MEMSA):
1. SANDO:
    1. PEO
    2. Dysarthria
    3. Sensory neuropathy
    4. Cerebellar ataxia
2. Other PEO: variable presence of PEO and/or myopathy

4. Myopathy, neurogastrointestinal encephalopathy (MNGIE):
    1. PEO
    2. Ptosis
    3. GI dysmotility
    4. Proximal myopathy
    5. Axonal polyneuropathy
    6. Leukodystrophy
5. Mitochondrial myopathy typically presenting without PEO:
    1. Childhood or adult onset:
        1. Myopathy, encephalopathy, lactic acidosis, stroke-like episodes (MELARS):
            1. Stroke-like episodes with encephalopathy, migraine, and seizures
            2. Variable presence of myopathy, cardiomyopathy, deafness, endocrinopathy, and ataxia
            3. PEO: present in a minority of patients
        2. Myoclonus, epilepsy, and ragged-red fibers (MERRF):
            1. Stimulus-sensitive myoclonus
            2. Generalized seizures
            3. Ataxia
            4. Cardiomyopathy
            5. PEO: present in a minority of patients
        3. Ataxia neuropathy syndromes (ANS) including MIRAS, SCAE, SANDO, and MEMSA:
            1. Sensory axonal neuropathy with variable degrees of sensory and cerebellar ataxia
            2. PEO: present in 50% of patients
            3. Epilepsy and dysarthria: present in some patients
    2. Congenital or infant onset:
        1. Mitochondrial DNA depletion syndrome:
            1. Diffuse myopathy
            2. Hepatocerebral syndrome
        2. Infantile myopathy with COX deficiency:
            1. Diffuse myopathy
            2. Lactic acidosis
            3. Encephalopathy

Diagnostic Investigations

1. Electromyography: often shows evidence of active or inactive myopathy (Pfeffer and Chinnery 2013).
2. Muscle biopsy:
    1. Light microscopy (Pfeffer and Chinnery 2013):
        1. Ragged-red fibers on modified trichrome Gomori stain.
        2. Ragged-blue fibers on SDH stain.
        3. Absence of COX staining: the COX reaction has subunits in the nuclear and mitochondrial DNA that make the COX stain valuable in diagnosing mitochondrial myopathies (Taylor et al. 2004).
    2. Muscle immunohistochemical findings may appear normal in patients who have genetic study results consistent with mitochondrial dysfunction (Taylor et al. 2004; Schaefer et al. 2005).
3. Confirmatory tests for organ dysfunction in mitochondrial myopathy:
    1. EEG for seizures/encephalopathy
        1. Epileptiform abnormality
        2. Diffuse slowing
    2. MRI of the brain for stroke-like episodes: high-signal T2 abnormality not conforming to vascular territories, posterior predominant
    3. Nerve conduction studies for sensory neuropathy: axonal sensory or sensorimotor neuropathy
    4. CK for myopathy:
        1. Normal or slightly elevated
        2. May be very high in CoQ_{10} deficiency
    5. EMG for myopathy: normal or myopathic changes

6. PFTs and sleep studies for respiratory failure:
    1. Decreased FVC
    2. Apneic episodes during sleep
7. EKG/echocardiogram for cardiac abnormalities:
    1. Conduction abnormalities
    2. Cardiomyopathy
8. Fasting glucose, glucose tolerance test, hemoglobin A1C, TSH, calcium, PTH, cortisol, synacthen test for endocrinopathy: abnormalities consistent with type 2 diabetes mellitus, and/or hypothyroidism, and/or hypoparathyroidism, and/or adrenal failure
9. Mental status testing for cognitive dysfunction: may indicate cognitive impairment
10. Audiography for hearing loss: sensorineural-type hearing loss
11. Ophthalmology referral for ocular symptoms/signs:
    1. Oculomotor abnormalities
    2. Optic atrophy
    3. Pigmentary retinopathy
12. Swallowing studies (video fluoroscopy or manometry) for dysphagia: cricopharyngeal achalasia or esophageal dysmotility
13. Other general tests:
    1. Serum lactate: normal or elevated
    2. CSF lactate: normal or elevated
    3. CSF analysis: normal or elevated protein
    4. CT of the brain: normal or basal ganglia calcifications +/− atrophy
    5. MRI of the brain:
        1. Basal ganglia signal abnormalities
        2. Nonspecific white matter abnormalities
        3. Stroke-like lesions
        4. Cerebellar or brain stem atrophy
        5. Normal
    6. MR spectroscopy of the brain: may demonstrate elevated lactate

4. Comprehensive next-generation sequence analyses (Cui et al. 2013; Milone and Wong 2013):
    1. Sanger sequencing does not detect mtDNA heteroplasmy less than 20%. This limitation hinders accurate genetic counseling. Next-generation deep sequencing of the circular mitochondrial genome allows the detection of low heteroplasmic mtDNA mutations, accurate diagnosis, and counseling.
    2. For example, an affected proband had 99.5% and 16% of mtDNA mutation in her muscle and blood, respectively, while her mother did not carry the mutation in her blood. Since this was detected and determined by next-generation deep sequencing, which provides reliable quantitative heteroplasmy results, we can conclude that the mutation is de novo in the proband, although germline mosaicism cannot be ruled out. Should the heteroplasmy be determined by Sanger sequencing or other less accurate methods, we would not be able to conclude that the mother did not carry the mutation because Sanger sequencing or other methods cannot detect low levels of heteroplasmy.
    3. On the other hand, an affected woman with 37% mtDNA mutation heteroplasmy in the muscle, but absolutely none in the blood, has almost zero chances of passing the mutation to her children, because the mutation is somatic in her muscle. This was confirmed by her unaffected sibling and daughter, who both did not carry mutation.

Genetic Counseling

1. Recurrence risk (Chinnery 2014):
    1. Patient's sib:
        1. Mitochondrial DNA defects:
            1. The risk to sibs depends on the genetic status of the mother.
            2. If the mother has the mtDNA pathogenic variant, all sibs are at risk of inheriting it.
            3. When a proband has a single mtDNA deletion, the current best estimate of

the recurrence risk to sibs is 1/24 (Chinnery et al 2004).

2. Nuclear DNA defect:
    1. Autosomal recessive inheritance: 25% risk.
    2. Autosomal dominant inheritance: 50% risk if one parent is affected.
    3. X-linked inheritance: 50% risk if the mother has a pathogenic variant (male sibs who inherit the pathogenic variant will be affected; female sibs who inherit the pathogenic variant will be carriers); if the proband represents a simplex case and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.

2. Patient's offspring:
    1. Mitochondrial DNA inheritance:
        1. Offspring of males with an mtDNA pathogenic variant will not inherit the variant.
        2. All offspring of females with an mtDNA pathogenic variant are at risk of inheriting the pathogenic variant.
    2. Nuclear gene defects:
        1. Autosomal recessive inheritance: not increased (all offspring are obligate heterozygotes) unless the spouse is a carrier.
        2. Autosomal dominant inheritance: 50% risk.
        3. X-linked inheritance: all daughters of an affected male are carriers; none of his sons will be affected.

2. Prenatal diagnosis (Milone and Wong 2013; Chinnery 2014):
    1. Prenatal molecular genetic testing and interpretation for mtDNA disorders are difficult because of mtDNA heteroplasmy.
    2. Since the mutant load in one tissue does not necessarily reflect the mutant loads in other tissues, prenatal diagnosis of mtDNA mutations cannot be accurately offered.
    3. It is also a danger to provide preimplantation genetic diagnosis for pregnant mother who carries mtDNA heteroplasmic mutations (Treff et al. 2012).
    4. For severe autosomal recessive disorders, carrier status of parents should be confirmed before prenatal diagnosis is considered; prenatal diagnosis for severe nuclear gene disorders is recommended.
    5. Biochemical genetic testing: prenatal biochemical testing for pregnancies at risk for respiratory chain complex defects is possible, provided the specific biochemical abnormality has been identified in an affected family member, using cultured amniocytes obtained from amniocentesis usually performed at about 15–18 weeks' gestation (Poulton and Turnbull 2000).

3. Management:
    1. Currently no disease-modifying therapy available for mitochondrial myopathy.
    2. Although extremely rare, myopathy caused by CoQ_{10} deficiency will sometimes respond to CoQ_{10} supplementation (Ikejiri et al. 1996; Montini et al. 2008).
    3. Supportive therapy:
        1. Seizures: anticonvulsants
        2. Stroke-like episodes: L-arginine, a possible therapy
        3. Respiratory failure: CPAP or BiPAP
        4. Cardiac abnormalities: antiarrhythmics, pacemaker, ACE inhibitors
        5. Endocrinopathy: oral antihyperglycemic agents, insulin, L-thyroxine, hydrocortisone
        6. Hearing loss: auditory aids, cochlear implantation
        7. Ocular symptoms: corrective lenses, surgery for strabismus or ptosis
        8. Dysphagia: dietary modification

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Fig. 1 A 2-year-old Caucasian female (*left*) was evaluated for failure to thrive, developmental delay, and hypotonia. She was born after a full-term pregnancy via Cesarean section due to mother's gestational diabetes and narrow birth canal. Her muscle tone was initially tight at birth but later hypotonic

Fig. 2 (**a**, **b**) The previous patient was seen again at 7 years of age (**a**) with her family. Her younger, older sister, older brother, and mother had similar muscle problems (**b**). The patient was evaluated for muscle weakness and tightness of the body. She does not pedal the tricycle, trouble going up or down the stairs. The fine motor was delayed with slight difficulty drawing a diamond and trouble with shoe laces. The nerve conduction test showed electrophysiological evidence of a diffuse myopathy with normal spontaneous activity. The muscle biopsy demonstrated a myopathic change with single necrotic fibers and the fibers demonstrating mitochondrial proliferation. The muscle specimen did not show any known deleterious mtDNA mutation but discovered an apparently homoplasmic familial m.13819 T > C (p.F495L, ND5) variant. The 9-year-old brother, who was completely floppy and extremely weak and has leg muscle weakness after birth, was found to have abnormal nerve conduction test and the same mtDNA variant. The mother was noted to getting more muscle weakness as she got older. She also showed apparent homoplasmic for the m.13819 T > C (p.F495L, ND5) variant in her blood (collaboration with Dr. Arun Kalra)

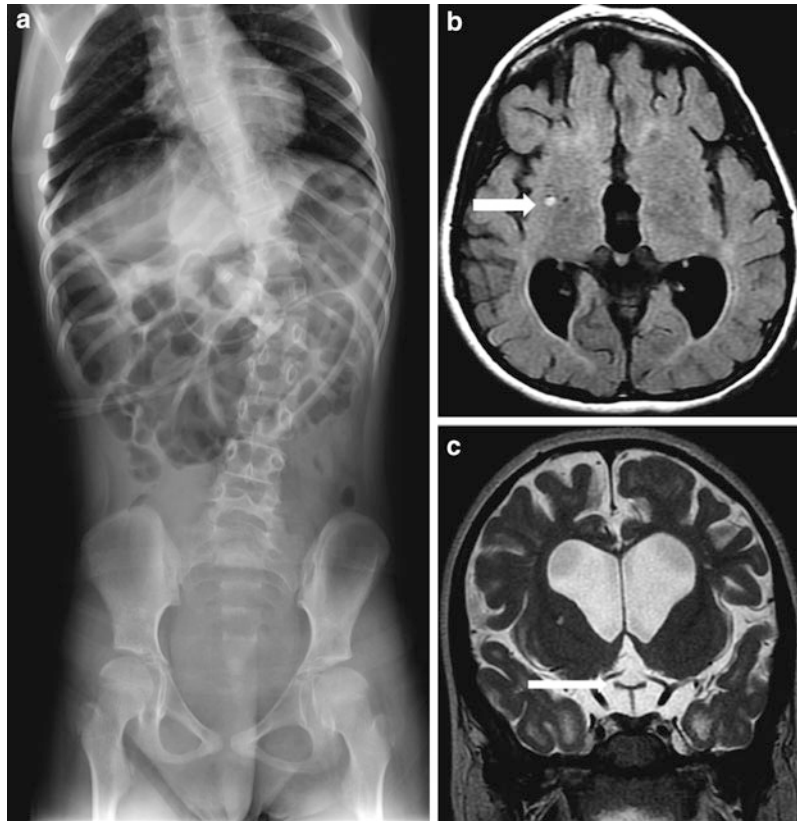

Fig. 3 (**a**–**c**) A 10-year-old girl was seen with mitochondrial disease characterized by severe multisystem involvement. She was the product of a 39-week gestation with induced delivery. The birth weight was 5 lbs 15 ozs. She was noted to have low fetal movements. She had a history of global developmental delay, chronic neutropenia, left ventricular dysfunction, GI dysmotility with GERD, neuromuscular scoliosis, severe sleep dysfunction, exercise intolerance, severe renal tubular acidosis, chronic transaminase elevation, swallowing dysfunction, and aspiration for which she was on continuous gastrojejunal tube feeds, ataxia, seizures, and mitochondrial encephalopathy. She had a generalized myopathic syndrome with hypotonia of the trunk and dystonic spasticity of the limbs. Muscle biopsy of her left thigh at 1 year of age revealed complex I and III disease and a chronic lactic acidosis. Previous molecular genetic study showed mutations (c.1067delG:p.Gly356AlafsX15 and c.1790A > C:p.Gln597Pro) in the *FBXL4* gene, which was considered as the genetic cause for her complex mitochondrial disease (Gai et al. 2013). POLG sequencing also identified maternally inherited G517V mutation (Tan et al. 2011). No deletion or mutation has been found on other alleles, and no additional POLG abnormalities were identified through research-based testing of fibroblasts. A body radiography (**a**) showed GJ tube placement, a severe thoracolumbar levoscoliosis, and bilateral coxa valgus. MRI of the brain (**b**, **c**) demonstrated extensive generalized cerebral atrophy, supratentorial white matter volume loss, and periventricular white matter signal abnormality with ventriculomegaly. Focal abnormality was present in the right basal ganglia (**b**, *arrow*), central tegmental tracts in the midbrain and in the posterior pons, which are consistent with the known mitochondrial encephalopathy. In addition, diffusely thinning corpus callosum and optic nerves (**c**, *arrow*) were observed (courtesy of Dr. Grace Guo)

Mowat-Wilson Syndrome

Contents

In 1998, Mowat et al. (1998) described a new syndrome, now known as Mowat-Wilson syndrome (MWS), consisting of Hirschsprung disease or severe constipation, microcephaly, mental retardation, and characteristic facial features, including hypertelorism, medially flared and broad eyebrows, prominent columella, pointed chin, and uplifted earlobes.

The prevalence of MWS is currently unknown. However, it seems probable that the syndrome is underdiagnosed, particularly in patients without Hirschsprung disease. Approximately 171 patients with *ZEB2* mutations, deletions, or cytogenetic abnormalities have been reported and over 100 mutations have been described.

Synonyms and Related Disorders

Hirschsprung disease-mental retardation syndrome; Microcephaly, mental retardation, and distinct facial features with or without Hirschsprung disease

Genetics/Basic Defects

1. Caused by heterozygous mutations and deletions in the gene ZEB2 on chromosome 2 (2q22-q24.1) (also known as ZFHX1B or SIP-1) (Yoneda et al. 2002; Cerruti Mainardi et al. 2004; Ishihara et al. 2004) in approximately 81% of cases
2. Typically resulting from a de novo dominant mutation
3. Mutations in SIP1 (Smad interacting protein 1) result in a complex developmental disorder with a great variety of clinical features including a syndromic Hirschsprung disease (Cacheux et al. 2001; Yamada et al. 2001; Zweier et al. 2002; Garavelli et al. 2003)
4. Atypical ZFHX1B mutation associated with a mild Mowat-Wilson syndrome phenotype (Zweier et al. 2006)
5. Cytogenetic deletions or translocations of the chromosome 2q21-q23 region were found in several patients

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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Clinical Features

1. Typical facial features (Adam et al. 2006)
    1. Seen in all individuals with this combination of characteristics were found to have mutations (Garavelli and Mainardi 2007) or deletions in the *ZEB2* gene (Zweier et al. 2005)
        1. Ocular hypertelorism
        2. Medially flared and broad eyebrows
        3. Prominent columella
        4. Prominent or pointed chin
        5. Open-mouthed expression
        6. Uplifted earlobes with a central depression
            1. Earlobes described as resembling "orecchiette pasta" or "red blood corpuscles."
            2. Ear configuration not changing significantly with age with the exception of the central depression, which is less obvious in adults.
    2. Additional suggestive facial features (Mowat et al. 2003; Adam et al. 2013)
        1. Telecanthus
        2. Deep-set eyes
        3. Broad nasal bridge with prominent and rounded nasal tip
        4. Full or everted lower lip
        5. Posteriorly rotated ears
    3. Natural history of facial phenotype (Wilson et al. 2003; Horn et al. 2004)
        1. More pronounced facial phenotype with age, making diagnosis easier in older individuals
        2. Lengthening of the nasal tip and becoming more depressed
        3. More pronounced columella, leading to appearance of a short philtrum
        4. Elongation of the face
        5. More prominent jaw
        6. Eyebrows becoming heavier with an increased medial flare
2. Spectrum of structural anomalies
    1. Gastrointestinal anomalies
        1. Hirschsprung disease
            1. A strong cross-reference marker when present
            2. Not a constant finding
            3. Present in approximately 45% of cases (Coyle and Puri 2015)
        2. Pyloric stenosis
    2. Genitourinary anomalies, particularly hypospadias in males
    3. Congenital heart defects, including abnormalities of the pulmonary arteries and/or valves
    4. Agenesis or hypogenesis of the corpus callosum
    5. Ophthalmologic malformations (Bourchany et al. 2015)
        1. Although rare, should be considered as a part of the clinical spectrum of the condition
        2. Microphthalmia
        3. Axenfeld anomaly
        4. Iris/chorioretinal/optic disk coloboma
        5. Optic nerve atrophy
        6. Retinal epithelium atrophy
        7. Cataract
        8. Korectopia
    6. Teeth anomalies
        1. Widely spaced teeth
        2. Dental crowding
        3. "Malpositioned" teeth
        4. Delayed tooth eruption
3. Other features
    1. Mental retardation/intellectual disability (Kilic et al. 2016), typically in the moderate to severe range, with severe speech impairment but relative preservation of receptive language
    2. Sleep disturbance (Evans et al. 2016)
    3. Seizures
    4. Growth retardation (short stature) with microcephaly
    5. Chronic constipation in those without Hirschsprung disease

Diagnostic Investigations

1. Cytogenetic testing
    1. Chromosomal rearrangements that disrupt the *ZEB2* gene cause MWS in

approximately 2% of cases (Lurie et al. 1994; Dastot-Le Moal et al. 2007)
2. FISH analysis: Large deletions encompassing all or part of the *ZEB2* gene detectable by FISH in approximately 15% of cases (Mowat et al. 2003; Dastot-Le Moal et al. 2007)
3. Smaller intragenic deletions will not be detected by FISH analysis.

2. Molecular genetic testing
   1. Pathogenic variant and deletions in *ZEB2* (also known as ZFHX1B or SIP-1) are known to cause MWS in approximately 100% of cases (Amiel et al. 2001; Kääriäinen et al. 2001; Wakamatsu et al. 2001; Dastot-Le Moal et al. 2007; Garavelli et al. 2009).
   2. Of 12 patients with the distinct facial gestalt of Mowat-Wilson syndrome analyzed, eight had truncating mutations and four had large-scale deletions, thus giving a ZFHX1B defect in 100% of patients and a deletion rate of 33% (Zweier et al. 2003).
   3. Chromosome microarray analysis: reported a case with a 393.68-kb deletion on chromosome 2q22.2q22.3 encompassing the ZEB2 gene and a 1.24 Mb duplication on chromosome 22q11.23, a variant of unknown clinical significance (Buraniqi and Moodley 2015)
   4. No evidence of locus heterogeneity for MWS
3. Hirschsprung disease evaluation
4. MRI imaging of the brain for CNS anomalies
5. Echocardiograph for congenital heart disease
6. Ophthalmologic evaluation for eye anomalies
7. Renal ultrasound for renal anomalies
8. EEG for seizures

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. De novo mutation: low recurrence risk
      2. Possibility of constitutional and/or germline mosaicism: low recurrence risk but greater than that of the general population (1–2%)
         1. Possibility of germline mosaicism suggested in two families with two (McGaughran et al. 2005) and three affected sibs, respectively
         2. Low-level paternal mosaicism observed in a family with two affected sibs has been reported
   2. Patient's offspring: individuals with MWS and an unbalanced chromosome rearrangement unlikely to reproduce
2. Prenatal diagnosis (Adam et al. 2013)
   1. Ultrasonography (Zhou et al. 2014).
      1. Despite well-reported association, the difficulty in prenatal detection is that the corpus callosum is not fully formed until 18–20 weeks (Schell-Apacik et al. 2008).
      2. It is not easy to be demonstrated in routine morphology scan.
   2. Prenatal diagnosis of a pregnancy at theoretically increased risk because of constitutional and/or germline mosaicism in a clinically unaffected parent.
      1. Disease-causing allele of an affected family member being identified prior to prenatal diagnosis
      2. Molecular genetic analysis on DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling
      3. Second-trimester detection of Mowat-Wilson syndrome using comparative genomic hybridization microarray testing (Choy et al. 2010)
   3. Prenatal diagnosis of a pregnancy at increased risk because of parental balanced structural rearrangement: possible by chromosome analysis of fetal cells obtained by amniocentesis or chorionic villus sampling.
   4. Preimplantation genetic diagnosis: available for families at increased risk because of parental mosaicism in which the disease-causing mutations have been identified.

3. Management
    1. Mostly supportive including seizure control and developmental intervention
    2. Specific management for structural anomalies, including Hirschsprung disease

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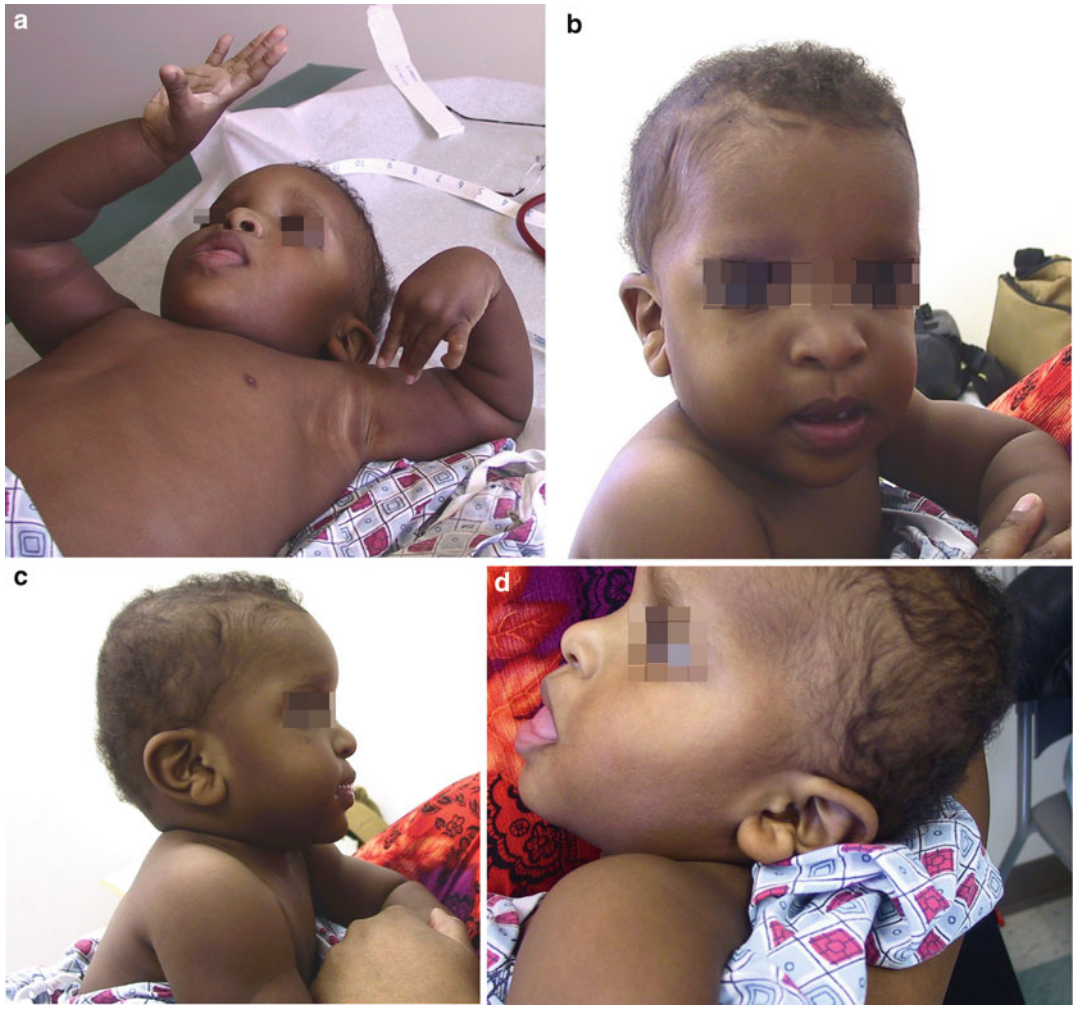

Fig. 1 (**a**–**d**) A three-and-a-half-year-old boy was noted to have Mowat-Wilson syndrome. Note the unusual facies (hypertelorism, telecanthus, strabismus, wide prominent nasal bridge, an unusual nose with a rounded tip and prominent columella, a prominent chin, and unusual ears with fleshy uplifted ear lobes), long tapering fingers, and an unusual stereotypic use of his hands in which he moves his fingers in front of his face and regards them. He is severely developmentally delayed and has hypotonia. Chromosome microarray analysis revealed a loss in copy number in the long arm of chromosome 2, detected with two clones, spanning at least 100 kb (including the ZFHX1B gene), and confirmed by FISH analysis. Deletions in this region have been associated with Mowat-Wilson syndrome

Mucolipidosis 2

Contents

Mucolipidosis II (ML II), or I-cell disease, is a rare autosomal recessively inherited storage disorder of lysosomal enzyme hydrolase trafficking due to deficient activity of the multimeric enzyme UDP-*N*-acetylglucosamine-1-phosphotransferase. The term "I-cell disease" is derived from the observation that fibroblasts from affected individuals show dense inclusions filled with storage material.

Synonyms and Related Disorders

I-cell disease; Inclusion cell disease; Leroy I-cell disease; ML II; Mucolipidosis II alpha/beta (ML alpha/beta)

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Leroy et al. 1971)
2. Uridine diphosphate (UDP)-*N*-acetylglucosamine-1-phosphotransferase (GlcNAc-PT) (Beck et al. 1995)
   1. An enzyme that transfers phosphate groups onto oligosaccharide units of lysosomal enzyme precursors.
   2. Deficient in mucolipidosis II (also in mucolipidosis III) (Bargal et al. 2006).
   3. Consequences of the enzyme deficiency.
      1. Not generating common phosphomannosyl recognition marker of acid hydrolases
      2. The enzymes not targeting the lysosomes
      3. Secretion of the enzymes into the extracellular space (high activities found in the serum of the patients)
      4. Considerable reduction of the enzyme levels inside the cells (fibroblasts)
   4. GlcNAc-PT is made up of three subunits: α, β, and γ (Reitman and Kornfeld 1981; Reitman et al. 1981).
      1. The α/β subunits are encoded by the *GNPTA* gene (Tiede et al. 2005) and have a catalytic function.
      2. The γ subunit which is encoded by the *GNPTAG* gene (Raas-Rothschild et al. 2000) has a recognition and regulation function.
   5. Mutations in *GNPTAB*, which encodes the α/β subunit, cause ML II and ML III α/β (Tiede et al. 2005). The γ subunit is encoded by *GNPTG*, and mutations in this gene lead

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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to the clinically milder condition known as ML III γ (Raas-Rothschild et al. 2000).

3. Genotype-phenotype correlations (Leroy et al. 2012)
    1. *GNPTAB* gene sequencings have confirmed that homozygous and compound heterozygous genotypes that predict enzyme inactivation (caused by premature translation termination and/or frameshift effects) result in the ML II phenotype.
    2. The combination of less "morbid" mutations, such as missense and most of the splice-site mutations that may decrease but not abolish enzyme activity, often yields the more slowly evolving ML III phenotype alpha/beta with later clinical onset (Paik et al. 2005; Tiede et al. 2005; Bargal et al. 2006; Kudo et al. 2006).
    3. Some children have clinically intermediate phenotypes between the delineated ML II and ML III alpha/beta.
    4. Correlating these phenotypes with the specific mutant genotypes requires more detailed and extensive clinical research efforts that are ongoing (Cathey et al. 2008).

Clinical Features

1. Symptoms and signs of ML II are similar to those encountered in patients with mucopolysaccharidoses and to a lesser extent gangliosidoses: characterized by coarse facial features, short stature, hyperplastic gums, organomegaly, and retarded psychomotor development (Maroteaux and Lamy 1966; Okada et al. 1985; Leroy and Opitz 1969).
2. A wide range of inter- and intrafamilial variability (Beck et al. 1995)
    1. Age of onset: present at birth or appear in the first few months of life
    2. Organ manifestation
    3. Radiological findings
    4. Unusual findings in some patients
        1. Pericardial effusion
        2. Profound brain atrophy
3. Features evident in affected newborn
    1. Coarse facial (gargoyle-like) features (Lee and O'Donnell 2003)
        1. Puffy eyelids with slight exophthalmia
        2. Excessive prominence of the epicanthal folds
        3. Depressed nasal bridge
        4. Full cheeks exhibiting multiple fine telangiectasia
        5. Gingival hyperplasia and alveolar enlargement with buried teeth
        6. Thick tongue
    2. Restricted joint mobility
    3. A tight, thickened skin
4. Early clinical features (Sprigz et al. 1978)
    1. Low birth weight
    2. Congenital hip dislocation
    3. Pes equinovarus
    4. Joint contractures
    5. Inguinal hernias
    6. Generalized hypotonia
    7. Ocular abnormalities (Libert et al. 1977)
        1. Corneal clouding
        2. Glaucoma
        3. Megalocornea
5. Older patients
    1. Predominant features
        1. Skeletal deformities (dysostosis multiplex)
        2. Progressive failure to thrive
        3. Developmental delay with variable mental retardation
    2. Other features
        1. Short stature
        2. Craniosynostosis (Aynaci et al. 2002)
        3. Progressive stiffness of all joints, first apparent in the shoulders
        4. Variable hepatosplenomegaly
        5. Congestive heart failure
        6. Recurrent pulmonary infections
6. Natural history (Leroy and Martin 1975)
    1. Slowly progressive course
    2. Fatal outcome usually before 4 years of age
7. ML III (see next chapter "▶ Mucolipidosis 3")
    1. Genetically heterogeneous
    2. A milder disorder with attenuated characteristics and survival to adult life (Kelly et al. 1975)

8. Differential diagnosis with other lysosomal storage disease (Leroy et al. 2012)
    1. Mucopolysaccharidosis type 1 H (see the chapter "► Mucopolysaccharidosis I (MPS I)")
    2. GM1 gangliosidosis type 1
        1. More severe hepatomegaly
        2. Dysostosis multiplex indistinguishable
        3. Beta-D-galactosidase deficiency in leukocytes and plasma
    3. Infantile galactosialidosis
        1. Storage phenomena less pronounce than in GM1 gangliosidosis but more than in ML II
        2. Absence of acid sialidase and of beta-D-galactosidase activity in leukocytes in addition to cathepsin A deficient in leukocytes and cultured fibrocytes
        3. May present as congenital nonimmune hydrops fetalis
    4. Infantile sialidosis (formerly sialidosis type 2 or ML I)
        1. May present as congenital nonimmune hydrops fetalis
        2. More chronic disorder with moderate organomegaly, dysostosis multiplex that is milder than that of ML II
        3. Mild limitation of joint mobility
        4. Growth and cognitive development considerably better than in children with ML II
    5. Infantile free sialic acid storage disease
        1. Excessive amounts of free sialic acid in the urine
        2. Deficient acid sialidase only
        3. Less facial dysmorphism and much less dysostosis multiplex than ML II

Diagnostic Investigations

1. Elevated activities of multiple lysosomal enzymes in serum or plasma, including the following enzymes: Activity of nearly all lysosomal hydrolases is 5- to 20-fold higher in plasma and other body fluids than in normal controls because of improper targeting of lysosomal acid hydrolases to lysosomes in ML II.
    1. Arylsulfatase A
    2. α-Mannosidase
    3. β-Glucuronidase
    4. β-Hexosaminidase
2. Deficient enzyme activities in cultured fibroblasts (Leroy et al. 1972), including the following enzymes:
    1. β-Galactosidase
    2. Arylsulfatase A
    3. β-Hexosaminidase
    4. β-Glucuronidase
    5. α-Galactosidase
3. Primary biochemical defect: decreased or absent *N*-acetylglucosamine-1-phosphotransferase in cultured fibroblasts and leukocytes.
4. Excessive urinary excretion of oligosaccharides.
5. Normal excretion of urinary mucopolysaccharide.
6. Radiography.
    1. Fetal radiography
        1. Diffuse decrease in bone mineralization
        2. A coarse, lacy, trabecular pattern
        3. Overall shortening and undermodeling of the long bones
        4. Subperiosteal bone deficiency in the diaphysis giving the appearance of periosteal new bone (cloaking)
        5. Retarded ossification of the vertebral bodies
        6. Hypoplasia of the anterior superior aspect of the upper lumbar vertebral bodies
        7. Broad ribs
        8. Abnormal pelvis with squared iliac wings and flattened acetabular roofs
        9. Brachyphalangy
        10. Mild tapering of the proximal ends of the metacarpals
        11. A small irregular calcaneal "ossification center"
    2. Radiographic findings in early infancy (Patriquin et al. 1977)
        1. Diffuse demineralization
        2. Metaphyseal cupping and fraying

3. Excessive periosteal new bone formation
4. Diaphyseal expansion of the long tubular bones
5. Irregular trabeculation without differentiation between the cortical and medullary zones
6. Mild anteriosuperior hypoplasia of the upper lumbar bodies
7. Pelvic dysplasia
8. Occasional punctate calcifications and bone defects following intrauterine calcific deposits
9. Skeletal changes in the neonatal I-cell disease resembling those of rickets, osteomyelitis, and hyperparathyroidism (David-Vizcarra et al. 2010)

3. Dysostosis multiplex
   1. Neurocranium
      1. Long/enlarged and thick skull
      2. Thickened and sclerotic cranial base
   2. Hypoplastic epiphyses
   3. Thickened diaphyses
   4. Widened/spatulate ribs
   5. Kyphoscoliosis
   6. Anterior beaking and wedging of the vertebral bodies
   7. Lumbar gibbus deformity
   8. Cloaking appearance of the long tubular bones
   9. Proximal pointing of the metacarpals
   10. Bullet-shaped phalanges
   11. Claw hand deformities
7. Slit lamp examination to demonstrate corneal clouding
8. Echocardiography for valve thickening and valve insufficiency
9. MRI or CT scan: mild brain atrophy in most cases
10. MRI/MR spectroscopy: delayed myelination or hypomyelination with decreased choline on MR spectroscopy (Takanashi et al. 2012)
11. Light microscopy and electron microscopy
    1. Inclusion bodies in peripheral lymphocytes in blood smear (Rapola et al. 1974)
    2. An increased number of empty, large vacuoles that may fill the cytoplasm of cultured skin fibroblast cells (Rapola et al. 1974; Cipolloni et al. 1980)
    3. Presence of numerous intracytoplasmic inclusions in cells of mesenchymal origin
       1. Membrane-bound vacuoles filled with fibrillogranular material
       2. Appear to contain a variety of lipids, mucopolysaccharides, and oligosaccharides
    4. Cytoplasmic inclusions also observed in various types of cells in fetal I-cell disease (Blank and Linder 1974; Abe et al. 1976)
12. Molecular genetic diagnosis (Leroy et al. 2012)
    1. Sequence analysis: Bidirectional sequencing of the entire *GNPTAB* coding region detects two disease-causing mutations in more than 95% of persons with ML II.
    2. Deletion/duplication analysis is also clinically available.
    3. Targeted next-generation sequencing (Yang et al. 2013).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not surviving to reproductive age
2. Prenatal diagnosis (Carey et al. 1999)
   1. Ultrasonography with previous affected sibling.
      1. Intrauterine growth retardation (Lees et al. 2001)
      2. Short tubular bones
      3. Short femur and periosteal cloaking of the femur and humerus (Lees et al. 2001)
   2. Radiography (Babcock et al. 1986; Aggarwal et al. 2014).
      1. Prenatal skeletal dysplasia phenotype in severe MLII alpha/beta with novel *GNPTAB* mutation
      2. Short and broad long bones with wide diaphyses and massive periosteal cloaking, dense metaphyses, and epiphyseal stippling
      3. Cardiomegaly

3. Measuring the levels of lysosomal enzymes (elevated activity of several lysosomal hydrolases) in cell-free amniotic fluid or cultured amniocytes (Aula et al. 1975).
4. Assay of the transferase activity (deficient) in fresh or cultured CVS cells (Poenaru et al. 1984; Ben-Yoseph et al. 1988) and amniocytes (Besley et al. 1990).
5. Electron microscopy of chorionic villus biopsy tissue for detection of inclusion bodies.
6. Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family (Leroy et al. 2012).

3. Management
   1. Supportive care
      1. Low-impact therapies to avoid joint and tendon strain, including aqua therapy
      2. Cognitive stimulation through interactive programs
      3. Gingivectomy as needed for oral health
      4. Myringotomy tube placement as needed for recurrent ear infections
      5. Supplementation of gamma globulin is useful in prophylaxis of infection for hypogammaglobulinemia patients (Maarschalk-Ellerbroek et al. 2011; Shibazaki et al. 2016)
      6. Difficult airway management (Mallen et al. 2015)
   2. Prevention of secondary complications
   3. Bone marrow transplant from an HLA-identical carrier sibling (Grewal et al. 2003)
      1. Neurodevelopmental gains
      2. Prevention of cardiopulmonary complications
      3. No alteration to the course of musculoskeletal disease
   4. Hematopoietic stem cell transplantation (HSCT): Although HSCT has demonstrated efficacy in treating some lysosomal storage disorders, the neurologic outcome and survival for patients with MLII were poor (Lund et al. 2014).
   5. Umbilical cord blood transplantation: no improvements in the clinical course (Shibazaki et al. 2016)

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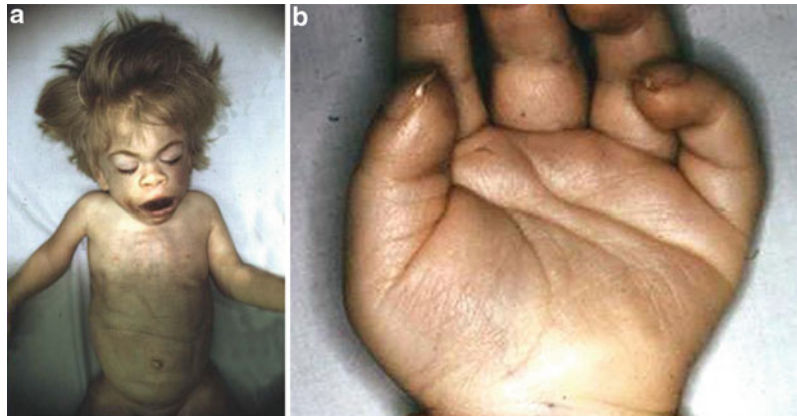

Fig. 1 (**a**, **b**) An 8-year-old girl with I-cell disease (**a**). She had severe growth retardation (67 cm), coarse facial features, claw hands (**b**), severe skeletal dysplasia, marked gingival hypertrophy, cardiomegaly with marked thickening and deformity of mitral and tricuspid valves, and bilateral duplication of ureters. Histological investigations showed foam cell infiltration in renal glomeruli, splenic corpuscles, atrioventricular valves, and thymus (Courtesy of Dr. Samuel Yang)

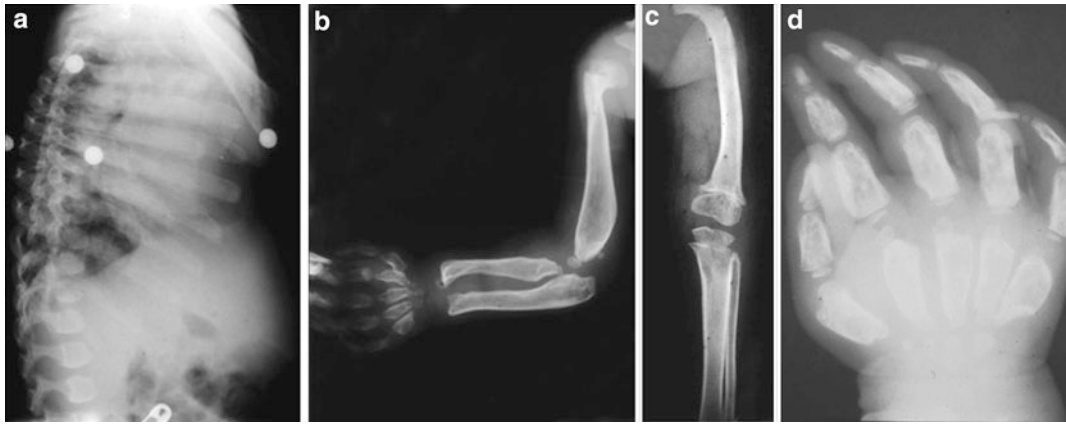

Fig. 2 Radiographs showed generalized dysplastic changes in the chest and upper and lower extremities. The ribs were extremely wide. Some vertebral bodies were slightly hook shaped. The pedicles were long and there was slight gibbus (**a**). Midshafts of the humerus, radius, and ulna were wide and the neck of the humerus in varus position (**b**). Widening of the midshafts of the lower extremities was less marked than in the upper extremities (**c**). Metacarpals and phalanges were wide, but distal phalanges were short and thin. Metacarpal bones pointed proximally. Carpal bones were hypoplastic (**d**)

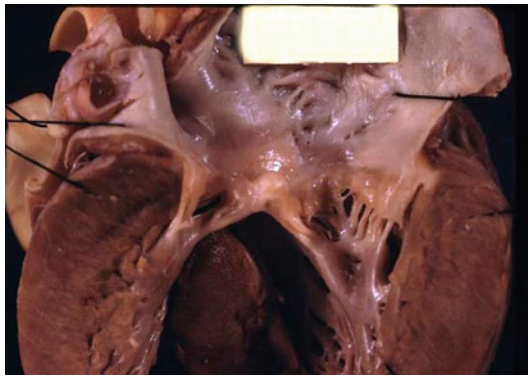

Fig. 3 Mitral valve was thickened and deformed

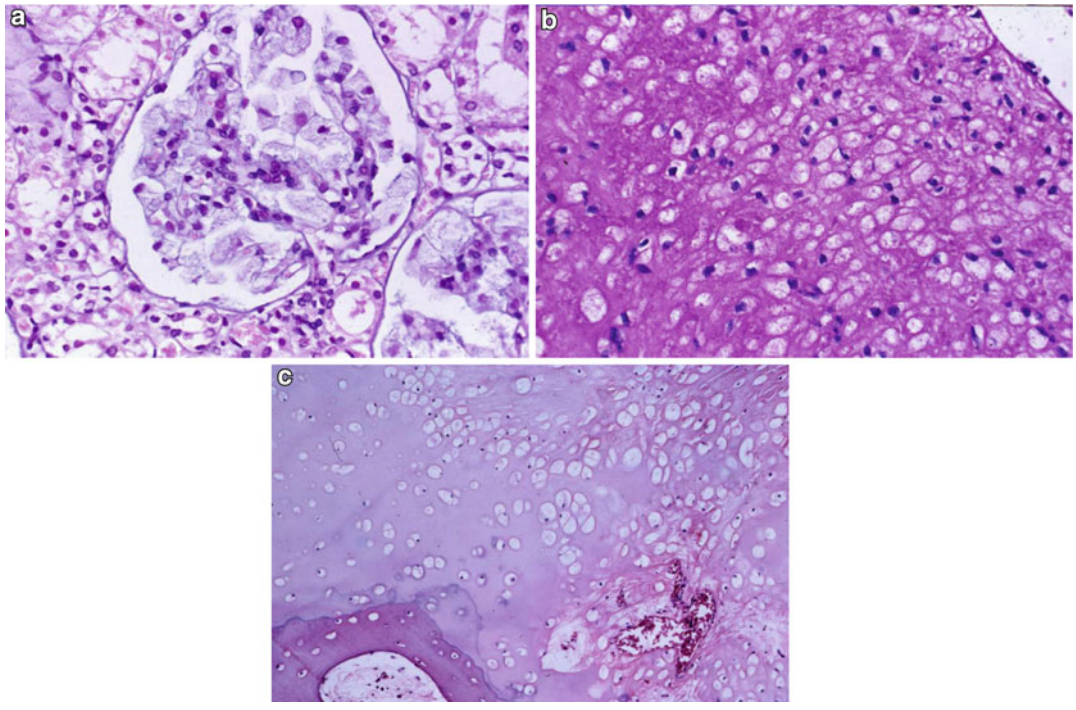

Fig. 4 (**a**–**c**) Foam cells were present in the renal glomeruli (**a**), mitral valve (**b**), and chondrocytes of cartilage (**c**)

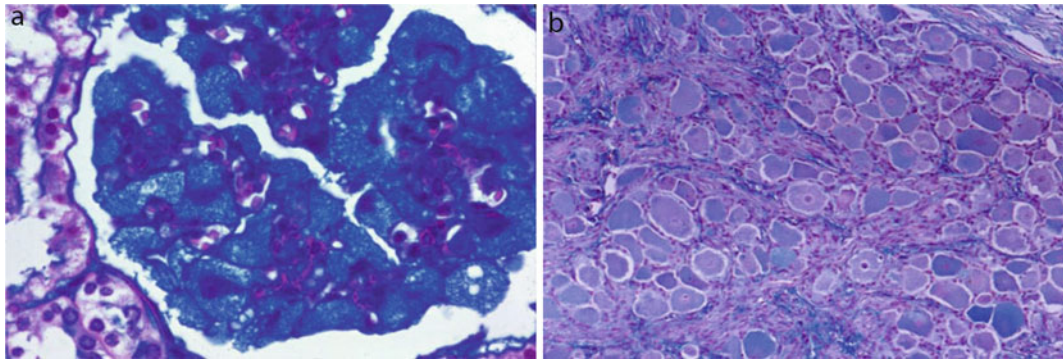

Fig. 5 (**a**, **b**) The foamy material was reactive with colloidal iron stain (renal glomeruli) (**a**) and sympathetic ganglion (Alcian blue stain) (**b**), indicating the presence of mucopolysaccharide

Mucolipidosis 3

Contents

In 1966, Maroteaux and Lamy first described four girls with pseudo-Hurler polydystrophy, a condition milder in severity than the Hurler syndrome and similar to the Scheie syndrome but without hepatosplenomegaly, cloudy cornea, or mucopolysaccharidiuria. In 1970, Spranger and Wiedemann (1970) designated pseudo-Hurler polydystrophy as mucolipidosis III because of Hurler-like features and vacuolated bone marrow cells (Kelly et al. 1975a, b).

Synonyms and Related Disorders

ML γ; Mucolipidosis (ML) III α/β (Pseudo-Hurler polydystrophy)

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. Basic defect
    1. Resulting from deficiency of the enzyme UDP-*N*-acetylglucosamine: lysosomal protein precursor *N*-acetyl glucosamine 1-phosphate transferase (G1cNAcPT) (Mucolipidosis II also caused by deficiency of the same enzyme) (Mueller et al. 1983; Bargal et al. 2006)
    2. Genetic complementation analysis of cultured fibroblasts derived from patients with mucolipidosis III identified complementation groups A, B, and C (Honey et al. 1982; Little et al. 1986).
    3. Inability to form the correct recognition marker on lysosomal enzymes resulting in a marked intracellular deficiency of most lysosomal enzymes in various tissues, impairment of many lysosomal catabolic processes, and concomitant increase in lysosomal enzymes in plasma (Tylki-Szymanska et al. 2002)
3. Recent finding of molecular basis for mucolipidosis IIIC (variant pseudo-Hurler polydystrophy): a mutation, in C at codon 167, in the γ subunit of the G1cNAcPT in mucolipidosis IIIC (Raas-Rothschild et al. 2000). Mutations in *GNPTAB*, which encodes the α/β subunit, cause ML II and ML III α/β (Tiede et al. 2005).
4. Three novel mutations of the *GNPTG* gene cause of MLIII gamma (Liu et al. 2014)
    1. In exon seven [c.425G > A (p.Cys142Val)] and [c.515dupC (p.His172Profs27X)]
    2. In exon eight [c.609 + 1G > C]

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_167

5. Mucolipidosis III GNPTG missense mutations cause misfolding of the γ subunit of GlcNAc-1-phosphotransferase (van Meel and Kornfeld 2016)

Clinical Features

1. ML III α/β
    1. Onset of disease
        1. Usually appear at 2–4 years of age
        2. Progress slowly
        3. First sign: stiffness in the hands and shoulders
    2. Short stature (Robinow 1974)
    3. Mild Hurler-like facial dysmorphism, usually apparent after age 6 years
    4. Ophthalmologic abnormalities (Traboulsi and Maumenee 1986)
        1. Constant ocular features
            1. Corneal opacities consisting of fine, peripheral infiltrates
            2. Hyperopic astigmatism
        2. Optic nerve head swelling
        3. Surface wrinkling maculopathy
        4. Retinal vascular tortuosity
    5. Mild mental retardation
    6. Mild organomegaly
    7. Mitral and aortic valve insufficiencies: the most common form of cardiac involvement (Abualsuod et al. 2014)
    8. Orthopedic problems
        1. Stiffness of the hands progressing to claw hand deformities by 6 years of age in all patients
        2. Slow progression of the skeletal dysplasia during school years, the resulting physical disability most apparent in the hands, hips, elbows, and shoulders
        3. Generalized joint stiffness (limited joint mobility)
        4. Spine abnormalities
            1. Kyphosis
            2. Lordosis
            3. Gibbus
        5. Hip pain
        6. Hip dysplasia
        7. Less common clinical features (Smuts et al. *2009*)
            1. Claw hand deformities
            2. Carpal tunnel syndrome further complicates the claw hand deformities.
            3. Recurrent, intermittent trigger fingers
            4. Claw toes
    9. Natural course of the illness
        1. Survive into beyond the fifth to sixth decade (Umehara et al. 1997)
        2. Cardiopulmonary complications are the usual causes of mortality
2. Mucolipidosis III γ (also known as variant ML III)
    1. Clinical features similar to but milder than those observed in individuals with mucolipidosis III alpha/beta (ML III alpha/beta)
    2. Affected individuals are mostly of Middle Eastern descent (Raas-Rothschild et al. *2000*, *2004*; Cathey et al. *2007*).
3. Differential diagnosis (Leroy et al. *2012*)
    1. Lysosomal storage diseases
        1. Attenuated MPS I (formerly called Hurler-Scheie syndrome or Scheie syndrome)
        2. Attenuated MPS II (Hunter syndrome)
        3. Morquio disease type B (MPS IV B)
        4. Maroteaux-Lamy disease type B (MPS VI B)
        5. Sly disease type B (MPS VII B)
    2. Disorders clinically allied to the oligosaccharidoses
        1. Late infantile sialic acid storage disorder or Salla disease (free sialic acid storage disorders) and mucosulfatidosis: In both disorders, the neurodegenerative aspects are much more prominent.
        2. In free sialic acid storage disorders, dysostosis multiplex is absent or minimal, and urinary excretion of free sialic acid is excessive.
        3. In mucosulfatidosis, urinary acid mucopolysaccharides and sulfatides are excessive.
    3. Osteochondrodysplasias

Diagnostic Investigations

1. Multiple elevated serum and urine enzyme activities (Herd et al. 1978)
2. Radiography showing dysostosis multiplex (Melhem et al. 1973; Freisinger et al. 1992)
    1. Pelvis
        1. Flaring of the iliac wings
        2. Constriction of the iliac bodies
        3. Oblique acetabular roofs
    2. Vertebral bodies
        1. Moderately flattened
        2. Presenting as a roughly ovoid contour
        3. Underdevelopment of posterior parts in the dorsal spine
        4. Hypoplasia of anterior third in the lumbar spine
        5. Irregular endplates
        6. Scoliosis secondary to vertebral abnormalities
    3. Tubular bones
        1. Shortened and wide
        2. The most striking changes observed in the proximal femur
            1. A small, flattened and irregular epiphysis
            2. Coxa valga deformity of the neck
            3. Subluxation
        3. Hands
            1. Short first metacarpals
            2. Mild proximal pointing of the metacarpals
            3. Mild to moderate claw hand deformities
            4. Relatively wide diaphysis of some phalanges
        4. Retarded bone age
    4. Skull: normal despite the presence of craniostenosis in some patients
3. Thoracolumbar X-ray and MRI-T2 (Zarza and Morrondo 2014)
    1. Irregularity of the vertebral end plates
    2. Intraspongy lumbar hernias
4. Cardiac MRI (Abualsuod et al. 2014)
    1. Frequent premature ventricular complexes (PVCs)
    2. Nonsustained ventricular tachycardia
5. Nerve conduction test and electromyography to confirm the carpal tunnel syndrome
6. Slit-lamp examination for cornea opacification
7. Normal urinary excretion of acid mucopolysaccharides
8. Presence of cytoplasmic inclusions within cultured fibroblasts as demonstrated by phase-contrast or dark-field microscopy
9. Bone marrow: large, vacuolated plasmocytes
10. ML III alpha/beta (Leroy et al. 2012)
    1. Activity of nearly all lysosomal hydrolases: up to tenfold higher in plasma and other body fluids than in normal controls because of inadequate targeting to lysosomes (also in ML III gamma).
    2. Urinary excretion of oligosaccharides, a nonspecific finding, can be excessive but is not always present.
    3. Significant deficiency (1–10% of normal) of the activity of the enzyme UDP-*N*-acetylglucosamine: Lysosomal hydrolase *N*-acetylglucosamine-1-phosphotransferase (GNPTA), encoded by *GNPTAB*, confirms the diagnosis.
11. Molecular genetic testing
    1. ML III alpha/beta (Leroy et al. 2012).
        1. Bidirectional sequencing of the entire *GNPTAB* coding region detects two disease-causing mutations in more than 95% of individuals with ML III alpha/beta. Such testing is clinically available.
        2. Duplication/deletion analysis is also available.
    2. In ML III gamma: Molecular testing of *GNPTG* detects two disease-causing mutations in more than 95% of individuals with ML III gamma (Raas-Rothschild and Spiegel 2012).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25%

   2. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis (Falik-Zaccai et al. 2003)
   1. Diagnosis confirmed by markedly reduced lysosomal enzyme activities in cultured chorionic villi.
   2. Identification of the disease-causing mutation in fetal DNA in a newly recognized large Bedouin-Moslem kindred, allowing prenatal diagnosis, carrier detection, and identification of couples at risk.
   3. Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family.
3. Management (Hetherington et al. 1999)
   1. Physiotherapy for joint stiffness and contractures
   2. Padded insoles for clawing of toes
   3. Carpal tunnel decompression for the median nerve entrapment
   4. Pelvic osteotomy for severe hip dysplasia
   5. Intravenous pamidronate treatment for osteodystrophy (Robinson et al. 2002)

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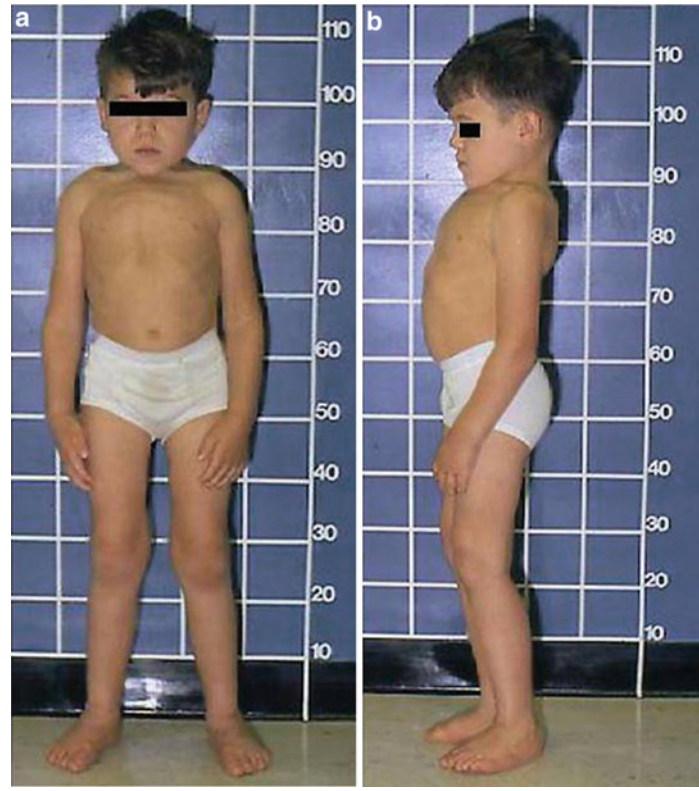

Fig. 1 (**a**, **b**) Patient 1 (9-year-old boy) with mucolipidosis III showing short stature, mild coarse facial features, and flexion contractures of knees, hips, elbows, wrists, and fingers. Fibroblast lysosomal acid hydrolase study revealed β-galactosidase 0.06 (control: 0.36 μmol/h/mg protein), β-glucuronidase 0.05 (0.21), β-glucosaminidase 0.03 (3.9), α-L-iduronidase 0.12 (0.87), and arylsulfatase A 0.10 (0.67)

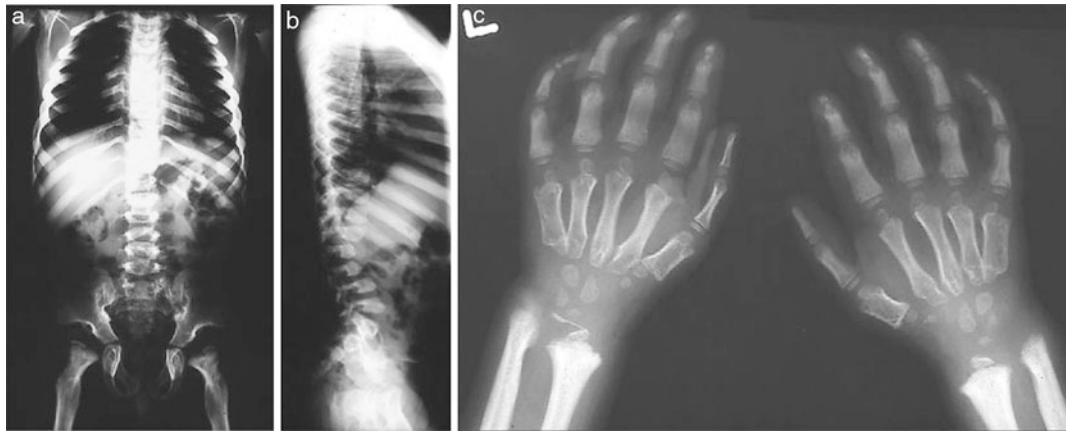

Fig. 2 (**a**–**c**) Radiographs of patient 1. Lateral lumbar spines showed severe hypoplasia with characteristic "beaked" configuration along their inferior aspects. Iliac bones were narrow and the basilar portions were hypoplastic with slanting acetabular roofs. Coxa valga deformity was present. Mild claw hand deformities with retarded bone age were evident

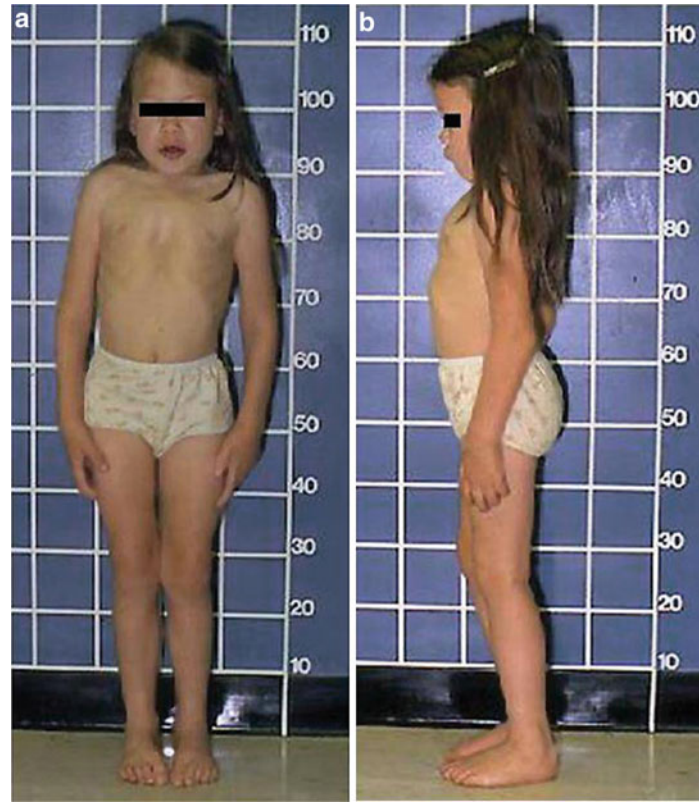

Fig. 3 (**a**, **b**) Patient 2 (sister of the patient 1) at age 7 years and 6 months showing similar clinical findings

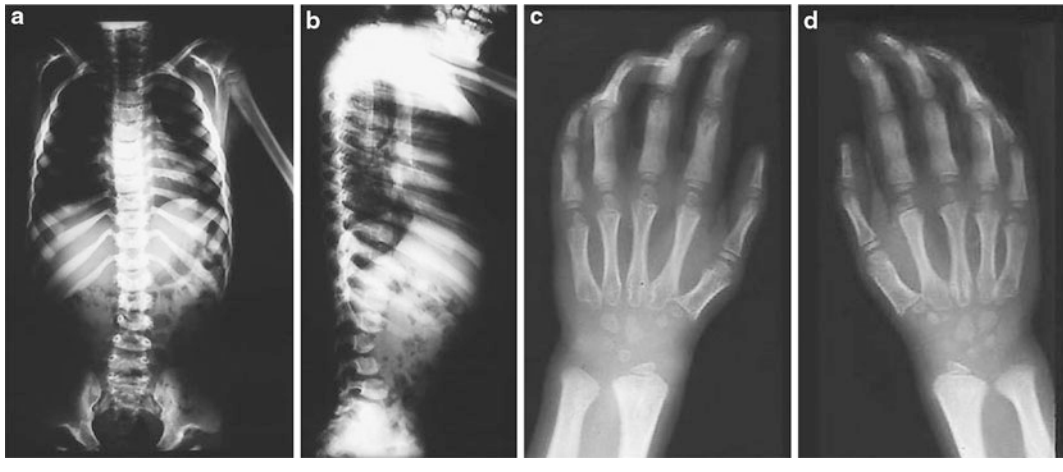

Fig. 4 (**a**–**d**) Radiographs of patient 2 showing similar radiographic findings

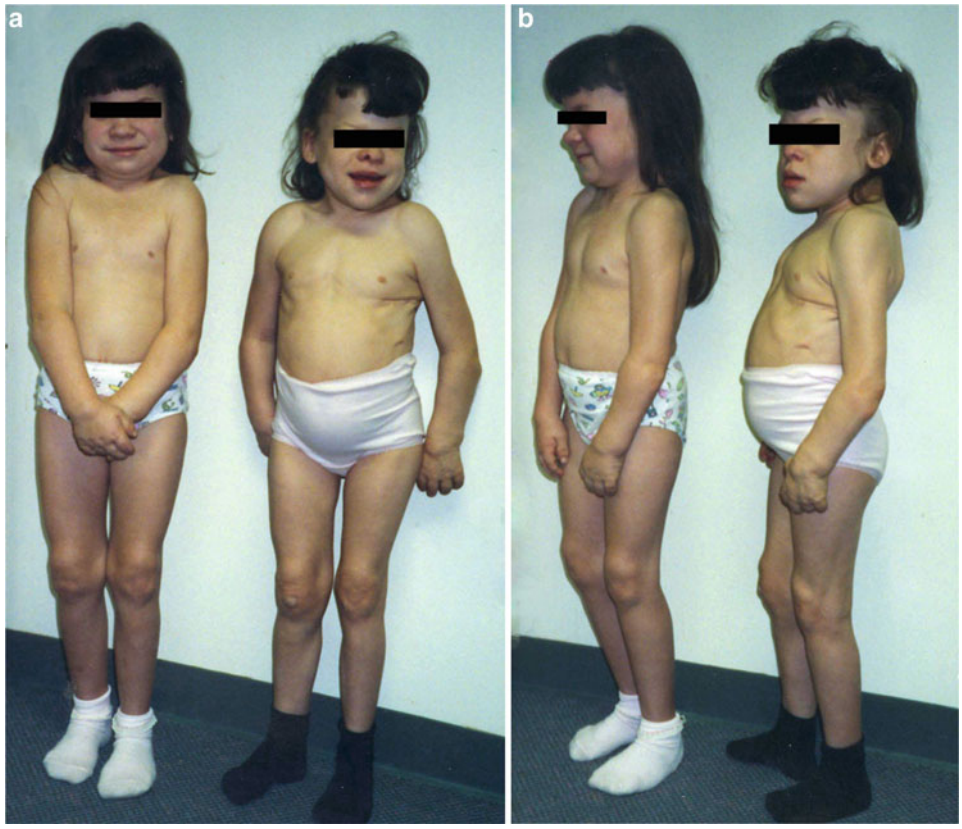

Fig. 5 (**a**, **b**) Two sisters (ages 10 years and 9 years) with mucolipidosis III showing developing delay, coarse facial features, claw hands, and more severe joint contractures. Radiographs (not shown) revealed bullet-shaped proximal phalanges, small carpal bones, and misshapen femoral heads

Mucopolysaccharidosis 2

Contents

In 1917, Hunter described the syndrome in two brothers. Hunter syndrome is an X-linked recessive form of the mucopolysaccharidosis. Severe and mild (attenuated) forms of the syndrome are caused by the same enzyme deficiency, iduronate-2-sulfatase with consequent increase of the urinary concentration of the glycosaminoglycan (GAG), dermatan sulfate and heparan sulfate. The estimated incidence is approximately 1 in 100,000 births.

Synonyms and Related Disorders

Hunter syndrome; Iduronate-2-sulfatase deficiency

Genetics/Basic Defects

1. Inheritance (Beighton 1993)
    1. X-linked recessive inheritance from pedigree data
    2. The gene for iduronate sulfatase mapped to Xq28
2. Primary biochemical defect and pathophysiology (Defendi 2015)
    1. Deficient iduronate-2-sulfatase (*IDS*), the enzyme required for cleavage of sulfate from iduronic acid moieties of dermatan and heparan sulfates
    2. Excessive intracellular accumulation of acid mucopolysaccharides (dermatan sulfate and heparan sulfate) due to deficient iduronate sulfatase activity, leading to multiple organ system involvement, including the musculoskeletal, integumentary, cardiovascular, pulmonary, and ocular systems
3. Molecular defect
    1. Mutations of *IDS* gene (Bunge et al. 1993; Goldenfum et al. 1996; Lissens et al. 1997; Froissart et al. 1998; Vafiadaki et al. 1998).
        1. Missense and nonsense mutations
        2. Mutations affecting splicing
        3. Small insertions and deletions
        4. Partial gene deletions
        5. Deletions and rearrangements (Froissart et al. 1993)
        6. Almost all recurrent point mutations involve CpG sites (Rathmann et al. 1996)
    2. Major structural alterations and gross deletions of the *IDS* gene result in the most

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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severe forms of Hunter syndrome (Timms et al. 1997).
3. Single-base substitutions causing diminished but not obliterated enzyme activity is observed in mild disease.

4. Genetic heterogeneity (Lichtenstein et al. 1972; Young et al. 1982a)
5. Hunter syndrome in females: an exceedingly rare event possibly due to the following mechanisms:
   1. As the offspring of a carrier female and affected male or an unaffected male whose sperm carries a new mutation
   2. Uniparental disomy of the mutant X chromosome from a heterozygous female or an affected male
   3. Genetic rearrangement: for example, translocation or deletion (Broadhead et al. 1986) resulting in nonrandom lyonization toward expression of a mutant allele
   4. Mucopolysaccharidosis type II in a female patient with a reciprocal X;9 translocation and skewed X chromosome inactivation (Lonardo et al. 2014)

Clinical Features

1. Clinical presentation showing a spectrum of mild to severe forms as a result of different mutations in the functional gene (Young et al. 1982; Beighton 1993)
2. Severe Hunter syndrome (MPS IIA) (Young and Harper 1983)
   1. Onset: usually between 2 and 4 years of age with progressive neurologic and somatic involvement
   2. More common than the mild form
   3. Short stature not pronounced
   4. Coarse facial features
      1. Frontal bossing
      2. Depressed nasal bridge
      3. Wide nostrils
      4. Depressed nasal bridge
      5. Thick lips
      6. Hypertrophic gums
      7. A large tongue
   5. Skeletal deformities
      1. Kyphosis
      2. Digital contractures
      3. Claw hands
      4. Joint stiffness
      5. Absence of gibbus
   6. CNS manifestations (Al Sawaf et al. 2008)
      1. Mental retardation
      2. Hydrocephalus
      3. Seizures
      4. Sleep apnea
      5. Cerebral infarction
      6. Spinal cord compression/cervical myelopathy
      7. Other CNS lesions
         1. Enlarged perivascular spaces
         2. Widening of subarachnoid spaces
         3. White-matter lesions
         4. Delayed myelination
   7. Ocular manifestations
      1. Absence of corneal clouding
      2. Thickened sclera
      3. Optic atrophy
      4. Papilledema
      5. Retinitis pigmentosa-like retinal fundus
      6. Night blindness
      7. Scotomas
   8. Hearing loss
   9. Respiratory difficulties (Yoskovitch et al. 1998)
      1. Upper airway obstruction due to adenoid hypertrophy, nasal congestion, and thick rhinorrhea
      2. Mouth breathing secondary to choanal stenosis
      3. Sonorous breathing, frank obstructive sleep apnea, and even death secondary to adenoid hypertrophy, tongue enlargement, and supraglottic swelling
      4. In adult MPS II patients, central airways diameters are strikingly reduced and upon expiration there is extensive collapse of the trachea and main bronchi. This central airways obstruction explains the severe respiratory symptoms in MPSII patients (Young and Harper 1979; Rotten et al. 2016)

10. Cardiovascular disorders
    1. Cardiac valvular involvement leading to congestive heart failure, the leading cause of death in affected individuals
    2. Mild thickening and shortening of the chordae tendineae contributing to the regurgitated valve dysfunction
11. Gastrointestinal problems
    1. Chronic diarrhea secondary to autonomic nervous system involvement and mucosal dysfunction
    2. Hepatosplenomegaly
    3. Umbilical and inguinal hernias
12. Thick skin often with nodular skin lesions over the scapular area or arms
13. Psychosocial problems (Young and Harper 1981)
14. Peripheral nervous system manifestations
    1. Carpal tunnel syndrome secondary to median nerve compression
    2. Cubital tunnel syndrome
15. Additional features of most severely affected patients caused by large deletions that include iduronate sulfate sulfatase and contiguous genes
    1. Hurler-like symptoms
    2. Early onset of seizures
    3. Ptosis
16. Prognosis: typically advancing to cachexia and death before 15 years

3. Mild Hunter syndrome (MPS IIB) (Young and Harper 1982; Young et al. 1982)
    1. Diagnosed slightly later than the severe form
    2. Much less frequent than the severe form
    3. Preservation of normal intelligence
    4. No central nervous system involvement
    5. Somatic involvement less progressive
    6. Hearing impairment
    7. Cardiovascular disorders
    8. Joint stiffness
    9. Cervical myopathy due to a narrowed spinal canal and cord compression
    10. Carpal tunnel syndrome more frequent and severe compared to the severe form
    11. Loss of hand function resulting from joint stiffness and carpal tunnel syndrome
    12. Prognosis
        1. Longer survival
        2. Typically surviving to adulthood
        3. Possible death in early adulthood or even in the late teens due to airway obstruction and cardiac failure

Diagnostic Investigations

1. Echocardiography
2. Electrocardiography
3. Radiographic features
    1. Kyphosis
    2. Claw hands
    3. Thick cortex of the bones progressively becoming thinner as the marrow cavities expand
    4. Large calvarium with shoe-shaped sella
    5. Broad and spatulate lower ribs
    6. Hypoplasia and beaking of the lumbar vertebrae
4. MRI of the brain (Al Sawaf et al. 2008)
    1. Most common findings: widely distributed white-matter lesions, predominantly found peri- and supraventricularly as well as in the basal ganglia and the corpus callosum. These changes were regarded as filling defects rather than immaturity of white matter and are suspected to progress with age.
    2. Even before the development of white-matter lesions, clearance of MPS deposits in white matter may result in demyelination. In addition, delay of myelination may also occur in Hunter disease.
    3. Common findings with questionable clinical relevance.
        1. Enlargement of the perivascular spaces
        2. Ventriculomegaly
        3. Mega cisterna magna
        4. Widening of the subarachnoid spaces
5. Biochemical/molecular studies (Liebaers and Neufeld 1976)
    1. Measurement of mucopolysaccharides in the urine: abnormal excretion of a large amount of dermatan sulfate and heparan sulfate in the urine.

2. Deficient iduronate sulfatase in leukocytes and fibroblasts.
3. Excessive intracellular accumulation of dermatan sulfate and heparan sulfate.
4. Peripheral lymphocytes, when stained with toluidine blue, exhibit metachromatic granules within vacuoles.
5. The gold standard for diagnosis of MPS II in a male proband is assay of I2S enzyme activity in white cells or serum (Martin 2007).
6. Molecular genetic testing of *IDS*, the only gene known to be associated with MPS II, is used to confirm the diagnosis in a male proband with an unusual phenotype or a phenotype that does not match the results of GAG testing (Martin 2007).
    1. Sequence analysis
    2. Deletion testing for exonic and whole gene deletions
    3. Southern blot analysis: used to detect complex rearrangements resulting from recombination with the pseudogene and accounting for 9% of all mutations (Froissart et al. 2007)
7. Highlight the utility of whole-exome sequencing in expanding the recognized phenotypic spectrum of known syndromes such as MPS II (Nikkel et al. 2014).

6. Heterozygote detection (Timms et al. 1998)
    1. Carrier detection by enzyme analysis for MPS II is unreliable (Archer et al. 1983; Zlotogora and Bach 1984)
    2. Identification of *IDS* gene mutations (Bunge et al. 1994)
    3. Germline and somatic mosaicism in a female carrier of Hunter disease (Froissart et al. 1997)

Genetic Counseling

1. Recurrence risk.
    1. Patient's sib
        1. Carrier mother: 50% of brothers affected, 50% of brothers normal, 50% of sisters carriers, 50% of sisters normal
        2. Noncarrier mother (mother of a sporadic case): recurrence possible due to presence of gonadal mosaicism
    2. Patient's offspring
        1. Severe form: not surviving to reproduction
        2. Mild form: none of the sons affected, all daughters carriers
2. Prenatal diagnosis (Muenzer 1986; Fensom and Benson 1994; Keulemans et al. 2002).
    1. Maternal serum analysis (Zlotogora and Bach 1986)
        1. Consistent increase of iduronate sulfate sulfatase in the serum of pregnant women from prepregnancy levels toward the end of pregnancy
        2. No change in the serum enzyme levels of heterozygous mothers until the affected fetuses are aborted
    2. Amniocentesis (Archer et al. 1984)
        1. Reduced enzyme activity in the amniotic fluid (Liebaers et al. 1977)
        2. Low enzyme levels in cultured amniotic cells
        3. Abnormal $^{35}SO_4$ incorporation into cultured amniotic fluid cells (Kleijer et al. 1979)
        4. Karyotyping for fetal sex
        5. Direct detection of *IDS* gene mutation, provided the disease-causing mutation in the family has been identified previously
    3. CVS (Pannone et al. 1986)
        1. Diminished enzyme activity in uncultured chorionic villi of affected male fetuses. This may be seen in female carrier fetuses (Cooper et al. 1991)
        2. Karyotyping for fetal sexing
        3. Direct detection of *IDS* gene mutation, provided the disease-causing mutation in the family has been identified previously
    4. Umbilical fetal blood sampling: severe deficiency of iduronate sulfate sulfatase in the plasma of affected male fetuses (Lissens et al. 1988)
    5. Preimplantation diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

3. Management (Beighton 1993).
    1. Tympanostomy, adenoidectomy, and provision of hearing aids for management of otologic complications
    2. Symptomatic management of airway obstruction (sleep apnea)
    3. Ventriculoperitoneal shunting for hydrocephalus, a relatively rare complication of Hunter syndrome
    4. Difficulties during anesthesia secondary to the following factors:
        1. Rigid thoracic cage
        2. Abdominal distention
        3. Macroglossia
        4. Temporomandibular ankylosis
        5. Atlantoaxial instability
        6. Short and wide neck
    5. Prophylactic antibiotics for at-risk procedures in patient with mucopolysaccharidosis.
    6. Surgical repair of inguinal and umbilical hernias.
    7. Surgical release to preserve apposition of the thumbs at the earliest sign of an electrophysical evidence of progressive median nerve compression.
    8. Musculoskeletal complications.
        1. Shoe orthotics and ankle braces well tolerated and useful in maintaining mobility
        2. Achilles tendon release in some patients with advanced disease
        3. Surgical stabilization of the spine rarely indicated for kyphoscoliosis which is only mildly progressive and not usually resulting in spinal cord compression
    9. To varying degrees, patients with the severe form manifest behavioral disorders such as hyperactivity, aggression, impulsivity, anxiety, and sleep disturbances. Medications, such as antipsychotics, benzodiazepines, and anticonvulsants, have been tried with varying degrees of success. Behavioral management strategies may be a worthwhile approach, although published data are lacking. For sleep disturbances, behavioral modification plus melatonin or benzodiazepine may be effective treatments (Roberts et al. 2016).
    10. Attenuated MPS II patients have increasing somatic disease burden and poor physical quality of life as they develop as well as decreasing self-esteem and sense of adequacy. Psychosocial quality of life, adaptive skills, and attention improve. Recognition of and intervention around these issues will be beneficial to MPS II attenuated patients who have the resources to use such assistance to improve their long-term outcomes (Shapiro et al. 2016).
    11. Bone marrow transplantation (McKinnis et al. 1996).
        1. Possible reduction in hepatosplenomegaly, improvement in airway disease, and reduction in urinary glycosaminoglycan excretion
        2. Long-term prognosis for longevity, cardiac complications, and neurologic outcome after marrow transplantation still remained to be determined (Bergstrom et al. 1994)
    12. Hematopoietic stem cell transplantation (HSCT) has been performed in numerous individuals with varying degrees of severity of MPS II but limited success and significant risk; therefore, HSCT is not currently recommended for individuals with MPS II (Martin et al. 2008).
    13. Enzyme replacement therapy (ERT) (Burrow and Leslie 2008; da Silva et al. 2014).
        1. Recently, recombinant iduronate-2-sulfatase (idursulfase, Elaprase®; Shire Human Genetic Therapies, Inc., Cambridge, MA), a recombinant human I2S produced in a human cell line, was approved in the United States and the European Union as a safe and effective treatment for individuals with MPS II.
        2. The rationale for therapy is that exogenous I2S would replace the iduronate-2-sulfatase that is deficient in patients and either stop or reverse disease progression.

3. Recent clinical trials have shown promise in the treatment of MPS II, with potential to help many patients, providing that it is started early in the course of the disease (Wraith et al. 2008).
4. ERT involves the intravenous administration of a recombinant human enzyme into individuals in whom the enzyme is missing or defective.
5. The recombinant enzyme undergoes receptor-mediated cell uptake and subsequent intracellular trafficking into the lysosomes, where it carries out its specific function.
6. Elaprase® does not cross the blood–brain barrier; thus, no effect on CNS disease is anticipated. Thus, CNS disease remains a major challenge, and an innovative approach to treatment will be needed if this is to be addressed fully (Wraith et al. 2008).

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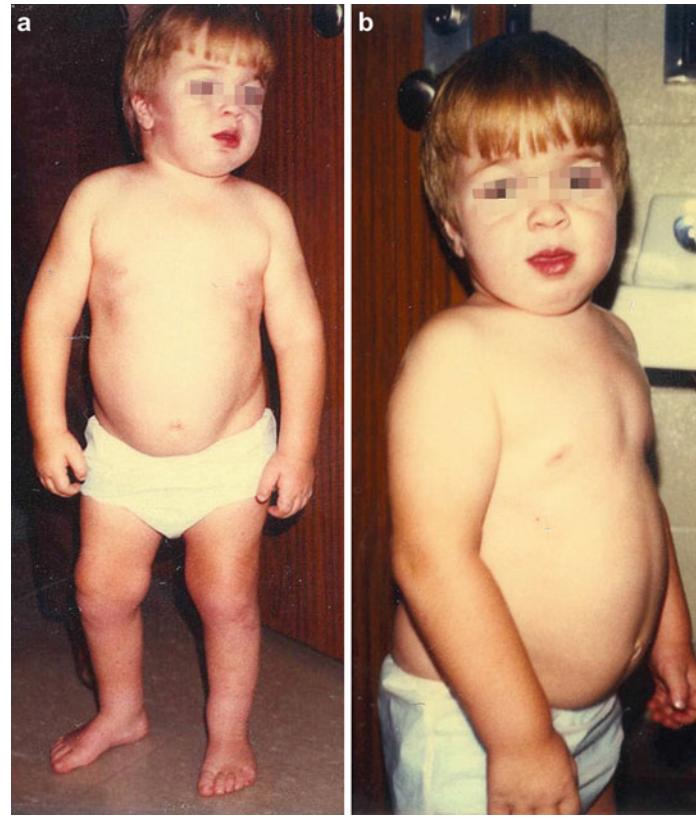

Fig. 1 (**a**, **b**) A boy with MPS II showing mild short stature, coarse facial features, large abdomen, and claw hands

Mucopolysaccharidosis 3

Contents

In 1962 and 1963, Sanfilippo et al. described eight children with mental retardation and heparan sulfate mucopolysaccharidoses and delineated the syndrome which now bears his name. Earlier in 1961, Harris reported a 6-year-old girl with hepatosplenomegaly, a normal skeletal survey, and excretion of large amounts of heparan sulfate in the urine. Sanfilippo syndrome is one of the most common mucopolysaccharidoses (MPS) (1/24,000–1/200,000).

Sanfilippo syndrome is comprised of four biochemically heterogeneous types (MPS IIIA, IIIB, IIIC, and IIID), which are clinically indistinguishable. Because the deficiency of these four various lysosomal enzymes involved the same breakdown of heparan sulfate, their clinical phenotype is similar. Type A is the most common type of MPS III in Northwest Europe, while type B is the most frequent type in Southeast Europe (Meikle et al. 1999; Poorthuis et al. 1999; Baehner et al. 2005). Types C and D appear to be much rarer (Valstar et al. 2008).

Synonyms and Related Disorders

Sanfilippo Syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. Genetic heterogeneity (Van de Kamp et al. 1981).
3. Failure to degrade heparan sulfate may result from deficiency of one of the following four lysosomal enzymes (Bodamer et al. 2014):
   1. MPS IIIA caused by deficient heparan *N*-sulfatase (sulfamidase) (Karpova et al. 1996; Blanch et al. 1997; Bunge et al. 1997; Chabas et al. 2001)
   2. MPS IIIB caused by deficient α-*N*-acetylglucosaminidase (Beesley et al. 1998, 2005; Bunge et al. 1999)
   3. MPS IIIC caused by deficient acetyl-CoA:α-glucosaminide-*N*-acetyltransferase
   4. MPS IIID caused by deficient *N*-acetyl-α-glucosamine-6-sulfatase (Beesley et al. 2003)
4. Four subtypes of MPS III (Bodamer et al. 2014):
   1. Clinically indistinguishable
   2. Each characterized by deficiency of a different enzyme

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_163

3. MPS IIIA mapped to 17q25.3
4. MPS IIIB mapped to 17q21
5. MPS IIIC mapped to 8p11.1
6. MPS IIID mapped to 12q14

Clinical Features

1. Severe CNS involvement (Nidiffer and Kelly 1983):
    1. Developmental milestones near normal prior to age 3–4 years.
    2. Developmental delay, especially in speech (first stage usually starts between 1 and 4 years of age).
    3. Behavioral problems (second stage usually starts around 3–4 years):
        1. Aggressiveness
        2. Hyperactivity
        3. Attention deficit
        4. Temper tantrums
        5. Destructive behavior
        6. Physical aggression
        7. Sleep disturbance:
            1. Setting difficulties
            2. Night walking
            3. Sometimes awake all night
            4. Crying out
            5. Wandering around the house
            6. Entering parents' bed
            7. Talking in sleep
            8. Body rocking
            9. Chewing bedclothes
        8. Poor attention span
        9. Marked mood swings
        10. Self-injury
    4. Progressive motor difficulties due to spasticity and joint stiffness and slowly disappearing behavioral problems, starting about 10 years of age (marking the third and final stage).
    5. Severe hearing loss common in the moderate to severely affected patient.
    6. Severe neurologic degeneration occurring in most patients by 6–10 years of age, accompanied by rapid deterioration of social and adaptive skills (mental deterioration).
    7. Progressive dementia resulting in withdrawal and losing contact with the environment.
    8. Seizures: uncommon.
    9. Patients usually die at the end of the second or beginning of the third decade of life, although survival into the fourth decade has been reported.
2. Mild somatic disease:
    1. Coarse hair (hirsutism): hypertrichosis often present, especially on the back
    2. Macrocephaly
    3. Copious nasal discharge
    4. Repeated upper respiratory tract infections
    5. Cardiac signs and symptoms much lesser degree compared to other types of mucopolysaccharidosis
    6. Mild hepatosplenomegaly
    7. Joint stiffness
    8. Recurrent and sometimes severe diarrhea, usually improves in later childhood
    9. Early onset of puberty
3. Prognosis:
    1. Type A:
        1. The most severe type
        2. Earlier onset
        3. More rapid progression of symptoms (natural history) (Buhrman et al. 2014):
            1. Severe hearing loss and speech delay, followed by a rapid decline in cognitive skills by 3 years of age.
            2. Significant somatic disease occurs in more than half of the patients.
            3. Behavioral difficulties presented between 2 and 4 years of age during a rapid period of cognitive decline.
            4. Gross motor abilities are maintained during this period, which results in an active child with impaired cognition.
            5. Sleep difficulties are concurrent with the period of cognitive degeneration.
        4. Shorter survival: death usually by late teens
    2. Type B: known to remain functional into the third or even fourth decades
    3. Type C: clinically heterogeneous

4. Type D (Jones et al. 1997):
    1. Least common type
    2. Clinically heterogeneous

Diagnostic Investigations

1. Increased urinary excretion of heparan sulfate.
2. Quantitative urinary glycosaminoglycan analysis (Bodamer et al. 2014) is strongly recommended, and measurement of disaccharides, heparin cofactor II–thrombin complex, and gangliosides is also used (Andrade et al. 2015).
3. Growth charts for height and weight for males and females are available for MPS III (de Ruijter et al. 2014).
4. Imaging features:
    1. Radiography: mild degree of dysostosis multiplex
    2. Echocardiography for rare cardiac abnormalities
    3. CT:
        1. Mild to moderate cortical atrophy at onset
        2. Severe cortical atrophy at late stage
    4. MRI (Barone et al. 1999):
        1. Cortical atrophy.
        2. Corpus callosum atrophy.
        3. Abnormal or delayed myelination.
        4. MRI findings may precede the onset of overt neurological symptoms.
5. Biochemical analysis (Defendi and Varma 2009):
    1. Biochemical differentiation of the different forms within MPS II is possible, and diagnosis is confirmed by specific enzymatic assay:
        1. Deficient heparan *N*-sulfatase (type A)
        2. Deficient *N*-acetylglucosaminidase (type B)
        3. Deficient α-glucosamine-*N*-acetyltransferase (type C)
        4. Deficient *N*-acetyl-α-glucosamine-6-sulfatase (type D)
    2. Enzymatic activity for all types of MPS III may be assayed in cultured skin fibroblasts and in peripheral blood leukocytes.
    3. Enzyme activity of the different enzymes in blood serum, leukocytes, or fibroblasts and mutational analysis for *SGSH*, *NAGLU*, *HGSNAT*, or *GNS* genes are required to confirm diagnosis and differentiate four subtypes of MPS III (Andrade et al. 2015).
6. Mutation studies are available clinically by sequence analysis and deletion/duplication analysis:
    1. MPS IIIA (Beesley et al. 2000; Yogalingam and Hopwood 2001; Lee-Chen et al. 2002a; Di Natale et al. 2003):
        1. Missense mutations (most common)
        2. Premature termination mutations
        3. Small deletion mutations
    2. MPS IIIB (Zhao et al. 1996; Yogalingam and Hopwood 2001; Lee-Chen et al. 2002b):
        1. Great molecular heterogeneity
        2. Most mutations: private mutations
    3. MPS IIIC: no mutation analysis available currently
    4. MPS IIID: frameshift and premature termination mutation
7. Very recent breakthroughs in high-throughput methods for sequencing only the protein-coding regions of the genome, called whole exome sequencing or targeted exome capture, present tempting future screening and diagnostic possibilities (Bodamer et al. 2014).
8. Carrier detection (Vance et al. 1981; Toone and Applegarth 1988).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: 25%
    2. Patient's offspring: not reproducing due to mental retardation
2. Prenatal diagnosis (Di Natale et al. 1999):
    1. Fetuses at risk for MPS IIIA:
        1. Measuring sulfamidase activity using radioactive assay in CVS and amniocytes (Thompson et al. 1993)

2. Using fluorimetric sulfamidase assay in CVS and amniocytes (Kleijer et al. 1996)
3. Molecular diagnosis in characterized families

2. Fetuses at risk for MPS IIIB:
   1. Assay of α-*N*-acetylglucosaminidase activity in cultured amniocytes (Mossman et al. 1983) and CVS (Kleijer et al. 1984; Minelli et al. 1988)
   2. Increased level of heparan sulfate in amniotic fluid by two-dimensional electrophoresis of glycosaminoglycans: used as an adjunctive method in prenatal diagnosis
   3. Molecular diagnosis in characterized families
3. Fetuses at risk for MPS IIIC:
   1. Assay of acetyl-CoA:α-glucosamine-*N*-acetyltransferase in amniocytes (Maire et al. 1993) and CVS (di Natale et al. 1987; He et al. 1994)
   2. Molecular diagnosis in characterized families
4. Fetuses at risk for MPS IIID:
   1. Spectrophotometric assay for the *N*-acetyl-α-glucosamine-6-sulfatase activity (Nowakowski et al. 1989)
   2. Molecular diagnosis in characterized families
5. Diagnostics using free fetal DNA or fetal cells recovered from maternal circulation to directly detect mutations causing the MPS III phenotype will enable prenatal diagnosis of MPS III without the need of invasive sampling procedures (Dhallan et al. 2004).

3. Preimplantation genetic diagnosis (Hopwood 2005):
   1. Allows embryos to be tested for MPS III before they enter the uterus and pregnancy begins.
   2. This requires embryos, obtained by in vitro fertilization, to undergo a biopsy procedure in which one or two cells are removed and tested for the specific disorder.
   3. Only embryos shown to be free of MPS III are then implanted (Thornhill and Snow 2002).

4. Management (Cleary and Wraith 1993):
   1. Supportive treatments:
      1. Antibiotics for otitis media and respiratory tract infections
      2. Anticonvulsants for seizure activities
   2. Muscle relaxants for painful spasms.
   3. Gastrostomy to maintain adequate nutrition.
   4. Special education program.
   5. Behavioral management to allow the family to function as near normal as possible:
      1. Alteration to the physical environment within home
      2. Drug treatment to control hyperactivity and aggression
   6. Physical therapy to maintain joint mobility.
   7. Recommend monitoring bone mineral density by dual-energy X-ray absorptiometry and checking vitamin D metabolism to assess low bone mass and fracture risk in older MPS III patients with immobility (Nur et al. 2016).
   8. Wheelchair for transportation.
   9. Respite care: availability of suitable respite accommodation.
   10. Identify professional and community resources.
   11. Risperidone treatment of behavioral disorder in children with MPS IIIA: appeared to be safe and effective (Ucar et al. 2010).
   12. Bone marrow transplantation (Vellodi et al. 1992; Sivakumur and Wraith 1999):
      1. Biochemical correction readily achievable
      2. Disappointing intellectual outcome
   13. Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective (Aldenhoven et al. 2015).

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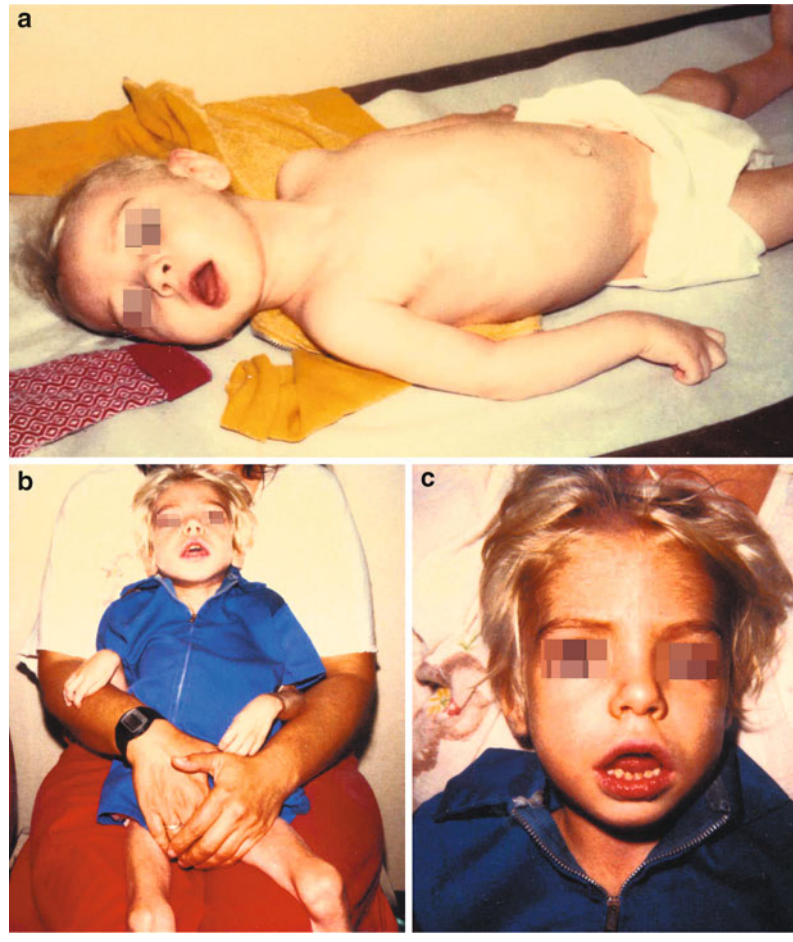

Fig. 1 (**a**–**c**) A child with MPS IIIA at 8 months (**a**) and 3 years (**b**, **c**)

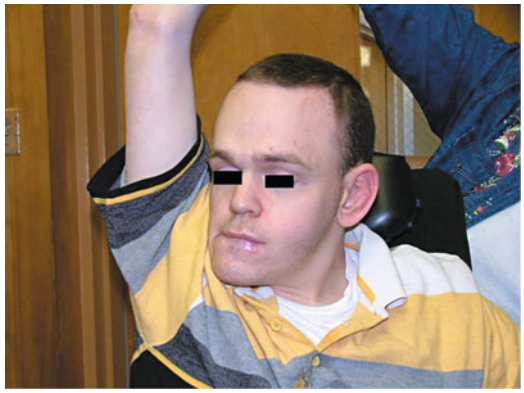

Fig. 2 A 32-year-old male with Sanfilippo syndrome type A showing mental retardation and severe behavioral problems. Molecular genetic analysis revealed heparan sulfamidase (SGSH) gene mutations. A C > T substitution was detected at nucleotide 892 resulting in a serine being replaced by a proline at amino acid 298 (S298P). The second nucleotide change resulted in insertion of a cystine at nucleotide 1,028 which creates a frameshift and premature truncation of protein (1028insC). The detection of two mutations in the heparan sulfamidase gene is associated with Sanfilippo A syndrome

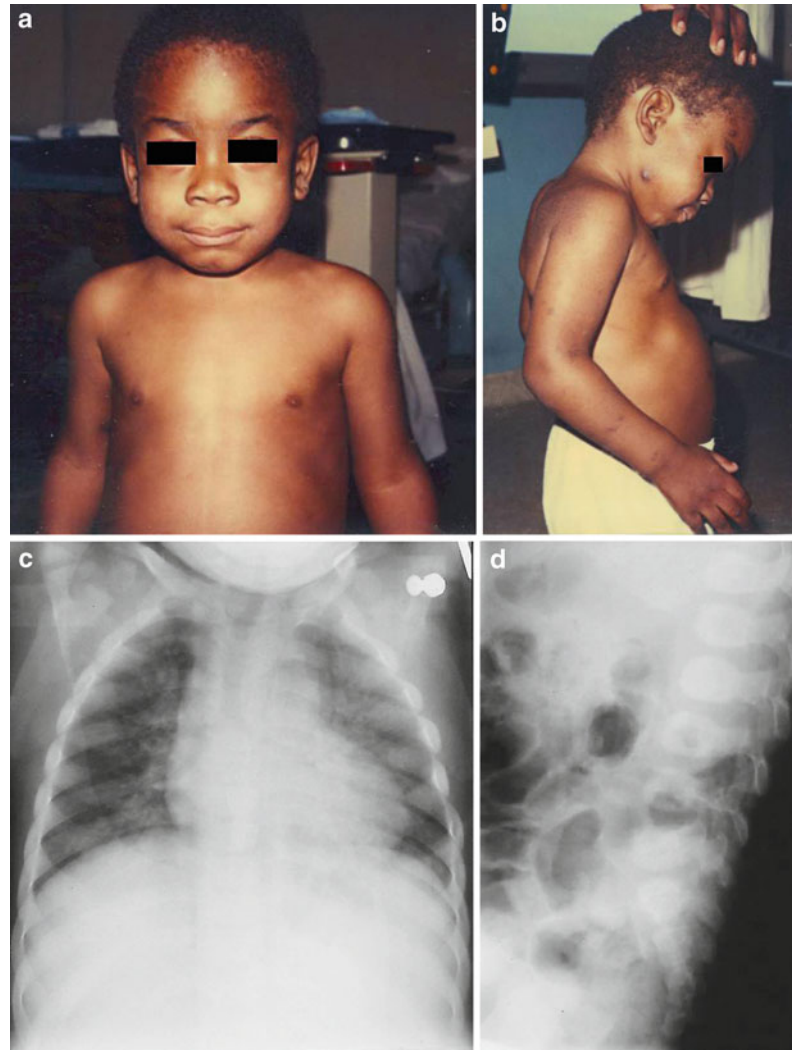

Fig. 3 (**a**–**d**) A child with MPS IIIB at 3 years of age (**a**, **b**). The radiographs (**c**, **d**) show mild degree of dysostosis multiplex

Mucopolysaccharidosis 4

Contents

In 1929, Morquio and Brailsford independently described cases of what is now believed to be Morquio syndrome (Brailsford 1929; Morquio 1929). The exact incidence is unknown but is estimated to be 1 in 75,000-1 in 200,000.

Synonyms and Related Disorders

Galactosamine-6-sulfatase deficiency; Morquio disease; Morquio syndrome; MPS IVA; MPS IVB

Genetics/Basic Defects

1. Genetic inheritance: autosomal recessive (Beck et al. 1987)
2. Two forms of MPS IV
    1. MPS IVA
        1. Deficient *N*-acetyl-galactosamine-6-sulfate sulfatase (*GALNS*) gene, which is mapped to 16q24.3 (Baker et al. 1993; Masuno et al. 1993).
        2. Excessive allelic heterogeneity among patients with Morquio A syndrome (Bunge et al. 1997). Heteroallelic missense mutations lead to GALNS deficiency and mild MPS IVA (Cole et al. 1996).
        3. Wide spectrum of clinical manifestations (Nelson et al. 1988; Tylki-Szymanska et al. 1998).
    2. MPS IVB (Paschke et al. 2001)
        1. Deficient β-galactosidase (*GLB1*) gene
        2. Wide spectrum of clinical manifestations
3. Pathogenesis (Braverman and Hoover-Fong 2003)
    1. Defective degradation of keratan sulfate secondary to deficiency of either *N*-acetyl-galactosamine-6-sulfate sulfatase (*GALNS* gene) in MPS IVA or β-galactosidase (*GLB1* gene) in MPS IVB
    2. Cartilage and cornea: the major organs affected in Morquio syndrome since keratan sulfate is predominantly found in these tissues

Clinical Features

1. MPS IVA
    1. Classic form

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1. The most common form
2. Appears normal at birth
3. Skeletal symptoms occurring between 1 and 3 years of age
4. Clinical diagnosis usually not made until 3–15 years of age
5. Skeletal manifestations
    1. Marked dwarfism
    2. Waddling gait with tendency to fall
    3. Short neck
    4. Hypoplasia or absence of the odontoid process of the axis with risk of resulting in life-threatening atlantoaxial subluxation (Blaw and Langer 1969). Odontoid dysplasia in the absence or presence of atlantoaxial instability in all cases (Nelson and Thomas 1988)
    5. Cervical myelopathy (Rigante et al. 1999)
    6. Gibbus
    7. Restrictive chest wall movement
    8. Pectus carinatum
    9. Kyphoscoliosis
    10. Genu valgum
    11. Semicrouching stance
    12. Progressive skeletal deformities frequently resulting in neurologic compromise
6. Joint manifestations
    1. Hypermobile due to ligamentous laxity
    2. Decreased mobility in large joints (e.g., hips, knees, elbows)
7. Unusual facial appearance
    1. Coarse facies
    2. Prognathism
    3. Broad mouth
8. Eye manifestations
    1. Mild corneal clouding
    2. Glaucoma
    3. Cataract
9. Dental features (Nelson and Kinirons 1988; Rølling et al. 1999)
    1. Abnormally thin enamel
    2. Spade-shaped incisors
    3. Pointed cusps
    4. Pitted buccal surfaces
    5. Frequent caries formation
10. Cardiac manifestations
    1. Aortic valve insufficiency or stenosis
    2. Mitral valve thickening and stenosis
    3. Cardiac failure
11. Progressive deafness
12. Hepatomegaly
13. Upper airway obstruction
    1. Obstructive sleep apnea
    2. Nocturnal dyspnea
14. Intelligence usually normal, rarely with progressive mental regression

2. Mild form
    1. Almost normal stature
    2. Mild skeletal abnormalities
        1. Odontoid dysplasia but without atlantoaxial instability
        2. Pectus carinatum deformity
        3. Dysplastic hips
        4. Waddling gait
        5. Kyphoscoliosis
        6. Deformity of femoral heads
        7. Platyspondyly
        8. Limitation of joint movement
        9. Deformities of metacarpals
    3. Enamel hypoplasia
    4. Mild corneal clouding
    5. Absent keratosulfaturia

2. MPS IVB
    1. Severe form: clinical manifestations as severe as MPS IVA
    2. Mild form
        1. Less severe progression of skeletal dysplasia
        2. Less severe short stature
3. Prognosis
    1. Atlantoaxial instability and subsequent cervical myelopathy
        1. Cord transection and subsequent quadriparesis or death secondary to a minor fall or extension of the neck
        2. Bowel and bladder dysfunction and apnea secondary to cervical myelopathy

3. Prolonged periods of hypoxia, pulmonary hypertension, and even death from obstructive sleep apnea
4. Airway obstruction secondary to thickening of tissue in the upper airway from mucopolysaccharide deposition

2. Predisposition to pulmonary infection because of progressive truncal deformity and immobility
3. Early-onset coronary heart disease and valve thickening (aortic and mitral) with resultant cardiac dysfunction
4. Visual disturbance and photophobia secondary to corneal clouding
5. Predisposition to dental caries secondary to enamel abnormalities

Diagnostic Investigations

1. Urine MPS spot tests: associated with false-positive and false-negative results. Mildly affected individuals do not always excrete keratan sulfate fragments (Chih-Kuang et al. 2002; Braveman 2014).
2. Excessive urinary excretion of keratan sulfate: determination by spectrophotometric assays with dimethylmethylene blue.
3. Metachromatic granules in cultured fibroblasts.
4. Diagnosis confirmed by direct enzymatic assay in leukocytes or fibroblasts.
   1. *N*-Acetylgalactosamine-6-sulfatase deficiency (classic form)
   2. β-Galactosidase deficiency (mild form)
5. Radiographic features (Langer and Carey 1966).
   1. Short trunk dwarfism
   2. Dysostosis multiplex
   3. Spondyloepiphyseal dysplasia (the hallmark of the syndrome)
   4. Odontoid hypoplasia
   5. Sternal protrusion
   6. Platyspondylia
   7. Kyphosis
   8. Hyperlordosis
   9. Scoliosis
   10. Ovoid deformities of the thoracic vertebrae
   11. Hook-shaped lumbar bodies
   12. Long pelvic configuration
   13. Coxa valga
   14. Genu valgum
   15. Ulnar deviation of the wrist
   16. Valgus deformity of the elbow
   17. Inclinations of distal ends of radius and ulna toward each other
   18. Metacarpal deformities
   19. Short phalanges
   20. Epiphyseal deformities of the tubular bones
   21. Wide metaphysis
   22. Osteoporosis
6. CT and MRI of the brain and cervical spine for evaluation of odontoid hypoplasia and cord compression (Borlot et al. 2014; Braveman 2014).
7. Echocardiography for cardiac involvement.
   1. Aortic valve insufficiency or stenosis
   2. Mitral valve thickening and stenosis
   3. Ventricular hypertrophy
8. Slit-lamp examination for corneal clouding.
9. Molecular genetic diagnosis.
   1. Sequence analysis
   2. Deletion/duplication analysis
10. Molecular testing of Morquio A: novel *GALNS* mutations (Morrone et al. 2014).
    1. Missense alleles
    2. Nonsense alleles
    3. Deletions
    4. Alterations affecting splice sites

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is a carrier in which case there will be 50% of offspring affected

2. Prenatal diagnosis (von Figura et al. 1982; Mossman and Patrick 1982; Zhao et al. 1990; Beck et al. 1992; Kleijer et al. 2000)
    1. Demonstration of GalNac-6S or Gal-6S sulfatase deficiency in cultured amniotic fluid cells or chorionic villi
    2. Abnormal glycosaminoglycan electrophoretic pattern in amniotic fluid
    3. Mutation analysis in amniocytes or chorionic villi, provided the disease-causing mutation has been identified in the family member
3. Preimplantation genetic diagnosis of Morquio syndrome: accomplished by mutation analysis from the embryos following whole-genome amplification of single blastomeres using multiple displacement amplification (Qubbaj et al. 2008)
4. Management (Mikles and Stanton 1997)
    1. Orthopedic management
        1. Surgery to stabilize the upper cervical spine, usually by spinal fusion, can be lifesaving for occipito-spinal cord compression (Blaw and Langer 1969; Northover et al. 1996; Ransford et al. 1996)
        2. Bilateral osteotomies to correct the knock-knee deformity (severe coxa valgum)
    2. Anesthetic difficulties (Bartz et al. 1999; Morgan et al. 2002)
        1. Difficult endotracheal intubation due to odontoid hypoplasia and atlantoaxial instability
        2. Compression of the cord during hyperextension of the neck
        3. Reduction in vital capacity, functional residual capacity, and total lung capacity due to chest cage dysfunction (kyphoscoliosis and pectus carinatum)
    3. Infection control
    4. Medications for glaucoma
    5. Cornea transplant not very helpful
    6. Hearing aids helpful
    7. Hernia repairs
    8. Cardiac management
        1. Aortic regurgitation
        2. Endocarditis prophylaxis
        3. Cardiac valve replacement historically not considered for these patients
9. Potential strategies for treatment including enzyme replacement, gene therapy, and allogenic bone marrow transplantation in which engrafted cells provide the normal enzyme
10. International guidelines for management and treatment of Morquio A syndrome (Hendriksz et al. 2015)
    1. Enzyme replacement therapy with recombinant human GALNS (elosulfase alfa) has recently been approved for Morquio A syndrome, providing a systemic treatment approach. Elosulfase alfa has shown to be effective with a favorable safety profile.
    2. Multidisciplinary approach.
    3. Hip subluxation: using pelvic and femoral osteotomy, shelf acetabuloplasty, or total hip arthroplasty.
    4. Knee valgus: using guided growth (8-plate hemiepiphysiodesis) effective in growing child; knee osteotomy or knee arthroplasty, an option for older patients.
    5. Ankle valgus: generally by orthotics.
    6. Spinal cord compression: spinal decompression, fusion, or a combination of both.
    7. Respiratory impairment: supportive therapies (regular influenza and pneumococcus vaccinations, bronchodilators, and aggressive and prompt treatment of upper respiratory infections), tonsillectomy and/or adenoidectomy frequently required in patients with obstructed upper airways, sleep disordered breathing (obstructive sleep apnea or sustained hypoventilation) generally managed successfully by continuous positive airway pressure or noninvasive ventilator support.

8. Cardiovascular abnormalities: valve replacement for severe aortic or mitral valve disease.
9. Ophthalmological manifestations: refractive correction or low vision aids for impaired vision filtering glasses and hats for photosensitivity, corneal transplantation for corneal clouding, cataract surgery for cataracts.
10. Hearing loss: ventilation tubes for conductive hearing loss due to retained middle ear fluid, post-aural hearing aids for progressive neurosensory hearing loss.
11. Hernia repair for umbilical, inguinal, or bilateral diaphragmatic hernias.
12. Dental caries: fluoride supplementation, fissure sealing of dentition.

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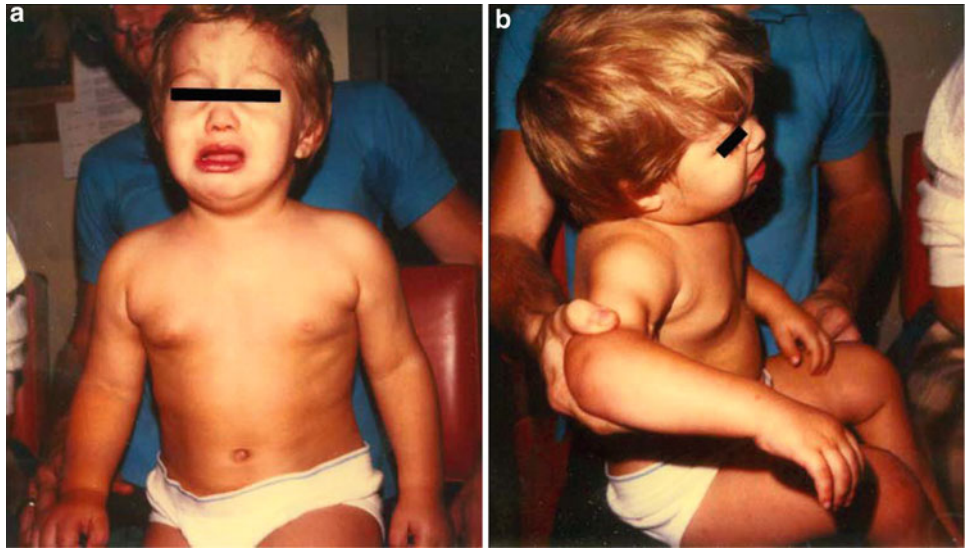

Fig. 1 (**a**, **b**) A boy with MPS IVB showing coarse facial appearance and short trunk

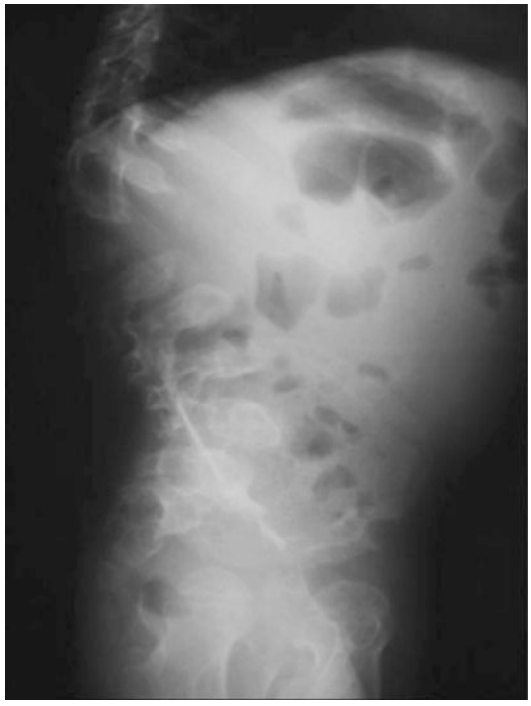

Fig. 2 Lateral view of the spine showing platyspondyly, anterior beaking of vertebral bodies, and lumbar gibbus similar to those seen in Hurler syndrome

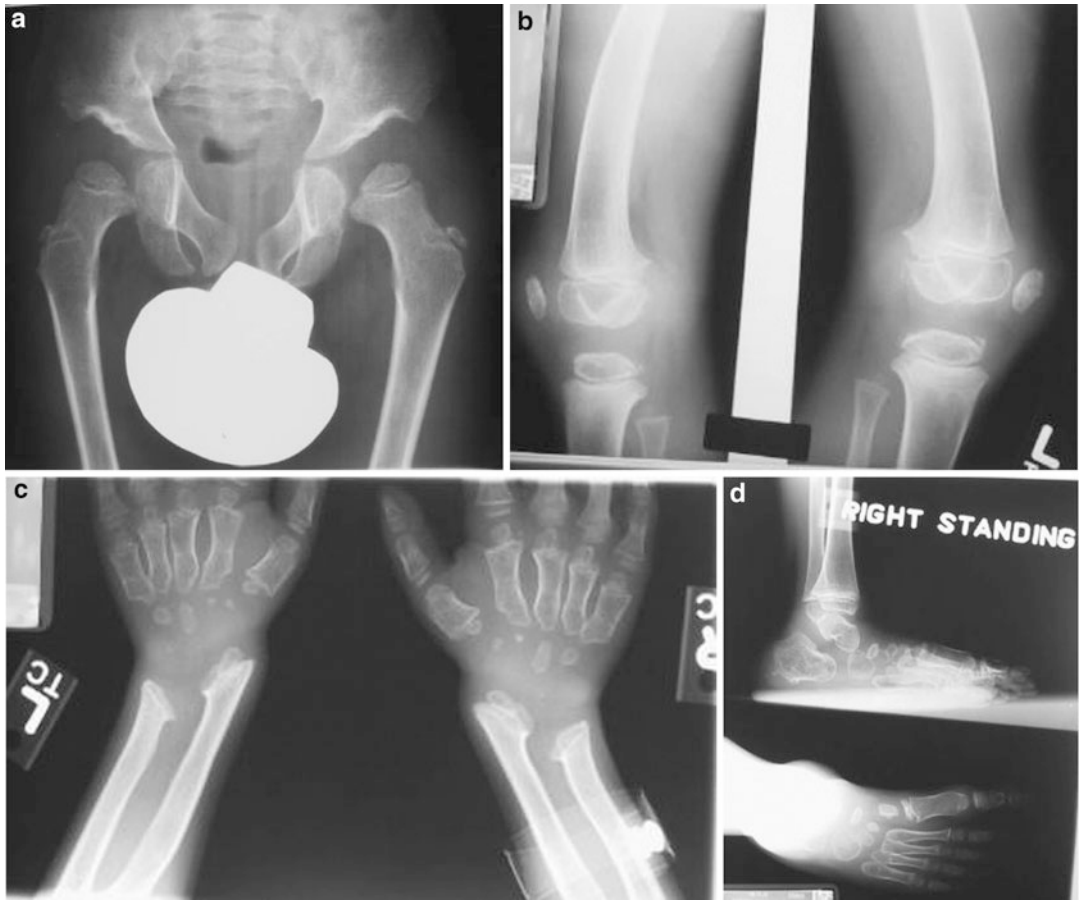

Fig. 3 (**a**–**d**) Radiographic studies showing dysostosis multiplex with proximal conical metacarpals and angling of the ulna toward the radius with dysplastic ulnar and radial growth plates

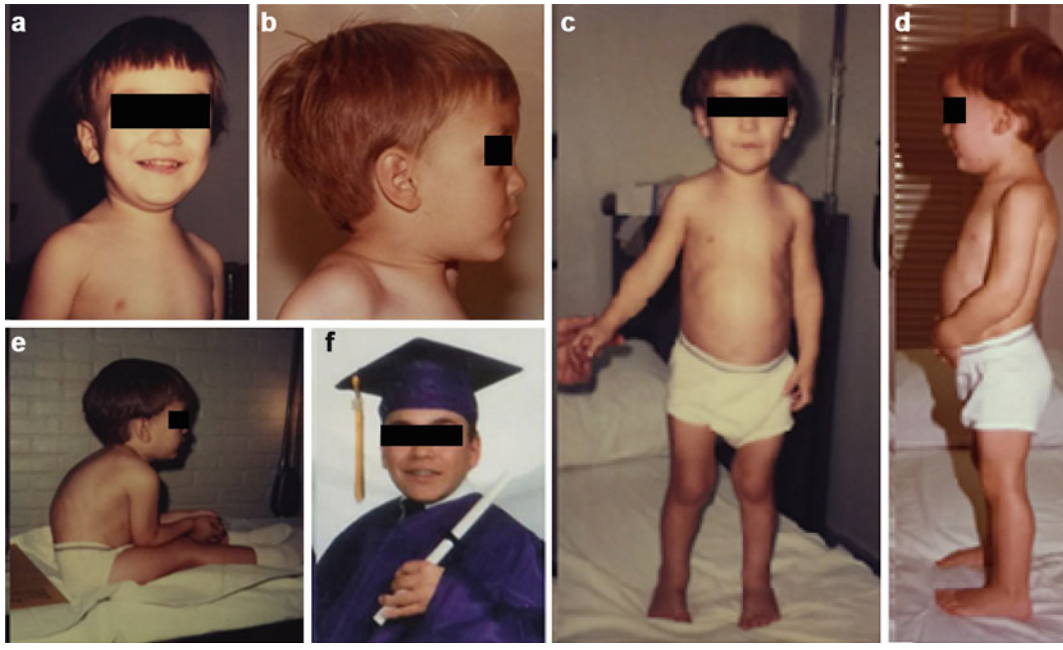

Fig. 4 (**a**–**f**) This French-Canadian (Acadian) boy was first seen at 2 years of age because of abnormal posture of kyphosis when sitting. He was evaluated again at 5 years of age, showing mild coarse facial appearance and short neck (**a**, **b**), short stature, mild pectus carinatum, and mild crouching stance (**c**, **d**) and kyphosis (**e**). His high school graduation photo is shown here in (**f**). The proband's blood keratin sulfate (KS) concentration was threefold higher than age-matched controls and higher than age-matched MPS IVA patients. The urine KS was over 3.5-fold higher than age-matched controls and lower than the age-matched MPS IVA patients. Gene mutation study showed the patient was homozygous for M41L. M14L mutation was found previously in one patient originated from Acadian with a homozygous form (performed at Dr. Tomatsu Shunji's Laboratory). Given all data from specimens, the patient has MPS IVA with substantial excessive excretion of KS in the urine and the blood (Courtesy of Dr. Susonne Ursin)

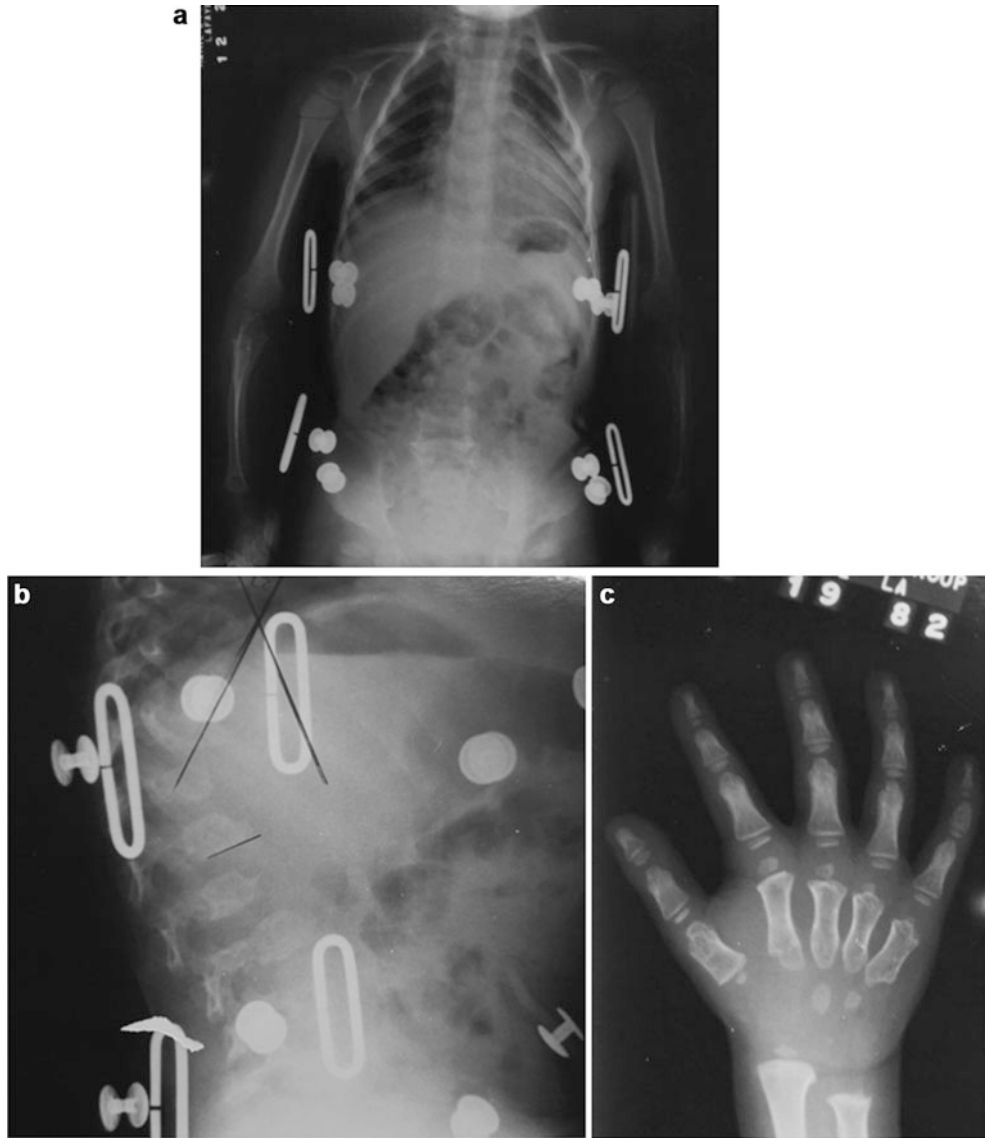

Fig. 5 (**a**–**c**) AP (**a**) and lateral view (**b**) of the spine showed platyspondyly of thoracolumbar vertebrae, anterior beaking of vertebral bodies, and lumbar gibbus. Radiographic studies showed dysostosis multiplex with proximal conical metacarpals and deficiency of carpal ossification centers (**c**) (Courtesy of Dr. Susonne Ursin)

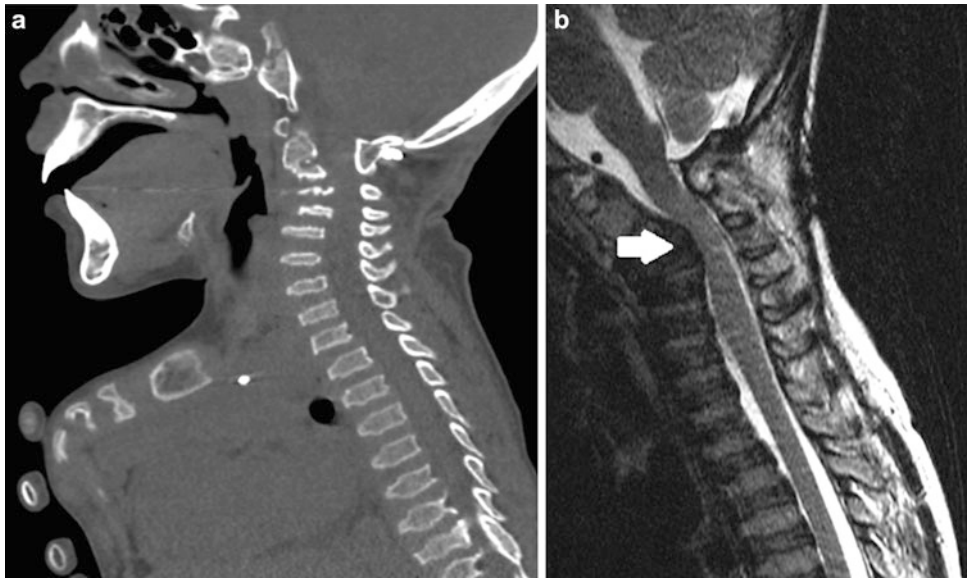

Fig. 6 (**a, b**) A 9 year old male with a history of mucopolysaccharidosis IV (Morquio syndrome), cervical spine instability, restrictive lung disease, hearing loss, and arrythmia. Multiple imaging studies demonstrated generalized osteopenia and Morquio syndrome related bony deformities (not shown). Sagital cervical CT (**a**) image showed skeletal dysplasia with flattened irregular vertebral bodies with posterior offset of the C3 and C4 vertebral bodies, resulting in a stenosis of spinal canal. Anterior beak deformity was present at multiple levels of the spine. There was a chest deformity (pectus carinatum). Sagital cervical MRI (**b**) showed significant spinal canal stenosis again with mild to moderate compression of the cord (*arrow*). (Courtesy of Dr. Grace Guo)

Mucopolysaccharidosis 6

Contents

Mucopolysaccharidosis (MPS) VI was first recognized by Maroteaux and coworkers in 1963 as a Hurler-like syndrome but with preservation of intelligence and excretion of dermatan sulfate unaccompanied by heparan sulfate. Milder forms of MPS VI have been recognized since the initial description of the disorder. The estimated birth incidence of MPS VI ranges from 1 in 100,000 to 1 in 1,300,000 in various populations (Harmatz et al. 2004).

Synonyms and Related Disorders

Arylsulfatase B (ASB) deficiency; Maroteaux-Lamy syndrome; *N*-acetylgalactosamine-4-sulfatase

Genetics/Basic Defects

1. Genetic inheritance: autosomal recessive
2. Cause
    1. Caused by deficiency of *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B) (Matalon et al. 1974) which:
        1. Is deficient in both mild and severe forms
        2. Is involved in the degradation of dermatan sulfate and chondroitin 4-sulfate
        3. Causes intralysosomal storage and urinary excretion of the glycosaminoglycan, dermatan sulfate
        4. The gene encoding *N*-acetylgalactosamine-4-sulfatase (ASB) mapped to chromosome 5q13-q14 (Litjens et al. 1989)
    2. Mutations: The vast majority of MPS VI mutant alleles are either unique to a patient or are present in a small number of patients (Litjens and Hopwood 2001).
        1. Null mutations
            1. Frameshift mutations
            2. Nonsense mutations
        2. Missense mutation giving rise to:
            1. Severe disease
            2. Intermediate disease
            3. Mild disease
    3. Genotype/phenotype correlation for missense mutations in MPS VI: not reliable enough for prognosis or counseling.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_165

Clinical Features

1. Variable clinical phenotypes (mild to severe) causing considerable difficulty in recognition and diagnosis of the syndrome
2. The severe form
    1. Somatic involvement similar to that in Hurler syndrome.
    2. Growth.
        1. Normal growth for the first few years of life
        2. Growth retardation (short stature) first noted at the age of 2–3 years
        3. Ultimate height of 110–140 cm in severely affected patients
    3. Other skeletal involvements.
        1. An enlarged head at birth
        2. Deformed chest at birth
        3. Joint stiffness (knee, hip, and elbow) developing in the first years of life
        4. Progressively restricted articular movements
        5. Crouching stance
        6. Shortened limbs
        7. Claw-hand deformities secondary to flexion contractures of the fingers
        8. Carpal tunnel syndrome contributing to the hand abnormality
        9. Shortened trunk
        10. Anterior sternal protrusion
        11. Lumbar gibbus
        12. Prominent lumbar lordosis/kyphosis
        13. Genu valgum
    4. Mental development usually normal.
    5. The facies.
        1. Mild coarseness of facies in some patients
        2. Coarse facies characteristic of Hurler syndrome in other patients
    6. Ocular findings.
        1. Corneal opacities (clouding) developing early, resulting in significant visual impairment
        2. Glaucoma (Cantor et al. 1989)
        3. Pigmented retinopathy
    7. Dentigerous cysts.
    8. Ear/labyrinth disorders: most commonly hearing impairment and otitis media.
    9. Upper airway obstruction.
    10. Cardiovascular involvement.
        1. Thickened atrioventricular valves of the heart (Tan et al. 1992)
        2. Endomyocardial fibroelastosis (Miller and Partridge 1983)
        3. Infantile/dilated cardiomyopathy (Hayflick et al. 1992)
    11. Associated neurologic complications.
        1. Not typically associated with progressive impairment of mental status (Vestermark et al. 1987), although physical limitations may impact learning and development
        2. Hydrocephalus (Goldberg et al. 1970)
        3. Spinal cord compression (Young et al. 1980; Wald and Schmidek 1984)
            1. Cervical cord compression (cervical myelopathy) is a common manifestation of MPS VI and can affect all patients at an early age, irrespective of phenotype (Solanki et al. 2016)
            2. Atlantoaxial subluxation associated with craniovertebral canal stenosis (Thorne et al. 2001)
            3. Hypertrophy of the posterior longitudinal ligament
            4. Dural thickening secondary to the deposition of glycosaminoglycans
        4. Spastic paraplegia resulting from compressive myelopathy
        5. Arachnoid cysts
        6. Pachymeningitis
        7. Nerve entrapment syndromes, particularly of the carpal tunnel
        8. Occasional hearing loss due to recurrent otitis media
    12. Abdomen and visceral involvement.
        1. Hepatomegaly always present after the age of 6 years
        2. Splenomegaly in 50% of patients
        3. Prominent abdomen
        4. Inguinal/umbilical hernias common
    13. Skin.
        1. Tightness
        2. Hirsutism

14. Most reported patients with the severe form died from heart failure in the second to third decades.

3. The mild (Di Ferrante et al. 1974; Paterson et al. 1982) to intermediate form (MPS VIB)
   1. Clinical recognition often delayed till 5 years of age
   2. Mildly affected
   3. Minimal dysostosis multiplex
   4. Aortic and mitral valvular dysfunction
      1. Primarily due to calcified thickened and stenotic valves
      2. The most prominent cardiac involvement in the milder phenotypes
   5. Spinal cord compression from thickening of the dura in the upper cervical spinal canal with resultant myelopathy: a frequent occurrence in patients with the milder forms
   6. Compression myelopathy associated with a kyphoscoliotic deformity of thoracolumbar spine

Diagnostic Investigations

1. Increased urinary excretion of glycosaminoglycans (Valayannopoulos et al. 2010).
   1. Dermatan sulfate accumulation
   2. The absence of chondroitin 4-sulfate, heparan sulfate, keratan sulfate, or hyaluronate using thin layer chromatography (TLC) or high-resolution electrophoresis fractionation
2. Biochemical diagnosis (Valayannopoulos et al. 2010; Harmatz and McGovern 2014).
   1. Demonstration of deficient *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B) in cultured skin fibroblasts or leukocytes (generally less than 10% of the lower limit of normal ASB activity)
   2. Identification of normal enzyme activity of a different sulfatase to exclude the diagnosis of multiple sulfatase deficiency
3. Demonstration by an accredited laboratory of intermediate levels of leukocyte ASB enzyme activity in both parents to support diagnosis of carriers
4. Dried blood spot sampled via heel stick of the newborn (Civallero et al. 2006)
5. Slit-lamp examination for corneal opacities
6. Radiographic features
   1. Skeletal changes similar to radiographic findings of Hurler syndrome in the severe form
   2. Striking examples of dysostosis multiplex, particularly severe pelvic changes
      1. Acetabular hypoplasia
      2. Small flared iliac wings
   3. Macrocephaly with a large sella
   4. Vertebrae
      1. Ovoid deformity of vertebral bodies
      2. A hood-shaped deformity or blunt anterior hypoplasia of vertebral bodies of L1 or L2
      3. Epiphyseal dysplasia of the proximal femur
      4. An elongated femoral neck in a valgus position
      5. Irregular diaphyseal distension of tubular bones
      6. Vertebral subluxation, especially atlantoaxial joint
7. Routine MRI assessments from the time of MPS VI diagnosis are critical for the prevention of irreversible spinal cord damage (Solanki et al. 2016).
8. Confirmation by mutational analysis of the *ARSB* gene (Karageorgos et al. 2007) should be considered if the diagnosis is in question and is important in carrier testing or prenatal diagnosis.
   1. Sequence analysis
   2. Duplication/deletion analysis

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis (Valayannopoulos et al. 2010)

1. Demonstration of deficient *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B) on viable fetal cells from chorionic villi or cultured amniotic-fluid cells from the pregnancy at risk (Kleijer et al. 1976; Van Dyke et al. 1981)
2. Mutation analysis of amniocytes and CVS in characterized families

3. Management (Giugliani et al. 2007)
    1. Supportive care.
        1. Optimizing general health with nutrition counseling
        2. Occupational and physical therapy
        3. Management of individual symptom complications
            1. Respiratory insufficiency requiring oxygen and/or positive airway pressure during sleep, tonsillectomy, adenoidectomy, or tracheostomy
            2. Cardiac failure requiring medications
    2. Keratoplasty for progressive opacification of the cornea and corneal transplantation (Varssano et al. 1997).
    3. Surgery to improve common nerve entrapment syndromes, particularly of the carpal tunnel.
    4. Successful single and double (aortic and mitral) valve replacements have been reported in MPS.
    5. Successful cardiac valve operations in patients with MPS VI are feasible, although extracardiac disease may have an impact on hospital morbidity. Even if mitroaortic involvement is common, we advise avoiding prophylactic replacement of mildly affected valves because the opportunity exists for enzyme replacement therapy to significantly delay the progression of cardiac valve disease (Torre et al. 2016).
    6. Substantial improvement following laminectomy and excision of the markedly thickened dura in myelopathy due to spinal canal stenosis.
    7. Bone marrow transplantation (Krivit et al. 1984; Herskhovitz et al. 1999) or hematopoietic stem cell transplantation in patients with the severe form of MPS VI.
        1. Efficacy
            1. Arylsulfatase B activity increased to normal levels in peripheral lymphocytes and granulocytes
            2. Decreased urinary excretion of acid mucopolysaccharide
            3. Decreased inclusions in the liver
            4. Improved cardiopulmonary function
            5. Improved visual acuity and joint mobility
            6. May provide better life quality (improved motor function, exertional dyspnea, severe snoring, and vertigo) (Wang et al. 2008)
        2. Not universally performed due to lack of a suitable donor and is associated with significant morbidity and mortality
    8. Allogeneic CD34-selected peripheral stem cell transplant with rapid hemopoietic and biochemical reconstitution (Alvaro et al. 1998).
    9. Successful umbilical cord blood transplantation (Lee et al. 2000).
    10. Enzyme replacement therapy (ERT).
        1. Clinical trials of enzyme replacement therapy with recombinant human *N*-acetylgalactosamine-4-sulfatase (rhASB) (Harmatz et al. 2006; 2004).
            1. Well tolerated
            2. Reduces lysosomal storage as evidenced by a dose-dependent reduction in urinary glycosaminoglycan
            3. An increase in distance walked
            4. Stair-climbing ability
            5. Shoulder range of motion
            6. Decrease in pain and arthritis
        2. The largest gains occurred in patients with advanced disease receiving high-dose rhASB.
        3. Before enzyme replacement therapy (ERT) with galsulfase (Naglazyme®), clinical management was limited to supportive care and hematopoietic stem cell transplantation. Galsulfase is now widely available and is a specific

therapy providing improved endurance with an acceptable safety profile (Valayannopoulos et al. 2010; Harmatz et al. 2014). Therapeutic response may be influenced by disease stage, and early intervention may lead to better outcomes (El Dib and Pastores 2009).

4. Long-term galsulfase ERT was beneficial and safe for Taiwanese patients with MPS VI. This treatment reduced urinary GAG and had positive effects on a wide range of clinical functional assessments including endurance, mobility, joint function, pulmonary function, liver and spleen size, cardiac hypertrophy, and diastolic dysfunction (Lin et al. 2016).

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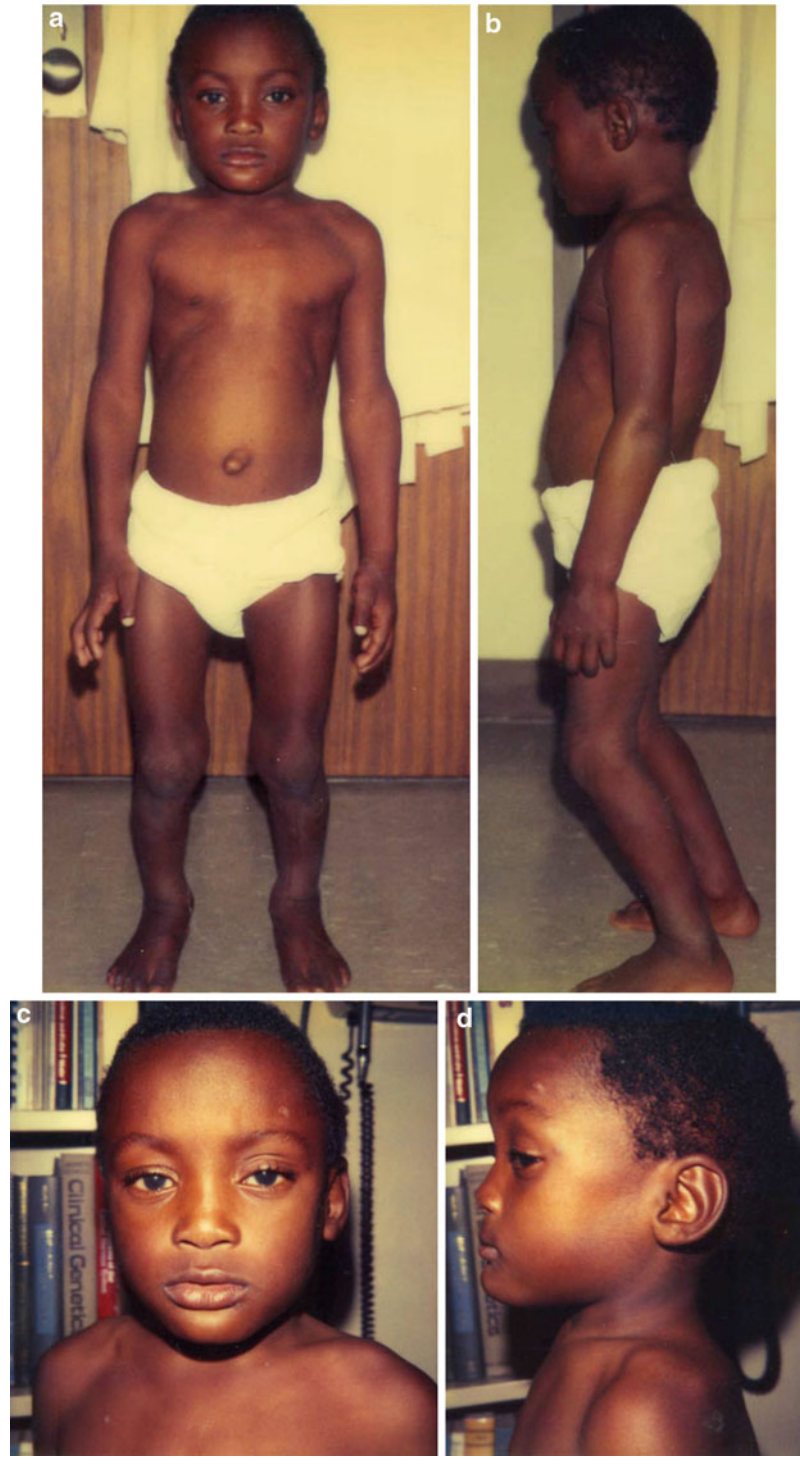

Fig. 1 (**a**–**d**) A boy with MPS VI showing dwarfism, short trunk with protruding sternum, and crouching stance

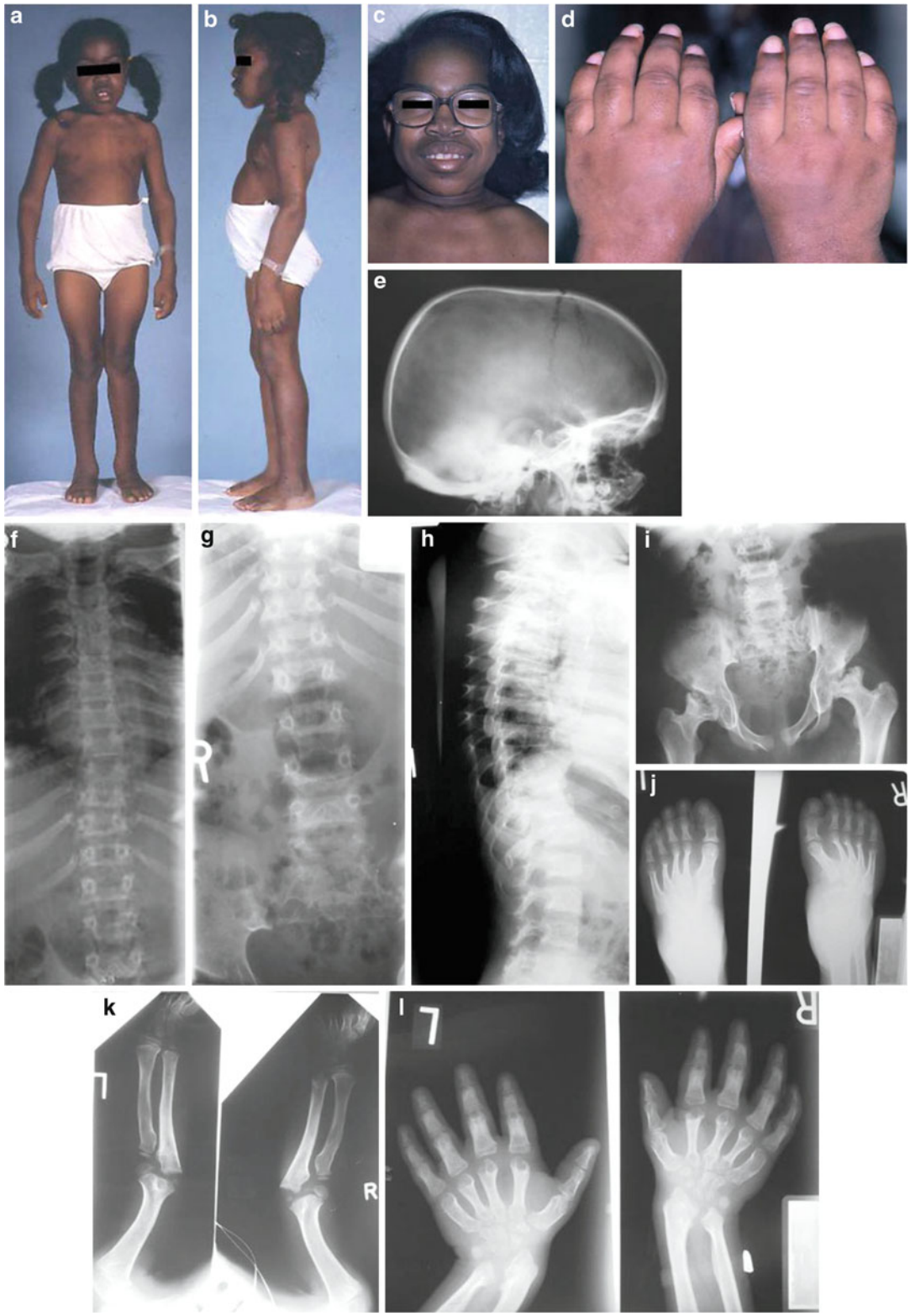

Fig. 2 (**a**–**l**) A girl with MPS VI showing dwarfism, short trunk with sternal protrusion, and claw hands (**a**–**d**). The patient's radiographs demonstrate dysostosis multiplex (**e**–**l**)

Mucopolysaccharidosis I (MPS I)

Contents

Mucopolysaccharidosis I consists of three clinical entities with varying degrees of clinical manifestations, all due to the same lysosomal enzyme deficiency, α-L-iduronidase. Hurler (MPS I-H) and Scheie (MPS I-S) syndromes represent phenotypes at the two ends of the clinical spectrum; the Hurler–Scheie syndrome (MPS I-H/S) represents a phenotype of intermediate clinical severity. In most instances, the subtype of MPS I can only be assigned on the basis of clinical criteria, including the rate of progression of symptoms. The incidences for MPS I-H, MPS I-H/S, and MPS I-S are estimated to be 1/76,000–1/144,000, 1/280,000, and 1/840,000–1/1,300,000 live births, respectively.

Synonyms and Related Disorders

α-L-Iduronidase deficiency; Hurler (MPS I-H); Hurler–Scheie (MPS I-H/S); Scheie (MPS I-S) syndromes

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. The *IDUA* gene (Scott et al. 1990)
   1. Localized to chromosome 4p16.3, close to the Huntington disease gene
   2. Spans 19 kb including 14 exons
3. Caused by mutations in the α-L-iduronidase (*IDUA*) gene (Scott et al. 1992, 1993, 1995; Lee-Chen et al. 1999)
   1. Two major alleles (W402X and Q70X) (Bunge et al. 1994; Beesley et al. 2001) and a minor allele (P533R) accounting for over half the MPS I alleles in the Caucasian population.
   2. No functional enzymes produced by above-mentioned alleles, giving rise to the severe form of α-L-iduronidase deficiency (MPS I-H).
   3. Limited mutations expected to cause the attenuated clinical phenotypes of MPS I-S or MPS I-H/S.
   4. One of the mutations resulting in Scheie syndrome is a base substitution in intron 7 that creates a new splice site and produces a frameshift. Since the old splice site is not obliterated, some normal enzymes still can be made to overcome the worst features of MPS I.
   5. Most other alleles that lead to MPS I-S or MPS I-H/S carry missense mutations (Lee-Chen and Wang 1997).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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6. In the Japanese population studied, MPS I-H/S results from compound heterozygosity of two mutations (704ins5 and R89Q), which, in homozygous form, would give rise to MPS I-H and MPS I-S, respectively (Yamagishi et al. 1996).

4. Genotype–phenotype correlations
   1. General principle (McKusick et al. 1972; Mueller et al. 1984)
      1. Any combination of two severe alleles leads to severe MPS I. A severe allele is one that produces the severe phenotype in either the homozygous state or compound heterozygous state.
      2. Intermediate and mild MPS I: usually associated with one severe allele and another allele that permits production of some residual enzyme activity.
   2. Alleles associated with severe phenotype
      1. Two common severe mutations (W402X and Q70X) always confer a severe phenotype whether present in a homozygous state or in a compound heterozygous state.
      2. Additional mutations (474-2a-g, A327P, P533R, A75T, L218P).
   3. Alleles associated with mild phenotype
      1. 678-7a-g
      2. R89Q
5. Pathophysiology
   1. Underlying molecular defect leads to a loss or marked reduction in α-L-iduronidase (*IDUA*), a lysosomal enzyme involved in the degradation of glycosaminoglycans heparan sulfate and dermatan sulfate.
   2. Because of the enzyme deficiency, excessive accumulation of acid mucopolysaccharides (glycosaminoglycans) in the tissue occurs, leading to a wide effect on various systems and remarkable changes in the morphogenesis.

Clinical Features

1. Hurler syndrome (MPS I-H)
   1. General clinical characteristics
      1. The prototype of MPS representing the severe end of clinical spectrum
      2. A progressive disorder with multiple organ and tissue involvement, leading to death in childhood
      3. Normal phenotype at birth and in early infancy but deteriorates progressively afterward
      4. Diagnosis usually made between 4 and 18 months of age
      5. Short stature (linear growth stops at 2–3 years of age)
      6. Developmental delay by age 12–24 months, with a maximum functional age at the level of 2–4 years, followed by progressive mental deterioration
   2. Coarse facial features (one of the earliest signs)
      1. Ocular hypertelorism
      2. Prominent eyes
      3. Bushy eyebrows
      4. Depressed nasal bridge
      5. Wide nostrils
      6. Large and thickened lips
      7. Large tongue
      8. Hypertrophy of the gum and the bony alveolar ridge
   3. Other craniofacial features
      1. A large scaphocephalic head with frontal bossing.
      2. Communicating hydrocephalus common after age 2–3 years. Shunting procedures may be beneficial for relieving increased intracranial pressure for some children.
      3. Noisy breathing with persistent nasal discharge (chronic rhinorrhea).
      4. Upper respiratory and ear infections.
   4. Ophthalmologic features
      1. Progressive clouding of the cornea (the hallmark of the syndrome) beginning at the first year of life, leading to impaired vision
      2. Open-angle glaucoma
      3. Retinal degeneration resulting in decreased peripheral vision
      4. Night blindness
   5. Auditory features
      1. Frequent sensorineural or mixed deafness

2. Contributing factors:
    1. Frequent middle ear infection from Eustachian tube dysfunction, caused by storage of glycosaminoglycans within the oropharynx
    2. Dysostosis of the ossicles of the middle ear
    3. Scarring of the tympanic membrane
    4. Damage to the eighth nerve
6. Cardiovascular features
    1. Cardiac valvular disease resulting from storage of mucopolysaccharide in the mitral, aortic, tricuspid, or pulmonary valves, leading to congestive heart failure.
    2. Thickened coronary artery valves, leading to angina pectoris and myocardial infarction.
    3. Possible fatal cardiomyopathy as a presenting feature for some MPS I infants less than 1 year old. Endocardial fibroelastosis has been noted postmortem in these patients.
    4. Aortic stenosis and uncontrolled hypertension (Taylor et al. 1991; Eakins and Kan 2010): although uncommon, aortic stenosis should be included in the differential diagnoses in children with Hurler syndrome and poorly controlled hypertension.
7. Gastrointestinal features
    1. Protuberant abdomen
    2. Progressive hepatosplenomegaly
8. Skeletal abnormalities: dysostosis multiplex
    1. Short neck
    2. Characteristic kyphoscoliosis when attempting to sit
    3. Ultimate frank gibbus deformity
    4. Stiff joints with limited mobility
    5. Claw hands (flexed stubby fingers and broad hands)
9. Connective tissue abnormalities
    1. Inguinal and umbilical hernias: common findings and usually present at birth
    2. Thick skin
10. Prognosis
    1. Bedridden before the end of the juvenile period
    2. Early demise prior to 10 years of age
    3. Usual causes of death
        1. Obstructive airway disease (Shapiro et al. 1985)
        2. Respiratory infection
        3. Cardiac complications

2. Scheie syndrome (MPS I-S)
    1. The mildest form of MPS I
    2. Normal stature
    3. Normal intelligence
    4. Onset of significant signs usually after 5 years
    5. Diagnosis commonly made between 10 and 20 years of age
    6. Coarse facial features
    7. Deafness in some patients
    8. Joint stiffness
        1. Claw hands
        2. Stiff painful foot
    9. Carpal tunnel syndrome
    10. Pes cavus
    11. Genu valgum
    12. Ocular manifestations
        1. Corneal clouding
        2. Glaucoma
        3. Retinal degeneration
    13. Aortic valvular disease (stenosis and regurgitation due to mucopolysaccharide deposits in the valves and chordae tendineae)
    14. Obstructive airway disease with sleep apnea in some patients
    15. Mild hepatosplenomegaly
    16. Mild dysostosis multiplex
    17. Less common pachymeningitis cervicalis (compression of the cervical cord by thickened dura) than MPS I-H/S
    18. Potential normal life span
3. Hurler–Scheie compound (MPS I-H/S)
    1. Clinical phenotype intermediate between Hurler and Scheie syndromes (Kajii et al. 1974; Kaibara et al. 1979)
    2. Progressive somatic involvement, including dysostosis multiplex, with little or no intellectual dysfunction

3. Age of onset: usually between 3 and 8 years
4. Survival to adulthood: common
5. Deafness
6. Craniofacial features
    1. Coarse facial features: less obvious
    2. Micrognathia in some patients
    3. Broad mouth
    4. Square jaw
    5. Short neck
7. Ophthalmologic features
    1. Corneal clouding in all patients
    2. Glaucoma
    3. Retinal degeneration
    4. Optic atrophy
8. Valvular heart disease (mitral valve insufficiency) developing by the early to mid-teens
9. Skeletal features
    1. Short stature
    2. Small thorax
    3. Severe joint involvement (stiffness)
    4. Kyphoscoliosis
    5. Back pain
    6. Characteristic claw hand deformity
    7. Carpal tunnel syndrome
10. Gastrointestinal features
    1. Varying degrees of hepatomegaly
    2. Hernias
11. Pachymeningitis cervicalis (compression of the cervical cord due to mucopolysaccharide accumulation in the dura)
12. Communicating hydrocephalus uncommon in patients who have normal intelligence
13. Spondylolisthesis of the lower spine, leading to spinal cord compression
14. Causes of death (age around teens and 20s)
    1. Upper airway obstruction
    2. Cardiac involvement

Diagnostic Investigations

1. Developmental assessment
2. Ophthalmologic examination
3. ECG and echocardiography for cardiovascular status (Nelson et al. 1990)
4. Cranial ultrasound for hydrocephalus
5. Skeletal survey
    1. Dysostosis multiplex
    2. Skull
        1. Large, thickened calvarium
        2. Premature closure of lambdoidal and sagittal sutures
        3. Shallow orbits
        4. Enlarged J-shaped sella
        5. Abnormally spaced teeth with dentigerous cysts
    3. Ribs
        1. Oar shaped and narrowed at the vertebral ends
        2. Flat/broad at the sternal ends
    4. Vertebra
        1. Beaked anteriorly (anterior hypoplasia) of lumbar vertebrae with kyphosis (an early sign)
        2. Scalloped posteriorly
        3. Thoracolumbar gibbus, resulting from anterior wedging of the vertebrae
        4. Hypoplasia of the odontoid, leading to atlantoaxial subluxation
    5. Pelvis
        1. Poorly formed pelvis
        2. Small femoral heads
        3. Coxa valga
    6. Long bones
        1. Widened diaphysis of the long bones
        2. Lack of normal modeling and tabulation
        3. Irregular metaphysis
        4. Poorly developed epiphyseal centers
        5. Distal ends of the radius and ulna angulate toward each other
        6. Claw hands
        7. Thickened and bullet-shaped phalanges
        8. Coarsening of the trabeculae of the phalanges and metacarpals
        9. Proximal narrowing of the metacarpals
        10. Marked irregularity and retarded ossification of the carpal bones
    7. Other bones
        1. Short, thickened, and irregular clavicles
        2. Shortened and trapezoid-shaped phalanges with widened diaphyses

6. Biochemical/molecular studies for MPS I-H, MPS I-HS, and MPS I-S
    1. Excessive urinary excretion of glycosaminoglycans (dermatan and heparan sulfates): a useful preliminary test
    2. Metachromatic staining of fibroblasts and leukocyte inclusions (nonspecific lab findings)
    3. Enzyme assay: deficient α-L-iduronidase in WBC, serum, cultured fibroblast, and CSF
    4. Accumulation of glycosaminoglycans in cultured fibroblasts correctable by uptake of α-L-iduronidase
    5. Mutation analysis or sequence analysis of *IUDA* gene: possible to identify both *IDUA* mutations in 95% of patients with MPS I
    6. Characterization of gene mutation: worthwhile for phenotype prediction and genetic counseling
7. Carrier testing
    1. Measurement of α-L-iduronidase enzyme activity: not a reliable method, requiring testing of obligatory carriers within the family first to determine if their levels of IDUA enzyme activity can be distinguishable from the normal
    2. Molecular genetic testing of *IUDA* to identify carriers among at-risk family members when both mutation alleles have been identified in an affected family member

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25% chance of being affected
    2. Patient's offspring:
        1. MPS I-S: not increased unless the spouse is a carrier
        2. MPS I-H and MPS I-H/S: not surviving to reproductive age
2. Prenatal diagnosis from samples of CVS, amniocentesis, and fetal blood (Fratantoni et al. 1969; Ikeno et al. 1981; Muenzer 1986; Young 1992; Fensom and Benson 1994)
    1. Enzyme assays (deficient α-L-iduronidase) and increased level of ^{35}S-sulfate incorporation measured in cultured cells obtained from amniocentesis or CVS for pregnancy at risk
    2. Mutation analysis of the *IDUA* gene in fetal DNA extracted from cells obtained by CVS or amniocentesis if both mutant *IDUA* alleles have been identified in a previously affected sib or in the parents of the at-risk fetus
3. Preimplantation genetic diagnosis (PGD) for at-risk pregnancies: requires prior identification of both *IDUA* disease-causing mutations in the family
4. Management (Clarke and Heppner 2011; Muenzer and Fisher 2004)
    1. Supportive care
        1. Early infant stimulation programs
        2. Eye care: corneal transplantation successful but donor grafts eventually becoming cloudy
        3. Range of motion exercises to preserve joint function
        4. Physical therapy
    2. Orthopedic surgery (Peters et al. 1998; Van Heest et al. 1998)
        1. Surgical decompression of the median nerve for carpal tunnel syndrome resulting in various restorations of motor hand activity
        2. Trigger digits
        3. Genu valgum
        4. Kyphoscoliosis
        5. Acetabular dysplasia
        6. Atlantooccipital stabilization
    3. Ventriculoperitoneal shunting for hydrocephalus
        1. Generally palliative
        2. May improve quality of life
    4. Tracheotomy or high-pressure continuous positive airway pressure with supplemental oxygen
    5. Tonsillectomy and adenoidectomy to correct Eustachian tube dysfunction and to decrease upper airway obstruction
    6. Cardiovascular care
        1. Bacterial endocarditis prophylaxis

2. Valve replacement surgery
3. Management of severe dilated cardiomyopathy: enzyme replacement therapy pre-transplant can improve cardiac function sufficiently to permit safe allogenic hematopoietic stem cell transplantation using myeloablative conditioning (Wiseman et al. 2013)
7. Surgical repair of inguinal hernias
8. Early surgical intervention to prevent severe complications from progressive compression of the spinal cord
9. Major anesthetic risks exhibited by patients with MPS I (Walker et al. 1994; Moores et al. 1996)
    1. Avoid hyperextension of the neck since dysostosis multiplex can lead to instability of the spine including the atlantoaxial joint.
    2. Difficulty in induction of anesthesia due to inability to maintain an adequate airway.
    3. Require fiberoptic laryngoscopy for intubation.
    4. Slow recovery from anesthesia.
    5. Common postoperative airway obstruction.
10. Allogenic bone marrow transplantation from an unaffected, HLA-compatible donor (Peters et al. 1996, 1998; Guffon et al. 1998)
    1. Beneficial effect: replacement of deficient macrophages by marrow-derived donor macrophages to provide ongoing source of normal enzyme capable of gaining access to the various sites of storage.
    2. Slows the course of cognitive decline if the therapy starts before the developmental delay is evident.
    3. Improves survival (Whitley et al. 1993), reducing facial coarseness, hepatosplenomegaly, hearing, and normal cardiac function.
    4. Skeletal manifestations (Vellodi et al. 1997) and corneal clouding continue to progress despite successful transplantation. Surgeries will be required for the persistent orthopedic problems.
    5. Significantly limited by the availability of donors. The immunosuppressive therapy for the prevention of rejection carries significant toxicity.
    6. The procedure of the transplantation carries a high risk of morbidity and mortality. Failure to achieve stable engraftment and development of graft-versus-host disease is a significant barrier to successful bone marrow transplantation for many children.
    7. Hematopoietic stem cell transplantation: the treatment of choice for a child with Hurler syndrome who is younger than 2 years of age and has minimal or no central nervous system disease (Muenzer 2004).
11. Cord blood transplantation (Staba et al. 2004)
    1. Use cord blood transplants from partially HLA-matched, unrelated donors.
    2. Donors readily available.
    3. An excellent source of stem cells for transplantation.
    4. Sustained engraftment can be achieved without total-body irradiation in young children.
    5. Low incidence for acute graft-versus-host disease (GVHD).
    6. Absence of extensive chronic GVHD.
    7. As effective as bone marrow transplantation.
    8. Unrelated umbilical cord blood transplantation was associated with improved somatic disease and neurodevelopment (Coletti et al. 2015).
12. Enzyme replacement therapy (ERT) (Kakkis et al. 2001; Kakkis 2002)
    1. An etiology-specific treatment that seeks to address the underlying

pathophysiology of MPS I by delivering sufficient IDUA activity to reverse and prevent glycosaminoglycan accumulation (Wraith et al. 2004)

2. Effectiveness depending on the ability of recombinant enzymes injected intravenously to enter cells and localize to the lysosome, the appropriate intracellular site
3. Use of recombinant human α-L-iduronidase (laronidase: Aldurazyme)
    1. Aldurazyme®: currently licensed in the USA, Europe, and Canada for use in treating non-CNS manifestations of MPS I. The current dose regime involves premedication with an anti-inflammatory and antihistamine drugs and intravenous weekly infusion of 100 U/kg of Aldurazyme® over 4 h (Clarke and Heppner 2011).
    2. Significant reduction in liver size.
    3. Increase in height and weight.
    4. Decrease in joint restriction.
    5. Improvement in breathing (respiratory function) and sleep apnea.
    6. Decreased glycosaminoglycan storage.
    7. Improvements in cardiopulmonary function, airway obstruction, and joint mobility in Hurler–Scheie syndrome (nonneuronopathic MPS I) (Bijarnia et al. 2009).
    8. Recommended for patients with milder or attenuated forms of MPS I. Infusions of recombinant enzyme are a safer alternative for treating the somatic disease and improving the quality of life of such patients. An intravenously administered enzyme is not expected to cross the blood–brain barrier and affect central nervous system disease (Muenzer 2004).
    9. Enzyme replacement therapy with laronidase can be used with pre- and peri-hematopoietic stem cell transplant, which is now the gold standard treatment in those patients diagnosed under 2.5 years of age (Jameson et al. 2013).
13. Hematopoietic stem cell transplantation (HSCT) (Bijarnia et al. 2009): treatment of choice for children <2 years of age with MPS I-H who have minimal or no central nervous disease
14. Combination of ERT followed by HSCT in neuronopathic Hurler syndrome
    1. Corrects the enzyme deficiency until endogenous enzyme production is established
    2. Reverses airway obstruction and cardiovascular complications, thus reducing mortality and morbidity at the time of transplant

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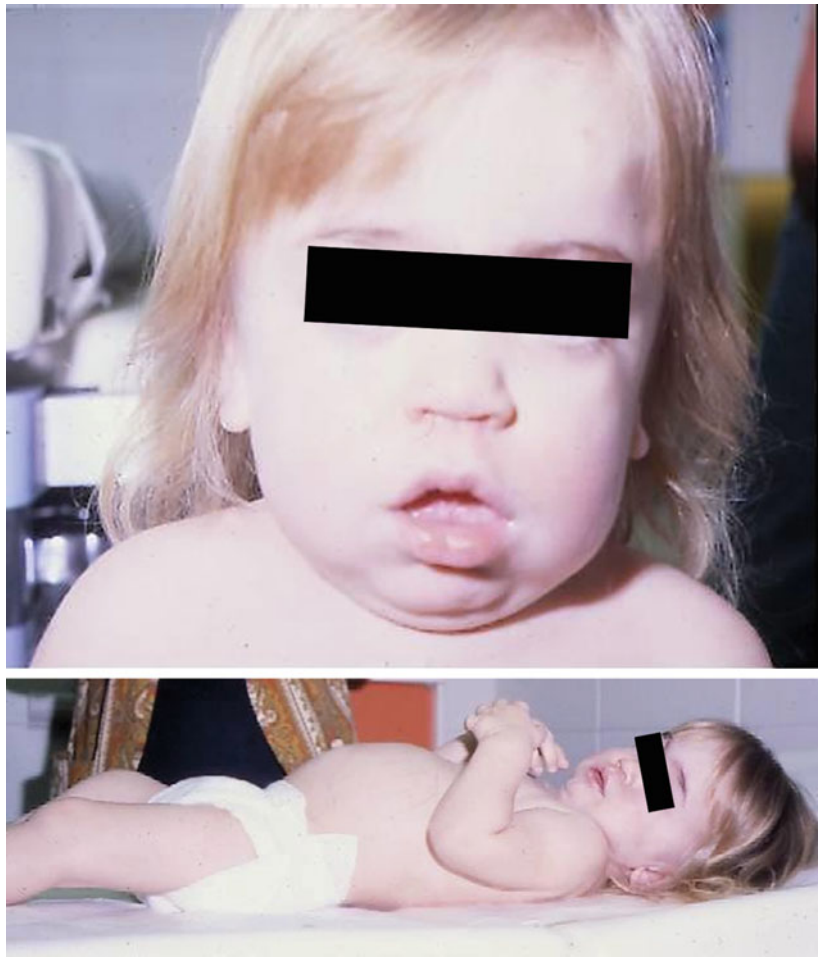

Fig. 1 (**a**, **b**) A child with Hurler syndrome showing a large head with frontal bossing, coarse facial features, ocular hypertelorism, cloudy (steamy) cornea, depressed nasal bridge, large tongue, short neck, protuberant abdomen, umbilical hernia, stiff joints, and claw hands

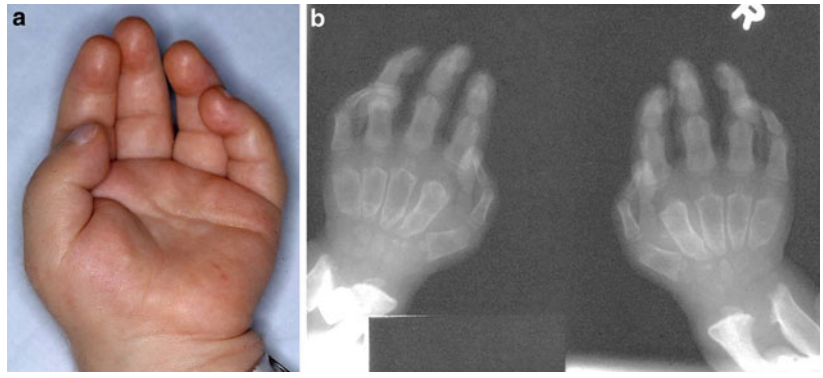

Fig. 2 (**a**, **b**) Claw hand. The radiographs show thick bullet-shaped phalanges, proximal narrowing of the metacarpals, poorly ossified carpal bones, and angulation toward each other of the distal ends of the radius and the ulnar

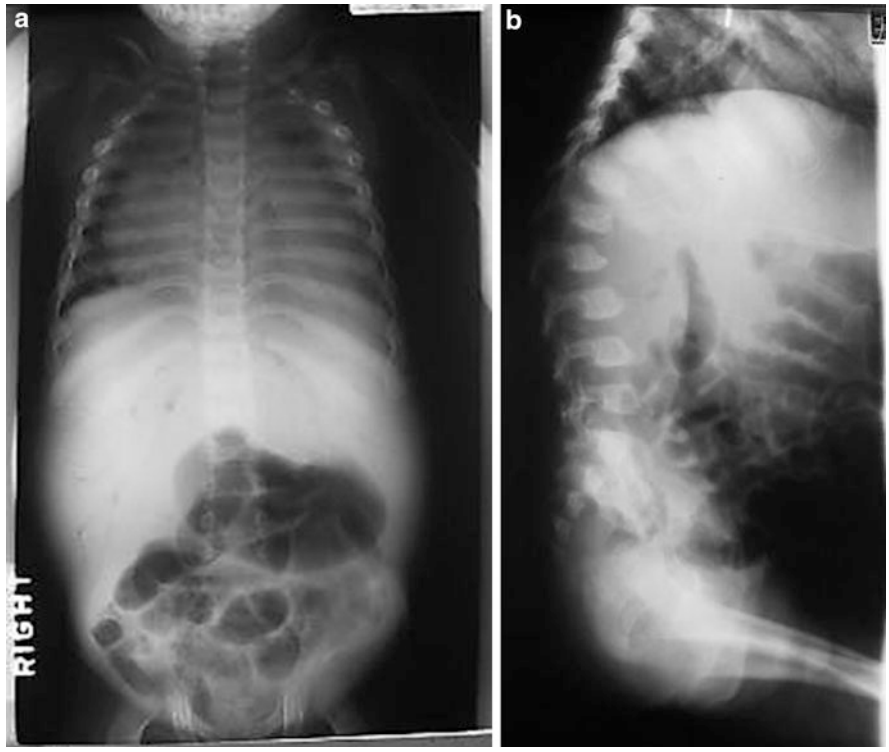

Fig. 3 (**a**, **b**) Radiographs showing oar-shaped ribs with relatively narrow proximal portion, narrow iliac bodies and flaring wings, shallow acetabula, coxa valga, anterior wedging of the lumbar vertebrae, decreased AP diameter of the vertebral bodies with posterior scalloping, and marked thoracolumbar gibbus

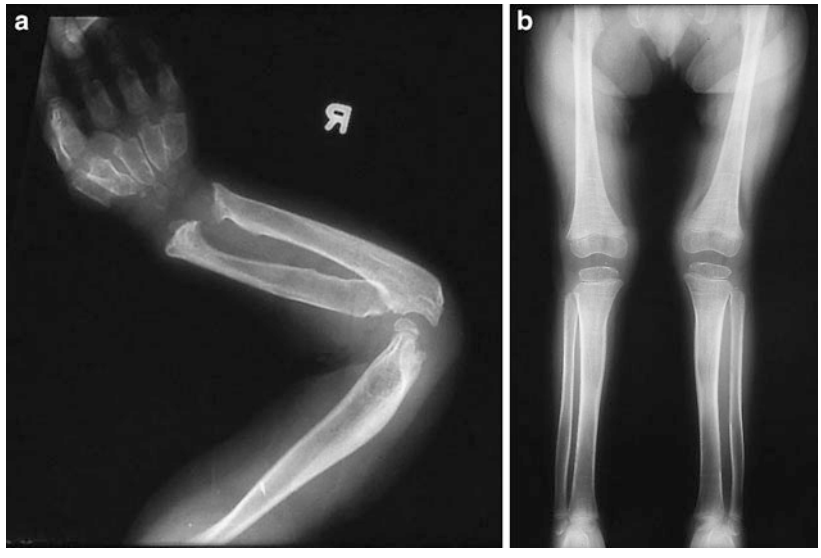

Fig. 4 (**a**, **b**) Radiograph of the upper extremities shows the lack of normal modeling and tabulation of the diaphyses, leading to short tubular bones. The radial and ulnar articular surfaces are angulated toward each other. Marked irregularity and retarded ossification of the carpal bones are noted. The findings in the lower extremities are less marked

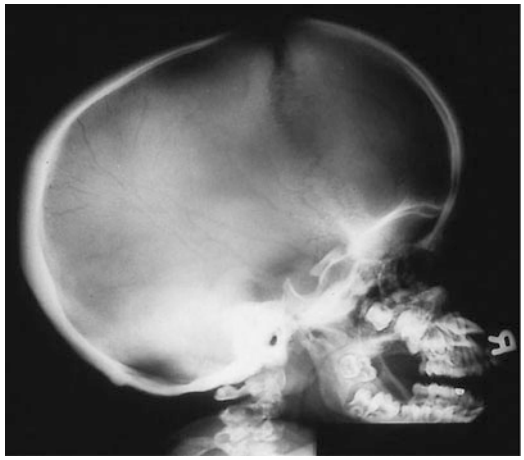

Fig. 5 Skull radiograph showing a large scaphocephalic calvarium with early appearance of the J-shaped sella turcica

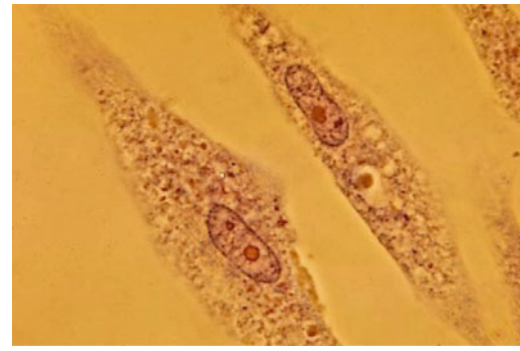

Fig. 7 Metachromasia of the cultured fibroblasts

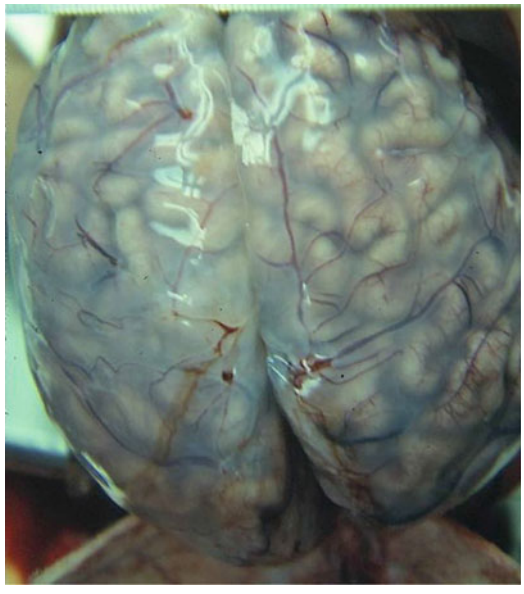

Fig. 6 Postmortem findings of the brain showing cloudy leptomeninges secondary to cloudy CSF

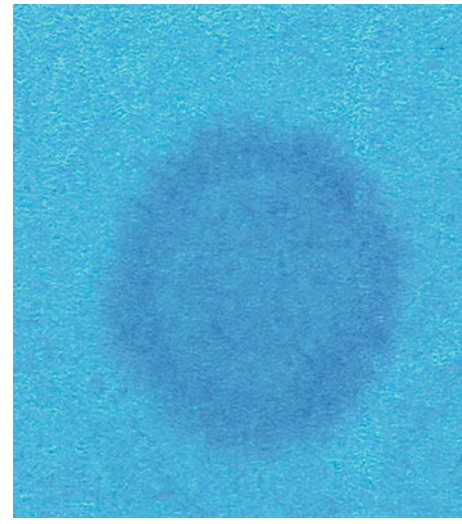

Fig. 8 Positive MPS spot test

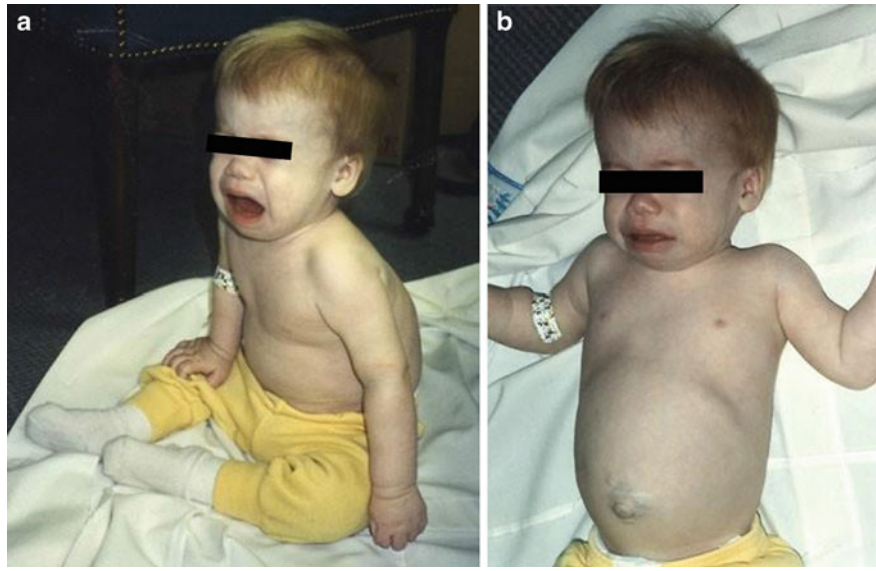

Fig. 9 (**a**, **b**) A 14-month-old boy with Hurler syndrome showing a large head, coarse facies, protuberant abdomen, umbilical hernia, a lumbar gibbus, and claw hands. The radiographs showed cardiomegaly, thickened ribs, and beaked vertebral body (L2). The α-L-iduronidase enzyme level was 0.0 (87.10–190.50 nmol/mg/h)

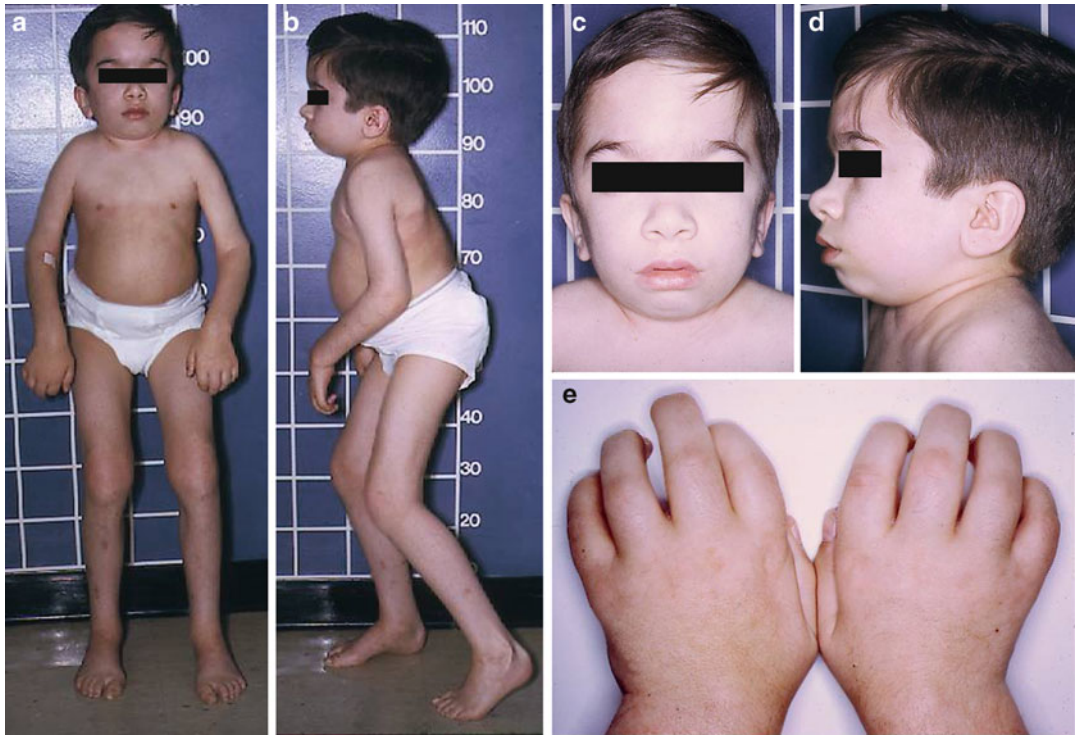

Fig. 10 A 14-year-old boy with Hurler–Scheie compound showing short stature, semi-crouching stance, joint stiffness (**a**, **b**), coarse facies (**c**, **d**), and claw hands (**e**). When he was 3½ years old, he started to complain difficulty in raising his arms above his head and difficulty in moving his hands and fingers because of bent fingers and joint contractures. He was noted to have dwarfism; coarse thickened skin; hirsutism; a big head with frontal bossing; coarse facies with hypertelorism; cloudy cornea; large lips and large tongue; short neck; short trunk with a mild kyphosis; hepatomegaly; claw hands; anteriorly converted shoulders; protuberant abdomen; flexion contractures of elbows, wrists, and knees; and crouching stance. The urine was positive for mucopolysaccharide, and the blood was positive for metachromasia. Skin fibroblasts were deficient in α-L-iduronidase

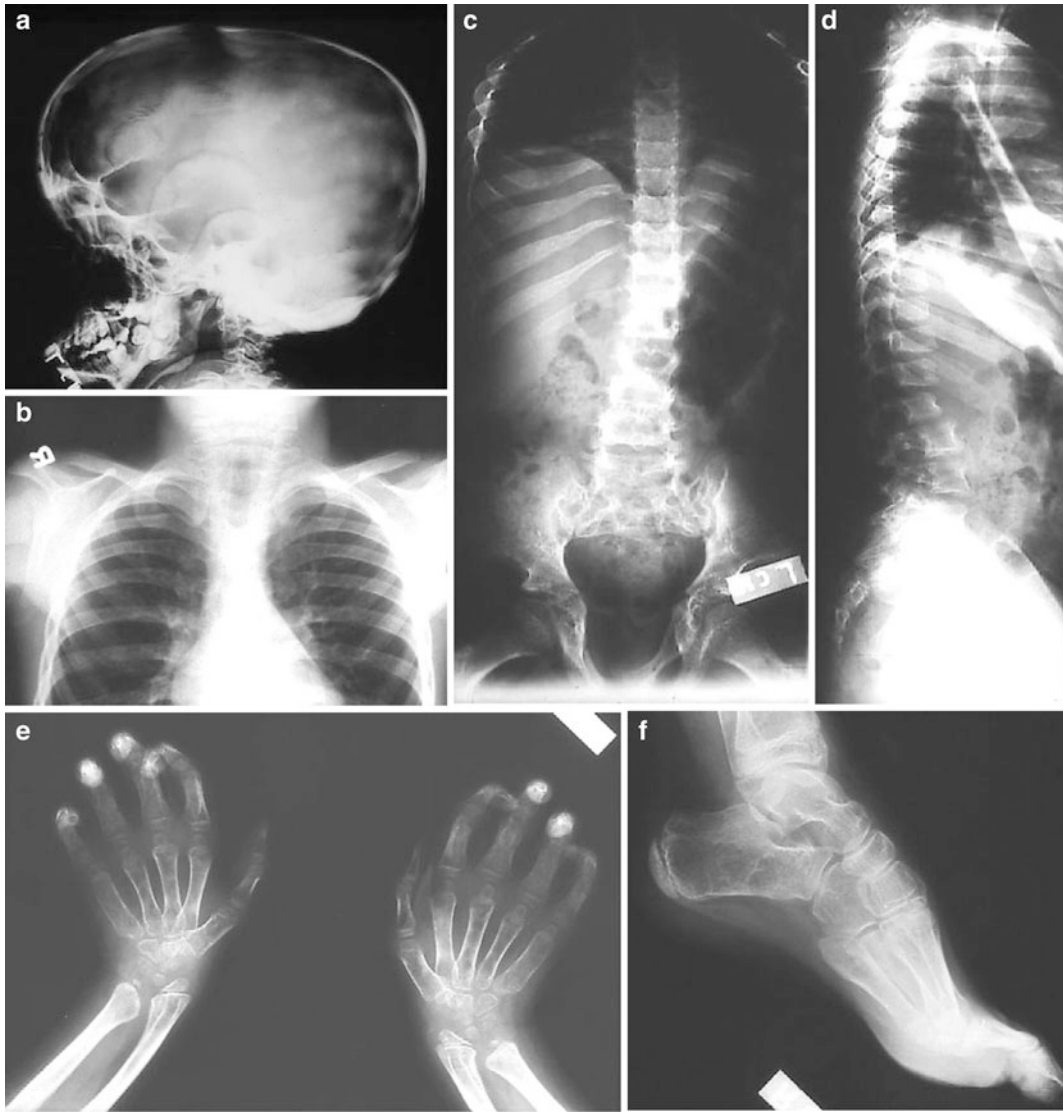

Fig. 11 Radiographs. The skull (**a**) shows macrocephaly, frontal bossing, small and airless mastoids, and anterior pocketing of the sella turcica ("shoe-shaped" or "J-shaped" sella). Clavicles (**b**) are short with widened medial aspects of both clavicles. Ribs are oar shaped and wide in their lateral and anterior portions with moderate narrowing of the paravertebral portions of the lower ribs (**c**, **d**). Vertebral bodies have concaved anterior and posterior margins and decreased in sagittal diameters. The second lumbar vertebra was hypoplastic with anterior inferior beaking forming almost a hook-shaped deformity. Claw hands were present with tapering of both distal ends of radius and ulna to form a "V shape" (**e**). Carpal bones were small, irregular, and crowded together. Metacarpals and phalanges were wide and short with proximal pointing of metacarpals. Bone age was retarded. Pes cavus was present (**f**)

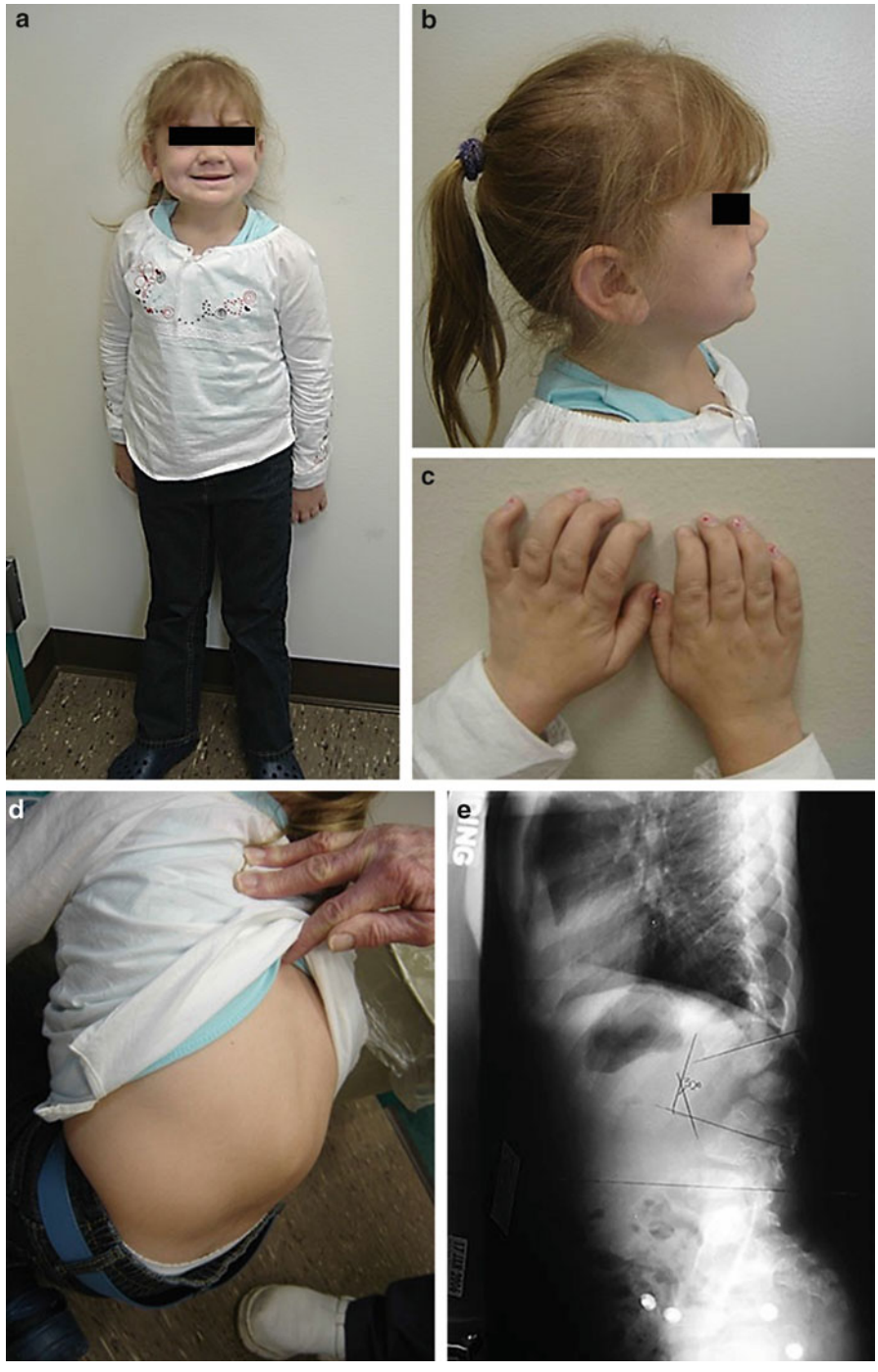

Fig. 12 (**a**–**e**) A 7-year-old girl was diagnosed to have Hurler syndrome at the age of 2. She received a male, 4/6 HLA-matched unrelated umbilical cord blood transplant. She engrafted quickly with an absolute neutrophil count greater than 500 on day +28. Her transplant complications included a *Klebsiella* UTI prior to admission, mucositis, medicine-induced hypertension controlled with nifedipine, diarrhea treated with Flagyl empirically, and graft-versus-host disease. Presently, she has less coarse facial features, resolving cloudy cornea, and improved cognitive capacity, but still has some claw hands and lumbar gibbus which are illustrated radiographically

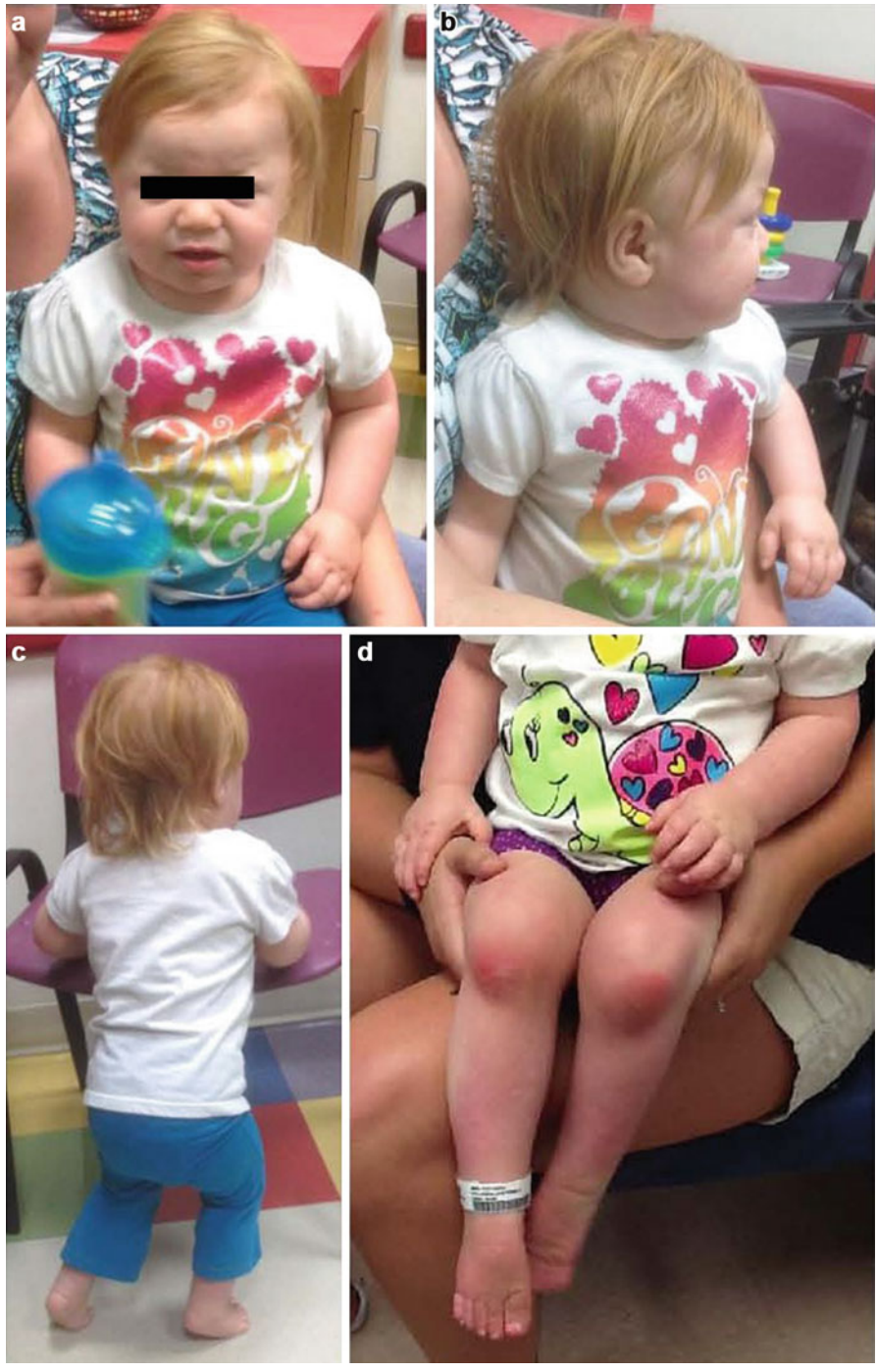

Fig. 13 (**a**–**d**) This is a 2 year-old girl evaluated originally for possible partial biotinidase deficiency from a newborn screening test. After a series of testings, she was found to be just a carrier for biotinidase deficiency (please see the chapter on "► Biotinidase Deficiency"). During the course of evaluation, she was noticed to have global delay, short stature, coarse facies, claw hands, and semi-crouching stance with knee crawling. The clinical and the following radiographic features (dysostosis multiplex) suggest Hurler syndrome. Urinary excretion of dermatan sulfate and heparin sulfate was elevated. Mucopolysaccharides were 171.9 which is markedly elevated (control:

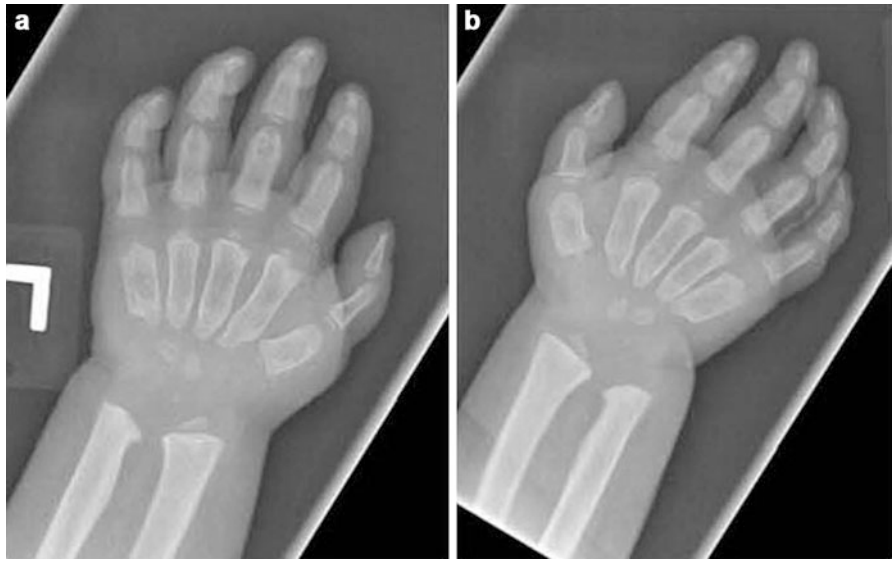

Fig. 14 (**a**, **b**) Radiographs of both hands showed claw hands, thickened bullet-shaped phalanges, proximal tapering of second to fifth metacarpals with widening of distal metacarpals, markedly retarded carpal bones, and slight tilting of distal radius and ulnar

Fig. 13 (continued) <24.0 mg/mmol). Lysosomal enzyme panel showed absent alpha-L-iduronidase activity which was consistent with the diagnosis of Hurler syndrome. IDUA gene sequencing showed homozygous in the IDUA gene for a sequence variant defined as c.1205G > A and predicted to result in premature termination p.Trp402Stop. This variant was documented as causative for MPS I. This result is consistent with diagnosis of MPS I. Interestingly, chromosome microarray analysis showed multiple regions of homozygosity >5 Mb including 4p16.3-p15.2 in which Hurler syndrome gene is located in 4p16.3

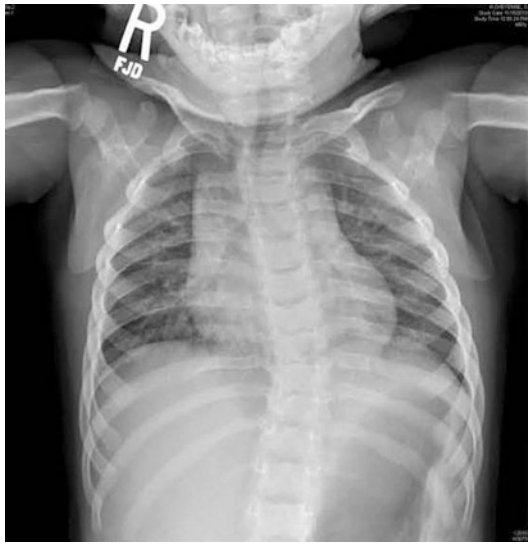

Fig. 15 AP view of the chest showed levoscoliotic curvature of lower thoracic spine, slight constriction of the posterior ribs at the costochondral joint junction (right, 9th to 11th; left, 11th), thickened scapula, and short and irregular clavicles

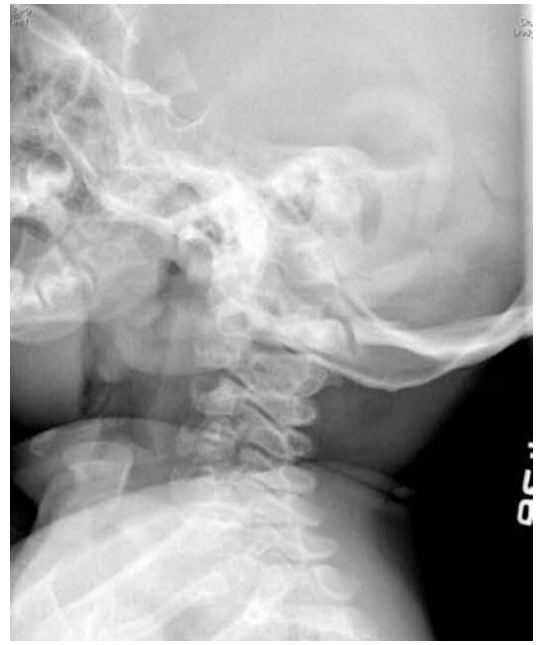

Fig. 17 Lateral view of the skull showed J-shaped sella turcica

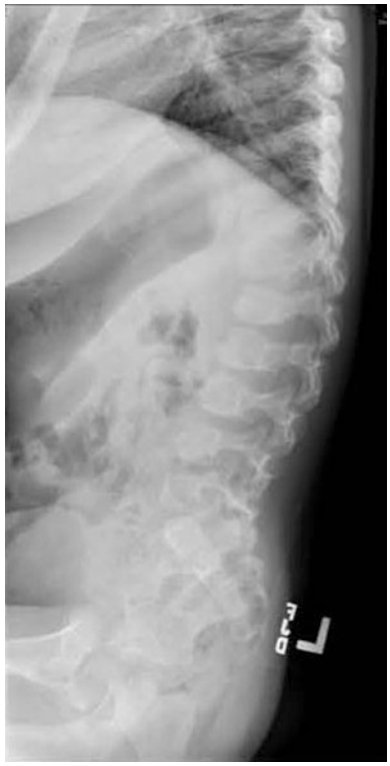

Fig. 16 Lateral lumbar spine showed anterior beaking of L1 and L2

Multiple Endocrine Neoplasia Syndromes

Contents

The multiple endocrine neoplasia (MEN) syndromes are rare autosomal dominant conditions predisposing affected individuals to benign and malignant tumors of the pituitary, thyroid, parathyroid, adrenal, endocrine, pancreas, paraganglion, or nonendocrine organs. The classic MEN syndromes include MEN type 1 (MEN1) and MEN type 2 (MEN2). The prevalence of MEN1 is estimated to be 1 in 20,000–40,000 individuals and that of MEN2 is estimated to be 1 in 35,000 individuals (DeLellis et al. 2004).

MEN1 is a rare endocrine disorder presenting with various combinations of parathyroid, gastroenteropancreatic, and anterior pituitary tumors, but it can also include various combinations of more than 20 endocrine and nonendocrine tumors such as foregut, bronchial, and thymic carcinoids, lipomas and skin tumors (Gagel and Marx 2007). Generally, tumors in MEN1 are benign, although gastrinomas and foregut carcinoids may exhibit a malignant course (Falchetti et al. 2008).

MEN2 is a rare hereditary syndrome characterized by medullary thyroid carcinoma (MTC), unilateral or bilateral pheochromocytoma, and other hyperplasia and/or neoplasia of different endocrine tissues (Falchetti et al. 2008). If not diagnosed precociously, MTC can be fatal. MEN2 includes three clinical subtypes: MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC).

Synonyms and Related Disorders

Familial medullary thyroid carcinoma; MEN1 (multiple endocrine adenomatosis, Wermer syndrome); MEN2A (pheochromocytoma and amyloid-producing medullary thyroid carcinoma, Sipple syndrome); MEN2B (mucosal neuroma syndrome)

Genetics/Basic Defects

1. MEN1
    1. Caused by a germline mutation in the *MEN1* gene, which encodes the tumor suppressor protein menin
    2. Mutated gene: *MEN1* (inactivating mutations of the MEN1 gene)
        1. Mapped on chromosome 11q13.
        2. Menin: consists of ten exons with noncoding first exon and produces a 610-amino acid protein.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_168

3. Two independent somatic mutations must occur within a single cell for tumor formation.
4. A single mutation is required in an individual with *MEN1*, since the first mutation is already present in all of the patient's cells (Pack et al. 1998; Vortmeyer et al. 1999).
5. This accounts for the multiple tumors and the tumors occurring at an earlier age.
6. Approximately 700 different somatic and germline mutations have been identified (Thakker 2001).

3. No genotype-phenotype correlations observed

2. MEN2 (Marquard and Eng 2015)
   1. Caused by germline-activating missense mutations of the rearranged during transfection (*RET*) proto-oncogene which:
      1. Mapped on chromosome 10q11.2
      2. Encodes a receptor tyrosine kinase that functions as a signal transducer upon interaction with the glial-derived neurotrophic factor family of ligands (Santoro et al. 2004)
      3. MEN2-associated mutations: almost always located in exons 10, 11, or 13 through 16, although mutations in exons 5 and 8 have been reported on rare occasions (Dvorakova et al. 2005; Da Silva et al. 2003)
   2. MEN2 is a genetic syndrome caused by mutations in the RET proto-oncogene with different penetrance producing three variants, MEN2A, MEN2B, and FMTC, each of which is characterized by MTC (Krampitz and Norton 2014).
   3. Strong genotype-phenotype correlations exist with respect to Raue and Frank-Raue (2012) and Romei et al. (2012).
      1. The MEN2 syndromes: characterized by a strong genotype-phenotype correlation and a specific RET mutation may be responsible for a particular phenotype and a more or less aggressive clinical course.
      2. This close association was firstly identified in an early study of 477 families affected by MEN2 (Eng et al. 1996) and confirmed by several other studies.
      3. MEN2 subtypes.
         1. MEN2A: at least 95% of individuals with MEN2A have an identifiable *RET* mutation (Schuffenecker et al. 1994; Mulligan et al. 1994).
         2. MEN2B: an identifiable *RET* mutation in at least 98% of patients. The mutation is almost invariably M918T. Some individuals with mutation A883F (Mulligan et al. 1995; Gimm et al. 1997).
         3. FMTC: mutated gene (*RET proto-oncogene*).
      4. Clinical subtype and associated diseases.
         1. MEN2A: cutaneous lichen amyloidosis, Hirschsprung disease
         2. MEN2B: ganglioneuromatosis, marfanoid habitus
         3. FMTC: rare
      5. Typical age at onset (years).
         1. MEN2A (10)
         2. MEN2B (2)
         3. FMTC (30)
3. MEN4 (Molatore and Pellegata 2010; Pellegata 2012)
   1. Heterozygous germline mutations in the human homologue, *CDKN1B*: identified in patients with multiple endocrine tumors.
   2. As a consequence of these observations, a novel human MEN syndrome, named MEN4, was recognized which is caused by mutations in p27.
   3. The recognition of both the MENX (rat) and the MEN4 (human) syndromes has demonstrated that Cdkn1b/CDKN1B is a new tumor susceptibility gene for multiple neuroendocrine tumors in both species.

Clinical Features

1. MEN1 (Marini et al. 2006a, b; Callender et al. 2008; Falchetti et al. 2008; Thakker et al. 2012; Giusti et al. 2015)

1. The presence of intrafamilial and interfamilial variation: highly variable in terms of the number of organ systems involved and the age of onset of tumors and symptoms
2. MEN1 should be considered in patients with the following diagnoses:
    1. Primary hyperparathyroidism under age of 30 years
    2. Primary hyperparathyroidism resulting from multigland involvement
    3. Familial primary hyperparathyroidism
    4. Zollinger-Ellison syndrome
    5. Multifocal pancreatic endocrine tumors or two or more MEN1-related tumors
3. Clinical diagnosis of MEN1 should be considered in:
    1. Patients with tumors in two of the three most commonly affected endocrine organs (parathyroid, pituitary, and pancreatic/duodenal endocrine tumors)
    2. Patients with one such tumor and a family history of MEN1
4. Clinical signs and symptoms: in order of decreasing frequency (Doherty 2005)
    1. Hypercalcemia
    2. Nephrolithiasis
    3. Peptic ulcer disease
    4. Hypoglycemia
    5. Visual field loss
    6. Hypopituitarism
    7. Acromegaly
    8. Galactorrhea-amenorrhea syndrome
    9. Rarely Cushing's syndrome
5. Includes varying combinations of more than 20 endocrine and nonendocrine tumors
6. Characteristic endocrine tumors (Schussheim et al. 2001)
    1. Parathyroid tumors: adenoma (90%).
        1. The main MEN1-associated endocrinopathy; onset in 90% of individuals is between ages 20 and 25 years with hypercalcemia evident by age 50 years.
        2. Hypercalcemia causes lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, diuresis, dehydration, hypercalciuria, kidney stones, increased bone resorption/fracture risk, hypertension, and shortened QT interval.
    2. Pituitary tumors.
        1. Prolactinoma (20%): the most common which manifests as oligomenorrhea/amenorrhea and galactorrhea in females and sexual dysfunction in males
        2. GH and GH plus prolactin (10%)
        3. NF1 (5%)
        4. ACTH (2%)
        5. TSH and others (rare)
    3. Well-differentiated endocrine tumors of the gastroenteropancreatic tract.
        1. Gastrinoma (40%): can manifest as Zollinger-Ellison syndrome
        2. Insulinoma (10%): hypoglycemia
        3. Nonfunctioning including pancreatic polypeptide (20%)
        4. Glucagonoma: hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, and skin rash
        5. Vasoactive intestinal peptide (VIP)-secreting tumor: watery diarrhea, hypokalemia, and achlorhydria syndrome
        6. Somatostatinoma
    4. Foregut carcinoid.
        1. Nonfunctioning (non-hormone-secreting) gastric enterochromaffin-like cell tumor (10%): can manifest as a large mass after age 50 years
        2. Bronchial carcinoid (2%)
        3. Thymic carcinoid (2%)
    5. Adrenocortical tumors can be associated with primary hypercortisolism or hyperaldosteronism.
7. Nonendocrine tumors
    1. Facial angiofibromas
    2. Collagenomas
    3. Lipomas
    4. Meningiomas
    5. Ependymomas
    6. Leiomyomas

8. Prognosis
    1. Decreased life expectancy, with a 50% probability of death by age of 50, and one half of MEN1 patients die as a result of a malignant tumoral process or sequela of the disease (Wilkinson et al. 1993; Doherty et al. 1998; Dean et al. 2000).
    2. Pancreatic neuroendocrine tumors are responsible for significant morbidity and mortality in MEN1 kindreds.
2. MEN2 (Marquard and Eng 2015)
    1. Following characteristics in a single patient
        1. Hallmark of MEN2: an extremely high lifetime risk of developing medullary thyroid carcinoma (MTC) (>95% in untreated patients)
        2. Unilateral or bilateral pheochromocytoma
        3. Other hyperplasia and/or neoplasia of different endocrine tissues
    2. Signs and symptoms (Richards 2015)
        1. Hypertension if a pheochromocytoma presents
        2. Chronic constipation: constant finding in MEN2B patients resulting from hyperplasia of the intrinsic autonomic ganglia in the intestinal wall
        3. A neck mass or dominant thyroid nodule with nontender anterior neck lymph nodes arising insidiously with progressive enlargement: may signify regional metastasis
        4. MEN2B patients
            1. Marfanoid habitus (high-arched palate, pectus excavatum, bilateral pes cavus, and scoliosis).
            2. Neuromas on the eyelids, conjunctiva, nasal and laryngeal mucosa, tongue, and lips (Wray et al. 2008).
            3. Prominent hypertrophied lips leading to a characteristic facies.
    3. The presence of three clinical subtypes
        1. MEN2A
        2. MEN2B
        3. Familial MTC (FMTC)
3. MEN2A
    1. The most common subtype.
    2. Associated with MTC.
    3. Risk of developing pheochromocytoma (approximately 50%).
    4. Risk of developing primary hyperparathyroidism (30–40%).
    5. Diagnosed clinically by the occurrence of two or more specific endocrine tumors (medullary thyroid carcinoma, pheochromocytoma, or parathyroid adenoma/hyperplasia) in a single individual or in close relatives.
    6. Familial MTC: diagnosed in families with four or more cases of MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia.
    7. Typical age at onset of biochemical evidence of MTC in untreated patients with MEN2A: 15–20 years. However, MTC is frequent in children ages 10 years and younger (Lips et al. 1994; Machens et al. 2003; O'Riordain et al. 1994).
    8. Rare variants of MEN2A can be associated with paraneoplastic syndromes.
        1. Cutaneous lichen amyloidosis
        2. Excessive production of corticotrophin
        3. Hirschsprung disease
4. MEN2B (also formerly known as MEN3) (Wray et al. 2008)
    1. Diagnosed clinically by the presence of early onset MTC, mucosal neuromas of the lips and tongue, as well as medullated corneal nerve fibers, distinctive facies with enlarged lips, and an asthenic "marfanoid" body habitus (American Thyroid Association Guidelines Task Force et al. 2009).
    2. The rarest and most aggressive subtype.
        1. Associated with the earliest onset (usually 10 years earlier than that for MEN2A) and most aggressive type of MTC
        2. Pheochromocytomas (40–50% of patients)
        3. Multiple neuromas and/or diffuse ganglioneuromatosis of the gastroenteric mucosa (approximately 40% of patients)
    3. Characteristic facial appearance: resulting from mucosal neuromas in the tongue, lips, and eyelids (Schimke et al. 1968).
        1. Enlarged lips

2. A "bumpy" tongue
3. Eversion of the eyelids

4. Often with a thin and lanky (Marfanoid) habitus with increased joint mobility and with decreased subcutaneous fat.
5. Frequently with thickening of the corneal nerves or ganglioneuromatosis of the gastrointestinal tract, which can result in abdominal distention, megacolon, constipation, or diarrhea.
6. The physical traits: usually evident in early childhood.
7. Without prophylactic thyroidectomy at a young age (before 1 year of age), most patients with MEN2B develop metastatic MTC in childhood or adolescence (O'Riordain et al. 1994).
8. Patients with MEN2B do not develop primary hyperparathyroidism.

5. Familial medullary thyroid carcinoma (FMTC)
   1. MTC is the only clinical feature.
   2. Refers to occurrence of medullary thyroid cancer in at least four affected members within the same family with documented absence of other endocrinopathies.
   3. Clinical course of MTC.
      1. More benign than that of MEN2A and MEN2B
      2. Prognosis: relatively good in most cases
6. MEN4 (Pellegata et al. 2006; Molatore and Pellegata 2010; Marinoni and Pellegata 2011; Lee and Pellegata 2013a, 2013b; Grajo et al. 2016)
   1. Pituitary tumors
      1. Prolactinomas
      2. Somatotropinomas
      3. Adrenocorticotrophinomas
   2. Parathyroid tumors: parathyroid adenoma
   3. Others
7. Mortality (Diaz-Thomas 2014)
   1. Complicated peptic ulcer disease.
   2. Metastases of endocrine pancreatic tumors.
   3. Severe hypercalcemia with arrhythmias.
   4. Metastatic MTC.
   5. Catecholamine release-related arrhythmias.
   6. Coronary heart disease.
   7. Stroke.
   8. Heart failure.
   9. Arrhythmias from cardiac myxomas.
   10. Zollinger-Ellison syndrome (ZES) is the major cause of morbidity and mortality in type 1 MEN.
   11. Mortality in type 2B MEN is mainly due to the aggressive nature of MTCs.
8. Differential diagnosis of other categories of MEN (Hoff et al. 2000; Callender et al. 2008)
   1. Von Hippel-Lindau syndrome (VHL)
      1. Mutated gene: *VHL*
      2. Manifestations
         1. Pheochromocytoma
         2. Retinal and central nervous system hemangioblastoma
         3. Renal cysts and clear cell carcinoma
         4. Pancreatic cysts and islet cell tumors
         5. Endolymphatic sac tumors
         6. Papillary cystadenomas of the epididymis and broad ligament
   2. Familial pheochromocytoma/paraganglioma syndrome
      1. Mutated gene: *SDHB*, *SDHC*, *SDHD*
      2. Manifestations: multiple paragangliomas and pheochromocytoma
   3. Cowden syndrome
      1. Mutated gene: *PTEN*
      2. Manifestations
         1. Nonmedullary thyroid cancer (usually follicular rather than papillary)
         2. Benign and malignant tumors of the skin, oral mucosa, breast, and uterus
   4. Carney complex
      1. Mutated gene: *PRKAR1A*
      2. Manifestations
         1. Endocrine tumors (including thyroid, pituitary, and primary pigmented nodular adrenocortical diseases)
         2. Characteristic skin pigmentation
         3. Myxomas
         4. Melanotic schwannomas

5. Familial isolated hyperparathyroidism
    1. Mutated gene: *MEN1*, *HRPT2*, *CASR*, and others
    2. Manifestations: nonsyndromic primary hyperparathyroidism
6. Hyperparathyroidism-jaw tumor syndrome
    1. Mutated gene: *HRPT2*
    2. Manifestations
        1. Primary hyperparathyroidism (usually single adenoma)
        2. Ossifying fibromas of maxilla or mandible
        3. Renal cysts and hamartomas
        4. Fifteen percent risk of parathyroid carcinoma
7. Familial hypocalciuric hypercalcemia
    1. Mutated gene: *CASR*
    2. Manifestations
        1. Benign hypercalcemia.
        2. Hypocalciuria.
        3. Low to normal parathyroid hormone levels.
        4. Renal calcium-to-creatinine clearance ratio <0.01.
        5. Parathyroidectomy does not cure hypercalcemia.
8. Neurofibromatosis type I
    1. Mutated gene: *NF1*
    2. Manifestations
        1. Pheochromocytoma
        2. Characteristic physical features (e.g., café-au-lait spots, neurofibromas, axillary and inguinal freckling)
9. Familial adenomatous polyposis
    1. Mutated gene: *APC*
    2. Manifestations
        1. Hundreds of adenomatous colon polyps
        2. Colon cancer
        3. Cribriform-morular variant of papillary thyroid cancer
10. Familial nonmedullary thyroid cancer
    1. Mutated gene: unknown
    2. Manifestations: nonsyndromic nonmedullary thyroid cancer

Diagnostic Investigations

1. Diagnosis of component tumors in MEN1 (Callender et al. 2008)
    1. Hyperparathyroidism
        1. An elevated or high-normal serum calcium level in concordance with an inappropriately elevated serum parathyroid hormone level.
        2. A 24-h urine collection documenting no evidence of hypocalciuria (urinary calcium excretion <100 mg/24 h) should be performed to exclude the possibility of familial hypocalciuric hypercalcemia.
    2. MEN1-related pituitary adenomas
        1. Most common functioning tumors produce prolactin (prolactinomas), growth hormone (somatotropinomas), or corticotropin
        2. Approximately 15% of tumors are nonfunctioning with no hormone production (DeLellis et al. 2004)
    3. Pancreatic and duodenal tumors
        1. Gastrinomas
            1. Gastrin level usually $>1{,}000$ pg/mL.
            2. A rise in the gastrin level of >200 pg/mL by a secretin stimulation test confirms the diagnosis.
            3. Tumors localized by a combination of octreotide scan, CT, and endoscopic ultrasonography.
        2. Insulinomas presents as "Whipple's triad":
            1. Fasting- or exercise-induced hypoglycemia
            2. Plasma glucose level <50 mg/dL
            3. Reversal of symptoms with administration of glucose
            4. Localized by CT and endoscopic ultrasonography
        3. Glucagonomas
            1. A serum glucagon level $>1{,}000$ pg/mL.
            2. A secretin stimulation test may be useful.
            3. Localized with an octreotide scan, CT, and endoscopic ultrasonography.

4. Vasoactive intestinal peptide tumors (VIPomas)
    1. Fasting plasma vasoactive intestinal peptide (VIP) levels >200 pg/mL
    2. VIPomas: usually located in the body and tail of the pancreas and are localized by an octreotide scan, CT, and endoscopic ultrasonography
5. Somatostatinoma
    1. A fasting somatostatin level of >100 pg/mL
    2. Localized with an octreotide scan, CT, and endoscopic ultrasonography
6. Nonfunctioning MEN1-associated pancreatic endocrine tumors: localized by an octreotide scan, CT, and endoscopic ultrasonography

4. Other tumor types: not part of the diagnostic criteria for MEN1, but their presence helps to support a diagnosis of MEN1
    1. Foregut (thymic, bronchial, or gastric) carcinoid tumors
    2. Adrenal cortex tumors (adenomas, pheochromocytoma, adrenocortical carcinomas)
    3. Thyroid tumors (follicular adenomas, goiters, nonmedullary thyroid carcinoma)
    4. Benign facial angiomas
    5. Collagenomas of the neck, upper limbs, and chest
    6. Subcutaneous or visceral lipomas
    7. Uterine or esophageal leiomyomas
    8. Meningiomas
    9. Spinal ependymomas

2. Diagnosis of component tumors in MEN2 (Falchetti et al. 2008; Marquard and Eng 2015).
    1. Medullary thyroid carcinoma and C-cell hyperplasia.
        1. The presence of an elevated plasma calcitonin concentration, a specific and sensitive marker.
        2. Pentagastrin or calcium stimulation to evaluate calcitonin secretion: earlier detection of MTC.
        3. Ultrasonography, CT, or MRI: localized tumor extension and possible distant metastases.
    2. Pheochromocytoma.
        1. Suspected when biochemical screening reveals elevated excretion of catecholamines and catecholamine metabolites (e.g., norepinephrine, epinephrine, metanephrine, and vanillylmandelic acid (VMA)) in plasma.
        2. 24-h measurement of urinary excretion of catecholamines and their metabolites to assess adrenal gland function: recommended on an annual basis.
        3. CT and MRI to localize the tumor.
    3. Primary hyperparathyroidism
        1. Diagnosis: made by elevated serum parathyroid hormone (PTH) and calcium concentrations.
        2. Postoperative parathyroid localizing studies with 99mTc-sestamibi scintigraphy may be helpful if hyperparathyroidism recurs.
        3. For preoperative adenoma localization, three-dimensional single-photon emission CT (SPECT) may also be used (Brenner and Jacene 2008).

3. Routine surveillance of presymptomatic patients and treated patients who are currently without evidence of disease (Brandi et al. 2001).
    1. Annual biochemical testing for all tumor types
        1. Parathyroid: serum calcium, parathyroid hormone (starts to screen at age of 8 years)
        2. Gastrinoma: serum gastrin (starting at age of 20 years)
        3. Insulinoma: fasting serum glucose, insulin (starting at age of 5 years)
        4. Other enteropancreatic: chromogranin A, glucagons, proinsulin (starting at age of 20 years)
        5. Anterior pituitary: prolactin, insulin-like growth factor 1 (starting at age of 5 years)

2. Imaging studies (CT or MRI) every 3 years
    1. Other enteropancreatic: octreotide scan, CT, or MRI (starting at age of 20 years)
    2. Anterior pituitary: MRI of the brain (starting at age of 5 years)
    3. Foregut carcinoid: CT (starting at age 30 years)
4. An excellent comprehensive imaging review (ultrasound, CT, PET-CT, MRI findings): available on multiple endocrine neoplasia syndromes (Grajo et al. 2016).
5. Molecular genetic testing for MEN1.
    1. Should be offered to patients in whom a diagnosis of MEN1 is being considered.
    2. The benefit of offering genetic testing: a diagnosis of MEN1 at an early age allows patients to be monitored for the development of subsequent MEN1-related tumors.
    3. Sensitivity of genetic testing: varies, depending on the combination of affected organs and whether the patient is an index or familial case.
    4. Mutations can be identified in only 75–90% of patients with a clinical diagnosis of MEN1.
        1. A negative test result cannot definitively rule out the risk for further MEN1-related tumors.
        2. Follow-up screening recommendations in such cases are controversial and require careful consideration of the index of suspicion of MEN1 based on the patient's personal and family history.
6. Molecular genetic testing for MEN2 (Moline and Eng 2010; Marquard and Eng 2015).
    1. MEN2A
        1. Approximately 95% of families with MEN2A have a *RET* mutation in exon 10 or 11.
        2. Other rare mutations, including codon 804 alterations, have been reported in a few cases.
    2. MEN2B
        1. Approximately 95% of individuals with the MEN2B phenotype have a single point mutation in the tyrosine kinase domain of the *RET* gene at codon 918 in exon 16 (M918T).
        2. Other rare mutations include second mutation at codon 883 in exon 15 (A883F) and two mutations (V804M and Y806C) in cis configuration.
7. Molecular genetic testing for FMTC (Moline and Eng 2010; Marquard and Eng 2015): approximately 88% of families with FMTC have an identifiable *RET* mutation.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: a 50% risk if a parent is affected or has a disease-causing mutation
    2. Patient's offspring: a 50% risk of inheriting the mutation
2. Prenatal diagnosis and preimplantation genetic diagnosis: possible for pregnancies at increased risk by analysis of DNA extracted from fetal cells by amniocentesis or CVS, provided the disease-causing allele of an affected family member must be identified or linkage established in the family
3. Management
    1. MEN1 (Callender et al. 2008)
        1. Parathyroidectomy for parathyroid tumors
        2. Transcervical thymectomy because there is an increased risk of supernumerary parathyroid glands and developing carcinoid tumors in the thymus
        3. Pituitary tumors
            1. Surgery (usually from a minimally invasive transsphenoidal approach)
            2. Medication for patients with prolactin- or growth hormone-producing tumors with dopamine agonists, such as bromocriptine or cabergoline, and a GH receptor antagonist, respectively
            3. Radiation
        4. Gastrinomas
            1. Proton pump inhibitors for medical control of acid hypersecretion
            2. Surgical approaches: no consensus
        5. Insulinomas
            1. Manage surgically

2. Treat unresectable tumors with diazoxide (Proglycem)
6. VIPoma
   1. Manage surgically
   2. Octreotide (Sandostatin) for diarrhea control

2. MEN2 (Falchetti et al. 2008)
   1. Medullary thyroid carcinoma
      1. Total thyroidectomy with lymph node dissection of at least the central compartment.
      2. An elevated serum calcitonin level after surgery can be a sign of persistent, recurrent, or generalized MTC.
      3. Total thyroidectomy within the first month of life should be performed in patients with the highest risk mutations (MEN2B, codons 883 and 918) (Lewis and Yeh 2008).
   2. Pheochromocytoma
      1. Surgical laparoscopy excision.
      2. Recommend lifelong follow-up after surgery.
      3. Long-term drug treatment with α and β adrenergic blockers should only be considered in those patients in whom the tumor is unresectable.
   3. Primary hyperparathyroidism
      1. Subtotal parathyroidectomy or total parathyroidectomy with autotransplantation of normal fresh or cryopreserved tissue in the forearm.
      2. All individuals who have undergone partial or total parathyroidectomy with autotransplantation need to be monitored for possible recurrences.

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Fig. 1 (**a**–**c**) The patient, a 13-year-old Caucasian female, was seen initially because of a history of weight loss of approximately 17 pounds over a period of 4–6 weeks and a mass in her neck. The biopsy of the neck mass revealed a medullary thyroid carcinoma. She has a long history of developmental delay and an unusual appearance with a thin body habitus, long face, and full lips. *MEN2* mutation screening revealed a sequence change in exon 16 of 2,753 T > C (ATG > ACG) with an amino acid change of M918T (Met918Thr). The presence of this mutation in codon 918 of the RET proto-oncogene is consistent with a clinical diagnosis of MEN2B

Multiple Epiphyseal Dysplasia

Contents

In 1945, Fairbank first described multiple epiphyseal dysplasia (MED). MED is a type of short-limbed dwarfism characterized by impaired endochondral ossification affecting multiple epiphyses and premature degenerative joint disease.

Synonyms and Related Disorders

Autosomal dominant multiple epiphyseal dysplasia (Fairbank type, Ribbing type); Autosomal recessive multiple epiphyseal dysplasia (with bilayered patellae, with clubfoot)

Genetics/Basic Defects

1. Inheritance: genetically heterogeneous (Deere et al. 1995)
   1. Autosomal dominant (Maudsley 1955; Murphy et al. 1973; Briggs et al. 2015)
      1. Multiple epiphyseal dysplasia type I (EDM1)
      2. Multiple epiphyseal dysplasia type II (EDM2)
      3. Multiple epiphyseal dysplasia type III (EDM3)
      4. Multiple epiphyseal dysplasia type V (EDM5)
      5. Multiple epiphyseal dysplasia type VI (EDM6)
   2. Autosomal recessive: multiple epiphyseal dysplasia type IV (EDM4) (Bonafé et al. 2014)
2. Causes
   1. EDM1: mutations in the gene (*COMP*) encoding cartilage oligomeric matrix protein (COMP) on the centromeric region of 19p (19p13.1-p12) (Oehlmann et al. 1994), same locus as (allelic to) pseudoachondroplasia (the disease that shares some clinical features with multiple epiphyseal dysplasia) (Briggs et al. 1995, 1998; Ballo et al. 1997; Deere et al. 1999; Ikegawa et al. 1998; Unger and Hecht 2001)
   2. EDM2 (Muragaki et al. 1996): mutations in the type IX collagen, alpha-2 polypeptide gene (*COL9A2*) on 1p33-p32.2
   3. EDM3: caused by heterozygous mutation in the *COL9A3* gene on 20q13 (Paassilta et al. 1999)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. EDM4 (Bonafé et al. 2014)
    1. Mutations in the diastrophic dysplasia sulfate transporter gene (*DTDST*) (SLC26A2) on 5q32-q33.1.
    2. Recessive mutations in the *DTDST* gene also cause a spectrum of osteochondrodysplasias, including achondrogenesis type IB, atelosteogenesis type II, and diastrophic dysplasia (Superti-Furga et al. 1999, 2000).
5. EDM5 (Chapman et al. 2001): mutations in the gene (*MATN3*) encoding matrilin-3 on 2p24-p23
6. EDM6: (Czarny-Ratajczak et al. 2001; Mortier et al. 2001): mutations in the type IX collagen, alpha-1 polypeptide gene (*COL9A1*) on 6q13

3. Mutations in extracellular matrix proteins, COMP, types II and IX collagens, and matrilin 3
    1. Produce a spectrum of mild to severe chondrodysplasias characterized by epiphyseal and vertebral abnormalities
    2. Disrupt protein processing and excessive accumulation of some of these proteins in the rough endoplasmic reticulum (rER) that appears to compromise cellular function
4. Genotype-phenotype correlations (Unger et al. 2001; Briggs et al. 2015)
    1. Patients with *COMP* mutations
        1. Significant involvement at the capital femoral epiphyses
        2. Irregular acetabuli
    2. Patients with type IX collagen defects
        1. More severe involvement of the knees
        2. Relative sparing of the hips
    3. Patients with *MATN3* mutations
        1. Abnormalities similar to those in patients with *COL9A2* mutations: more severe hip abnormalities.
        2. More intrafamilial/interfamilial variability.
        3. Clinical manifestations of MED caused by *MATN3* were milder than manifestations of the COMP mutation group. These differences in clinical manifestation and prognosis justify molecular differentiation between the two genotypes (Seo et al. 2014).

Clinical Features

1. Broad historical classification: has not proved useful (Chapman et al. 2003)
    1. Ribbing: milder form with flat epiphyses and minimal involvement of the hands and feet
    2. Fairbank: more severe form with late-appearing epiphyses and greater involvement of the hands and feet
2. Onset usually in childhood: as a rule, not recognizable at birth or during the first 1–2 years of life
    1. Joint pain after exercise initially: a common presenting sign
    2. Limp, pain, and stiffness in hip, knee, and ankle joints
    3. Waddling gait
    4. Easy fatigue
3. Mild to moderate short stature with normal body proportion
4. Mild short-limbed dwarfism
5. Stubby hands and feet
6. Osteoarthritis: severe osteoarthritis of the hip develops in early childhood.
7. Limited joint motions
8. Proximal muscle weakness with mild variability in muscle fiber size in EDM3
9. Association with diabetes mellitus in early infancy (Wolcott-Rallison syndrome)
10. Consider MED (Unger et al. 2008) in
    1. Any child with bilateral Perthes disease
    2. Any child with noninflammatory joint pain, especially involving the knees
    3. Family history of early joint replacement
11. Prognosis
    1. Normal life expectancy
    2. Joint deformities resulting from abnormal epiphyseal ossification frequently leading to early degenerative arthroses
12. Distinctive features of the different forms of MED (Unger et al. 2008)
    1. EDM1 (COMP-MED)
        1. Distinctive clinical features
            1. Muscular hypotonia
            2. Pseudomyopathy

3. Joint laxity
4. Mild genu vara

2. Distinctive radiographic features
1. Hand: carpal bones more delayed than phalangeal epiphyses; ragged carpal bones, small, rounded phalangeal epiphyses
2. Proximal femoral epiphyses: round and small
3. Knee: small epiphyses with lateral thinning, additional ossification centers with "glacier crevice" sign before puberty

2. EDM2 (*COL9A2*)
1. Rare but may be under reported
2. Knee epiphyses: more affected than proximal femoral epiphyses

3. EDM3 (*COL9A3*)
1. Rare but may be under reported
2. Knee epiphyses: more affected than proximal femoral epiphyses

4. EDM4 (rMED)
1. Homozygous and compound heterozygous mutations in the *DTDST* gene lead to a relatively mild phenotype that seems to be clinically dominated by a tendency to recurrent dislocation of a bilateral multilayered patella and by early onset osteoarthritis of the hip joints (Miyake et al. 2008; Cho et al. 2010; Hinrichs et al. 2010).
2. Distinctive clinical features.
1. Clubfeet at birth
2. Genu valga rather than genu vara
3. Joint contractures
4. Mild to moderate brachydactyly
3. Distinctive radiographic features.
1. Hand: phalangeal epiphyses delayed, but maturation of carpal bones normal or advanced; flat epiphyses or phalanges and radius; "snow cap" sign of metacarpals
2. Proximal femoral epiphyses: small and flat
3. Knee: double-layered patella

5. EDM5 (MATN3-MED)
1. Distinctive clinical features: not specific
2. Distinctive radiographic features
1. Hand: unspecific changes at the hands
2. Proximal femoral epiphyses: small but not as rounded as in COMP-MED
3. Knee: small epiphyses with "harlequin hat" appearance; metaphyseal striations

6. EDM6 (*COL9A1*): very rare (only single family reported)

Diagnostic Investigations

1. Radiography (Chapman et al. 2003; Mäkitie et al. 2004).
1. Radiographic abnormalities may be present before the onset of physical symptoms.
2. Predominantly epiphyseal involvement.
1. Initial stage: delayed appearance of epiphyseal ossification
2. Later stage in the appearance of epiphysis
1. Usually small ossification centers.
2. Sometimes fragmented ossification centers with irregular contours.
3. Adjacent metaphyseal borders may be slightly abnormal.
3. Adulthood
1. Flattened and dysplastic articular surfaces
2. The presence of early features of osteoarthrosis
4. Characteristic epiphyseal involvement
1. Epiphyses of the hips and knees: most affected
2. Ivory epiphyses in the hands
3. Schmorl nodes in the spine
4. Double-layered patella (Sheffield 1998; Superti-Furga et al. 1999)
3. Vertebrae.
1. Ovoid vertebral bodies
2. Mildly irregular vertebral endplates

4. Limbs.
    1. Late ossifying epiphyses
    2. Small, irregular, fragmented, and in some cases flattened epiphyses
    3. Osteoarthritis
    4. Short femoral neck
    5. Markedly dysplastic capital femoral epiphyses
    6. Often initially diagnosed as Legg-Perthes disease (avascular necrosis of the femoral head)
    7. Genu varum or valgum
    8. Short metacarpals and phalanges with irregular epiphyses
    9. Small, irregular carpal and tarsal bones
    10. Normal metaphyses
5. Irregular acetabuli.
6. Patella.
    1. Double-layered
    2. Dislocation or subluxation
7. The absence of severe spinal involvement and minimal metaphyseal defects allows differentiating multiple epiphyseal dysplasia from other disorders with similar clinical features such as spondyloepimetaphyseal dysplasia and spondyloepiphyseal dysplasia.

2. Histology: chondrocytic inclusion (ultrastructurally, a dilated rER containing accumulated material) (Stanescu et al. 1993).
3. Molecular genetic diagnosis is important for accurate prognosis and genetic counseling: mutation analyses are available on clinical basis.
    1. Mutations in the *COMP* gene
    2. Mutations in the *COL9A1* gene
    3. Mutations in the *COL9A2* gene
    4. Mutations in the *COL9A3* gene
    5. Mutations in the *MATN3* gene
    6. Mutations in the *DTDST* gene

Genetic Counseling

1. Recurrence risk.
    1. Autosomal dominant inheritance
        1. Patient's sib
            1. 50% if one of the parent is affected
            2. Not increased if parents are normal
        2. Patient's offspring: 50%
    2. Autosomal recessive inheritance (Bonafé et al. 2014)
        1. Patient's sib: 25%
        2. Patient's offspring: not increased unless the spouse is also carrying the gene
2. Prenatal diagnosis and preimplantation genetic diagnosis for pregnancies at risk for *COMP* and other mutations is possible if the disease-causing allele of an affected family member has been identified (Bonafé et al. 2014; Briggs et al. 2015).
    1. Amniocentesis
    2. CVS
3. Management (Briggs et al. 2015).
    1. Initial aims of management.
        1. Control pain
            1. Can be difficult
            2. Combination of analgesics and physiotherapy including hydrotherapy
        2. Limit joint destruction and the development of osteoarthritis
    2. Weight control.
    3. Avoid exercise that causes repetitive strain on affected joints.
    4. Realignment osteotomy and/or acetabular osteotomy to slow the progression of symptoms.
    5. Total joint arthroplasty in some cases.
    6. Psychosocial support to address issues of short stature, disability, and employment.

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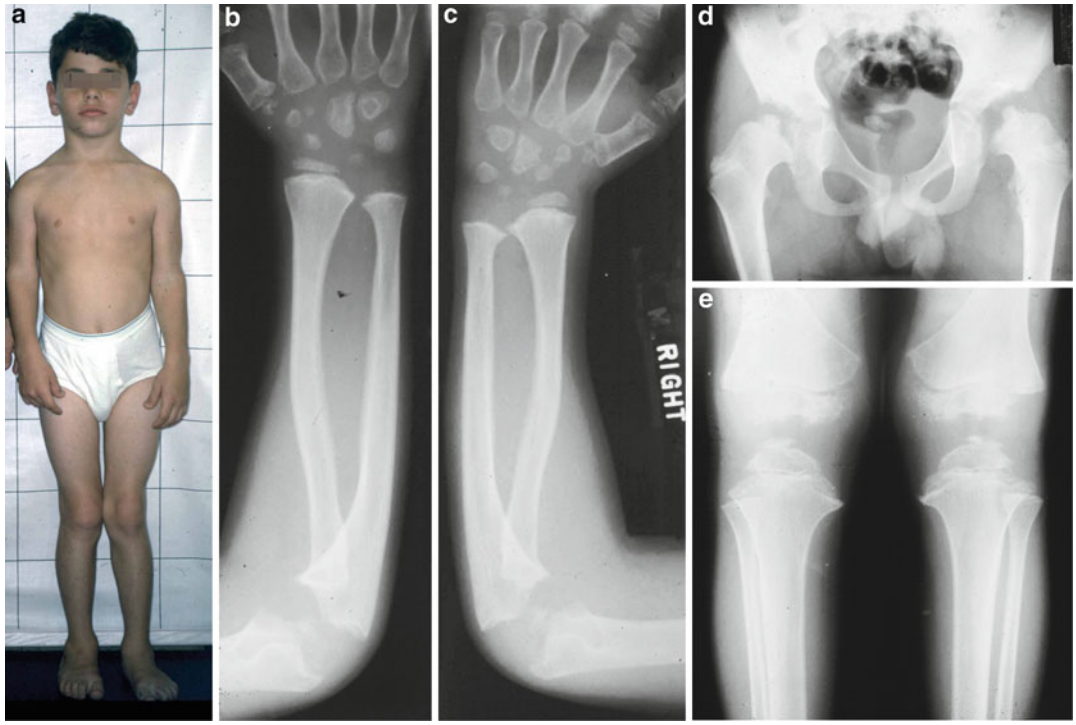

Fig. 1 (**a**–**e**) A boy with multiple epiphyseal dysplasia showing short stature (**a**) and epiphyseal dysplasia in the wrists (**b**, **c**), hips (**d**), and knee joints (**e**)

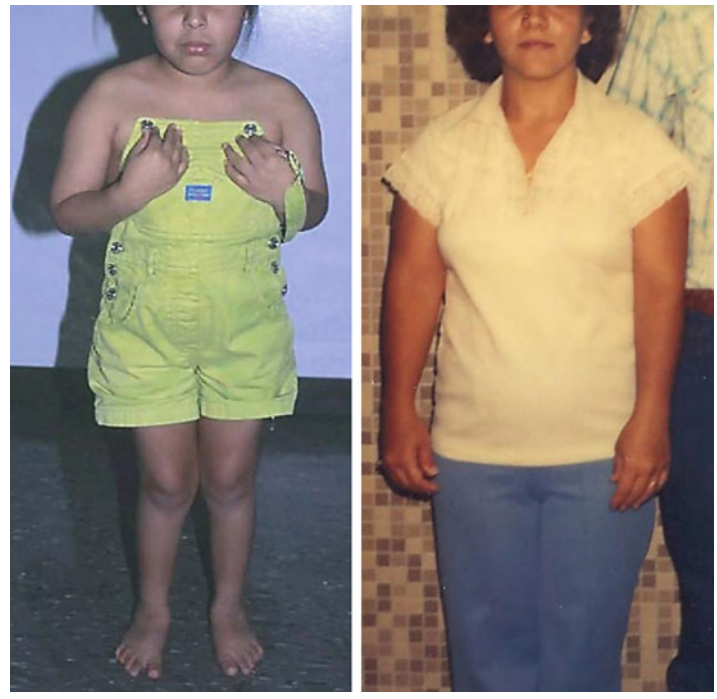

Fig. 2 (**a**, **b**) A girl (**a**) and an adult female (**b**) with multiple epiphyseal dysplasia showing mild short stature with normal body proportion

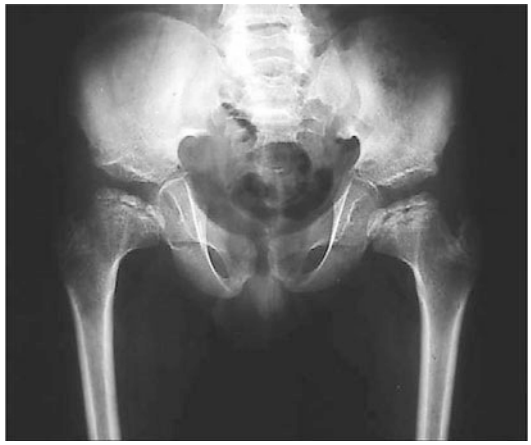

Fig. 3 Radiograph of the pelvis of a 12-year-old boy with multiple epiphyseal dysplasia showing poorly developed acetabular fossae and flat, fragmented femoral heads

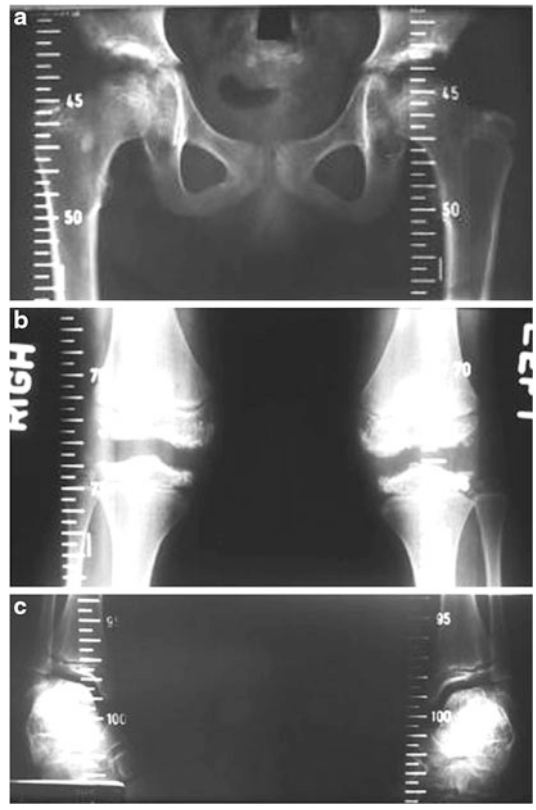

Fig. 4 (**a**–**c**) Radiographs of another patient with multiple epiphyseal dysplasia showing poorly formed acetabular fossae, poorly ossified femoral heads (**a**), and flattened epiphyses of the knees (**b**) and ankles (**c**)

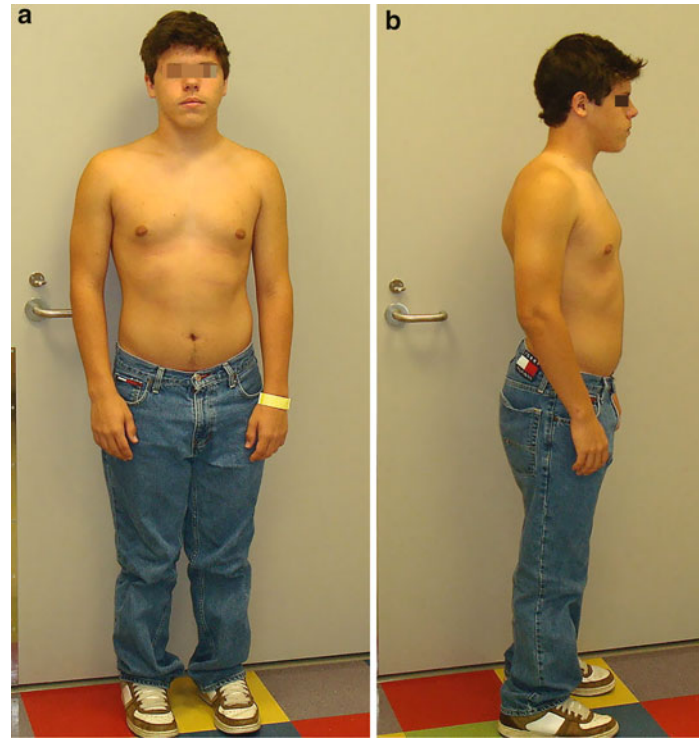

Fig. 5 (**a**, **b**) A 13-year-old boy with multiple epiphyseal dysplasia has been complaining of pain in the knees, legs, and feet since 4 years of age. He was also noted to have limp, joint stiffness, and worsening waddling gait. Mutation analysis showed a heterozygous G > A nucleotide substitution in exon 16, resulting in the replacement of an aspartic acid codon (GAC) with an asparagine codon (AAC) at amino acid position 605 (c.1813G > A or p. Asp605Asn (D605N)). The D605N missense mutation in the COMP gene has been reported previously in association with multiple epiphyseal dysplasia and is consistent with the diagnosis of this patient

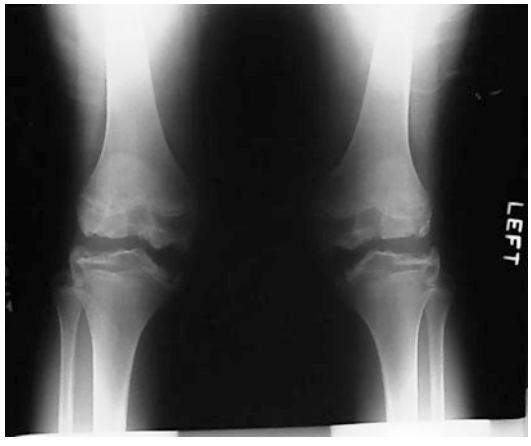

Fig. 6 Radiographs of the same patient showing epiphyseal dysplasias at the distal femoral epiphyses and the proximal tibial epiphyses causing weakness and pains at the knees

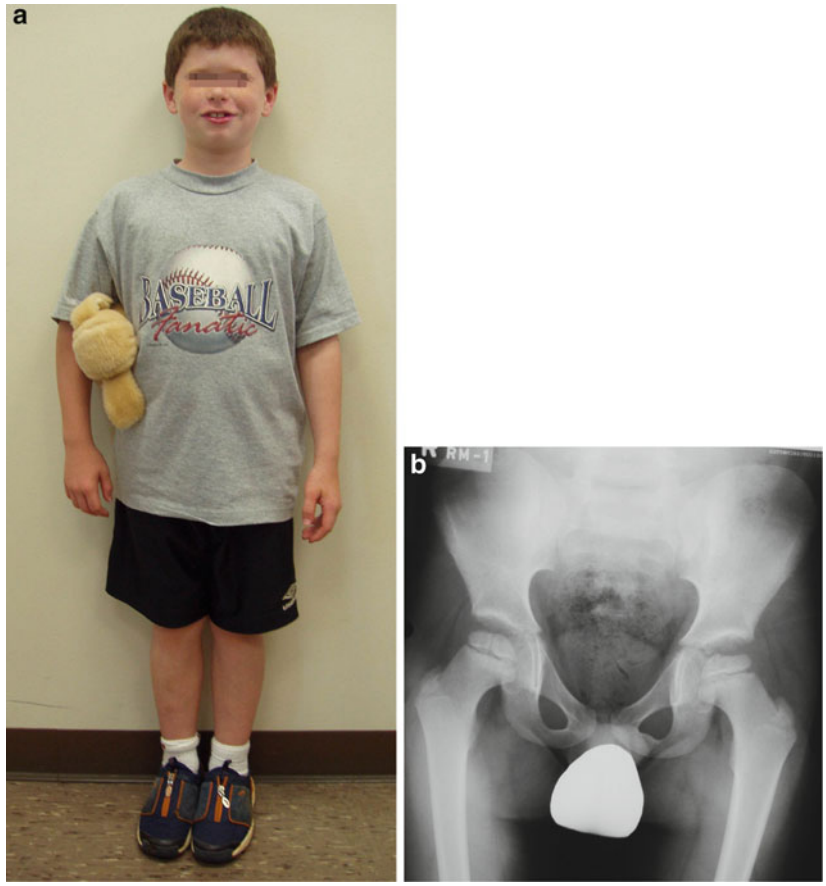

Fig. 7 (**a**, **b**) A 12-year-old boy (**a**) with multiple epiphyseal dysplasia. Radiograph of the pelvis at 8 years of age showed poorly developed acetabular fossae and flat femoral heads (**b**)

Fig. 8 A 10-year-old girl was seen because of short stature. The radiographs were consistent with multiple epiphyseal dysplasia. DNA sequencing revealed a c.1445A > G transition in exon 13 of the *COMP* gene. This change converts a codon for aspartic acid (GAC) to a codon for glycine (GGC). The patient is heterozygous for the mutation. The mutation confirms the diagnosis of multiple epiphyseal dysplasia. She was also diagnosed to have growth hormone deficiency and was receiving daily Humatrope injection

Fig. 9 Note the short upper arms with short fingers

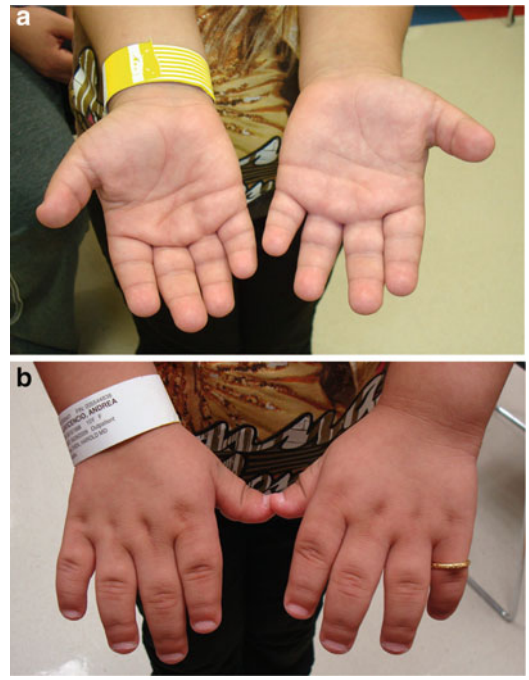

Fig. 10 (**a**, **b**) Note the short and stubby fingers

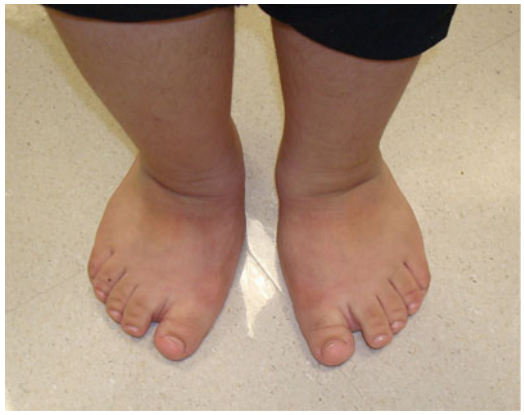

Fig. 11 Note short and stubby toes

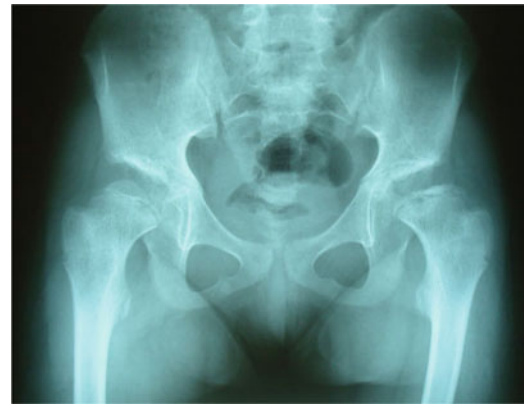

Fig. 12 Hip radiograph 6 months earlier shows poorly developed acetabular fossae and flat fragmented femoral heads

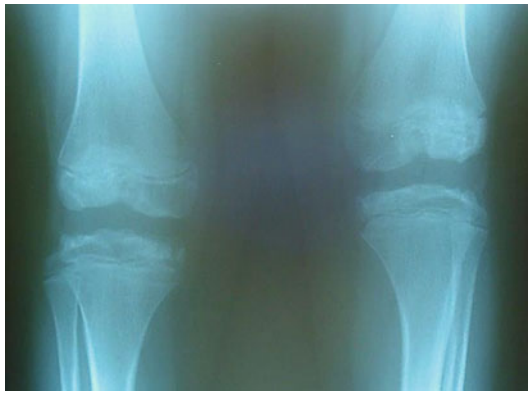

Fig. 13 Knee radiograph shows flattened epiphyses of the knees

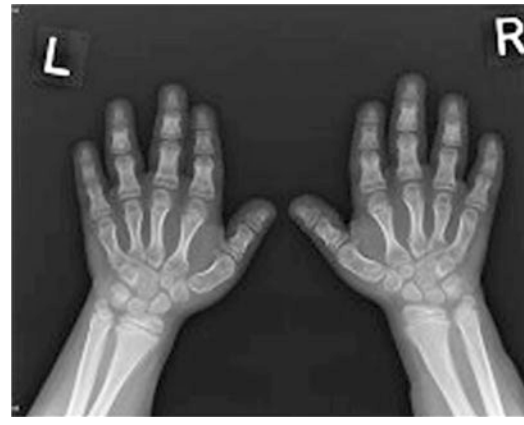

Fig. 14 Hand radiograph shows short and broad phalanges

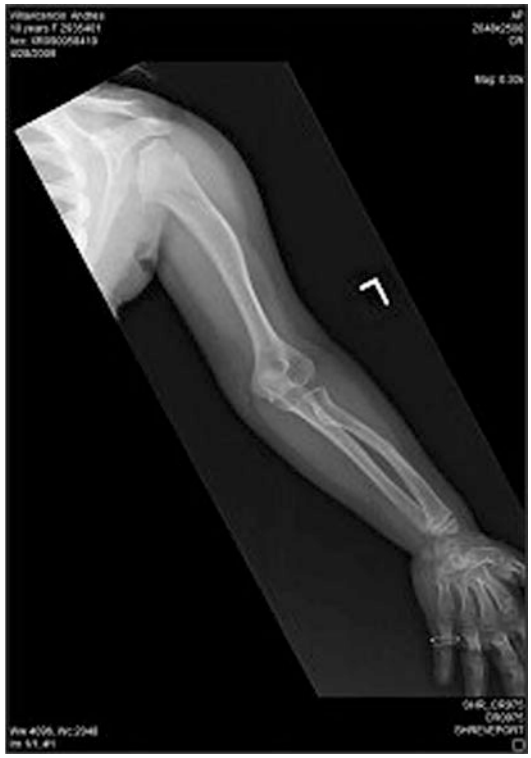

Fig. 15 Radiograph of left upper extremity shows relatively short tubular bones with small proximal epiphysis of the left humerus

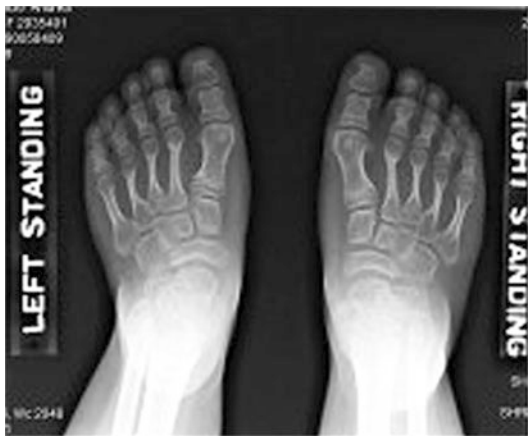

Fig. 16 Radiograph of feet shows short and stubby phalanges

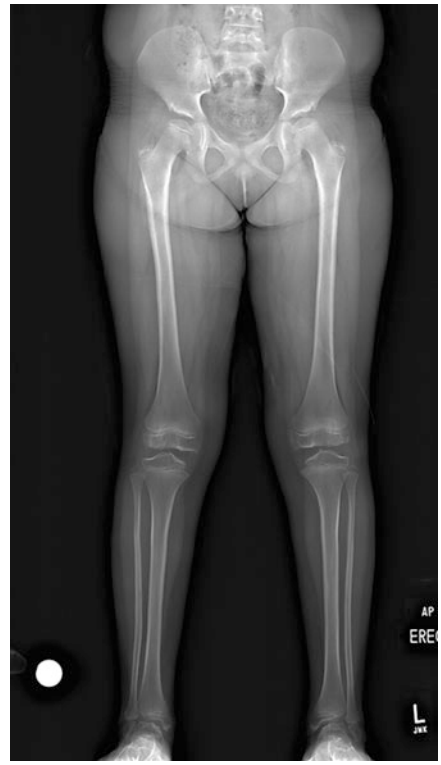

Fig. 17 A 9-year-old female presented to clinic with a diagnosis of multiple epiphyseal dysplasia. She was short and had intermittent complaints of knee pain and discomfort with difficulty in going up and down the stairs. Radiograph of bilateral lower extremities demonstrated mild lobulation along bilateral acetabulum. Flattened epiphyses were seen with mild lobular contour along the long bones. Tibial and femoral condyles were hypoplastic with shallow intercondylar notch (Courtesy of Dr. Grace Guo)

Multiple Pterygium Syndrome

Contents

Multiple pterygium syndrome is a distinct syndrome consisting of a constellation of congenital anomalies characterized by pterygia of the neck, antecubital, popliteal, and intercrural areas, numerous flexion contractures of the joints, growth retardation, ptosis, antimongoloid slant with or without epicanthal folds, cleft palate, scoliosis, vertebral anomalies, rocker-bottom deformity of the feet, and genital anomalies.

Synonyms and Related Disorders

Escobar syndrome (Escobar et al. 1978); Fetal akinesia deformation sequence; Lethal multiple pterygium syndrome

Genetics/Basic Defects

1. Inheritance: genetic heterogeneity (Chen 2015)
    1. Autosomal recessive inheritance in most cases
        1. Presence of similarly affected siblings born to normal parents (Gillin and Pryse-Davis 1976; Stoll et al. 1980; Fryns et al. 1988; Aslan et al. 2000) or to consanguineous parents (Naguib et al. 1987)
        2. A relatively common disorder among Arabs (Teebi and Daoud 1990)
        3. Recessive forms of MPS: clinically and genetically heterogeneous
            1. May result from early-onset fetal akinesia
            2. Traditionally classified into prenatally lethal MPS and nonlethal Escobar variant-MPS
        4. Escobar syndrome: Mutations in *CHRNG* gene, which encodes the acetylcholine receptor γ-subunit, cause the autosomal recessive Escobar syndrome, one of the most common types of MPS, although other genes may be involved (Hoffmann et al. 2006; Morgan et al. 2006; Prontera et al. 2007)
        5. Fetal akinesia deformation sequence (FADS) and/or MPS (Escobar syndrome) has been recently described as a prenatal form of myasthenia associated with recessive mutations in genes of the neuromuscular junction (*CHRNG*, *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNG*, *CNTN1*, *DOCK7*, *RAPSN*,

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and SYNE1) (Hoffmann et al. 2006; Morgan et al. 2006; Michalk et al. 2008; Vogt et al. 2008; Chen 2012). This observation expands the cause of Escobar variant-MPS to a component of the contractile apparatus
6. The first report of the clinical expression of the complete absence of TPM2 in human indicated that TPM2 expression at the early period of prenatal life plays a major role for normal fetal movements (Monnier et al. 2009)
7. Clinical features
   1. Multiple joint contractures with marked pterygia
   2. Dysmorphic facies (flat, sad, motionless facial appearance)
   3. Cervical vertebral anomalies
8. Truncating CHRNG mutations associated with interfamilial variability of the severity of the Escobar variant of multiple pterygium syndrome (Kariminejad et al. 2016)

2. Autosomal dominant inheritance in some cases (Mckeown and Harris 1988)
   1. Caused by mutations in embryonic myosin heavy chain (*MYH3*) (Chong et al. 2015)
   2. Great variation in severity between affected individuals
   3. Characterized by multiple pterygia with or without mental retardation
3. X-linked inheritance (MacArthur and Pereira 1996)
4. Sporadic occurrence (Ramer et al. 1988; Spranger et al. 1995; Aslani et al. 2002)

2. Phenotypic analysis
   1. Multiple congenital pterygia, joint contractures, and severe foot defects: deformation sequence secondary to reduced frequency of fetal movement
   2. Micrognathia: resulting from reduced use and represents "disuse hypotrophy"
   3. Cleft palate: a mechanical disruption due to presumed interposition of tongue between palatine shelves
   4. Neck pterygia
      1. Able to exert a downward pull on facial structures
      2. Responsible for the following effects:
         1. Down-turned angles of the mouth
         2. Long philtrum
         3. Antimongoloid slant of palpebral fissures
         4. Low posterior hairline
         5. Anteversion and apparently low-set position of auricles
         6. Often with strikingly abnormal directional hair patterning in posterior and posterior-lateral areas of scalp
      3. Short neck due to:
         1. Lateral cervical pterygia
         2. Secondary fusion of upper vertebrae
   5. Congenital scoliosis: secondary to abnormal prenatal position, movement, and/or muscle pull
   6. Genital anomalies
      1. Small scrotum and apparently absent or hypoplastic labia majora: resulting from the pull of the intercrural pterygia which affects a flattening of these structures
      2. Cryptorchidism: representing mechanical obstruction of the processus vaginalis from pull of intercrural web or some intrinsic defect of the gubernaculums testis which is unable to effect descent of the gonads
3. Pathogenesis
   1. The underlying pathogenesis of the secondary deformities and distortions, hypotrophies, disruptions, bony fusions, and incomplete or impeded morphogenetic movements is unknown
   2. A neuromuscular disease causing fetal akinesia (Chen et al. 1980; Bhargava et al. 2002) is suspected
   3. Intrauterine crowding and oligohydramnios are contributory factors to joint contractures associated with MPS (Chen 2015)

Clinical Features

1. Intrafamilial variability of clinical features (Naguib et al. 1987; Kariminejad et al. 2016)
2. Short stature

3. Cutaneous and musculoskeletal (Penchaszadeh and Salszberg 1981; Thompson et al. 1987)
    1. Pterygia involving the following areas:
        1. Neck
        2. Axillary
        3. Antecubital
        4. Popliteal
        5. Digital
        6. Intercrural
    2. Limb pterygia and multiple joint contractures (Hall et al. 1982)
    3. Rib or vertebral anomalies
    4. Scoliosis (Di Gennaro et al. 1996)/lordosis
    5. Rocker-bottom feet with vertical talus
4. Standing with a crouching or semi-crouching stance
5. Orofacial features
    1. A flat, sad, motionless facial appearance
    2. Epicanthal folds
    3. Ptosis
    4. Antimongoloid palpebral fissure
    5. Long philtrum
    6. Pointed, receding chin
    7. Down-turned angles of the mouth
    8. Cleft lip+/− palate
    9. Apparent low-set ears
6. Genitalia
    1. Males
        1. Small penis and scrotum
        2. Cryptorchidism
    2. Females
        1. Apparent aplasia of the labia majora
        2. A small clitoris
7. Association with myopathy
    1. Absence of β-tropomyosin is a new cause of Escobar syndrome associated with nemaline myopathy (Monnier et al. 2009)
    2. Progressive form of multiple pterygium syndrome in association with nemalin myopathy (Papadia et al. 1987)
    3. Multicore myopathy associated with multiple pterygium syndrome and hypertrophic cardiomyopathy (Ohkubo et al. 1996)
8. Phenotypic characteristics of autosomal dominant MPS (Frias et al. 1973; Kawira and Bender 1985; McKeown and Harris 1988; Prontera et al. 2006; Chong et al. 2015)
    1. Downslanting palpebral fissures
    2. Ptosis
    3. Camptodactyly of the fingers
    4. Scoliosis
    5. Vertebral fusions
    6. Short stature
    7. Neck webbing

Diagnostic Investigations

1. Radiography
    1. Multiple joint contractures
    2. Fusion of cervical vertebrae
    3. Scoliosis/lordosis
    4. Flexion contractures of fingers
    5. Rocker-bottom feet with vertical talus
2. Pathological evaluations of muscle and nerve tissue (Wee et al. 1990): no consistent abnormality
3. Genetic analysis of mutations in the genes associated with neuromuscular junction may unveil the pathogenetic cause of FADS/MPS, and the information acquired is helpful for genetic counseling and clinical management (Chen 2012)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive inheritance: 25%
        2. Autosomal dominant inheritance: not increased unless a parent is also affected
    2. Patient's offspring
        1. Autosomal recessive inheritance: not increased unless the spouse is a carrier
        2. Autosomal dominant inheritance: 50%
2. Prenatal diagnosis possible by ultrasonography usually for the family at risk
    1. Decreased fetal movement, oligohydramnios, and arthrogryposis (Bissinger and Koch 2014)
    2. Micrognathia
    3. Low-set ears
    4. Hypertelorism

5. Cystic hygroma colli (Fryns et al. 1984)
6. Rocker-bottom feet
7. Fetal akinesia deformation sequence associated with multiple pterygium syndrome may phenotypically overlap with the lethal type of multiple pterygium syndrome (please see the chapter of "► Lethal Multiple Pterygium Syndrome") (Chen 2012)
8. Prenatal diagnosis of fetal akinesia along with cystic hygroma, increased nuchal translucency, nuchal edema, hydrops fetalis, arthrogryposis, pterygia, and other structural abnormalities should include a differential diagnosis of neuromuscular junction disorders (Chen 2012)

3. Management (McCall and Budden 1992)
   1. Correction of the hand deformities
      1. Attention given to any deformities in the shoulder and elbow to maximize function of the limb before initiating correction of hand deformities
      2. Intensive physiotherapy and occupational therapy preferable to surgery for management of the upper extremity and hand anomalies
   2. Correction of mild hip flexion contractures of $<30^\circ$ due to inguinal webbing and crouched stance: responding well to active and passive stretching programs
   3. Correction of popliteal webbing
      1. Physiotherapy
      2. Traction
      3. Popliteal skin web Z-plasty with serial casting or with cable grafting the sciatic nerve (to achieve further knee extension and independent ambulation)
      4. Arthrodesis
      5. Amputation
      6. Excision of a significant fibrous band extending from the ischium to the calcaneus allows significant improvement in extension
   4. Correction of knee flexion contracture $<25^\circ$ without severe ambulatory limitations: conservative, consisting of a stretching program and night splints
   5. Correction of knee flexion contracture of $25–90^\circ$
      1. Physiotherapy followed by popliteal Z-plasty, fibrous band excision, and lengthening of all tense structures that are not neurovascular
      2. Post-operative serial casting
      3. Cable grafting or femoral shortening for neurovascular compromised cases
   6. Correction of knee flexion contracture of $>90^\circ$ which poses significant ambulatory difficulty
      1. Arthroses in extension
      2. Disarticulation
   7. Correction of vertical talus
      1. Children 6 years or younger: treated with soft tissue procedures and/or Grice subtalar arthrodesis
      2. Children over 6 years: undergo triple arthrodesis at age 12

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Fig. 1 (**a**–**f**) Two Honduran siblings (a 5-year-old girl (**a**–**c**) and a 9-year-old boy (**d**–**f**)) with multiple pterygium syndrome showing multiple pterygia involving neck, axillary, antecubital, popliteal, and intercrural areas. In addition, they had multiple joint contractures affecting hips, elbows, and interphalangeal, and popliteal joints; semi-crouching stance; and rocker-bottom feet due to vertical tali. Vigorous physiotherapy was performed initially for both upper and lower extremity contractures. Popliteal Z-plasty with release of the posterior capsule and excision of a fibrous band extending from the ischial tuberosity to the calcaneus resulted in better knee extension, but further correction was limited by tight neurovascular structures. Vertical tali were addressed surgically with triple arthrodeses on the boy at age 12, and soft tissue release combined with a Grice subtalar arthrodesis on the girl at age 6. Both children attained painless plantigrade feet at discharge

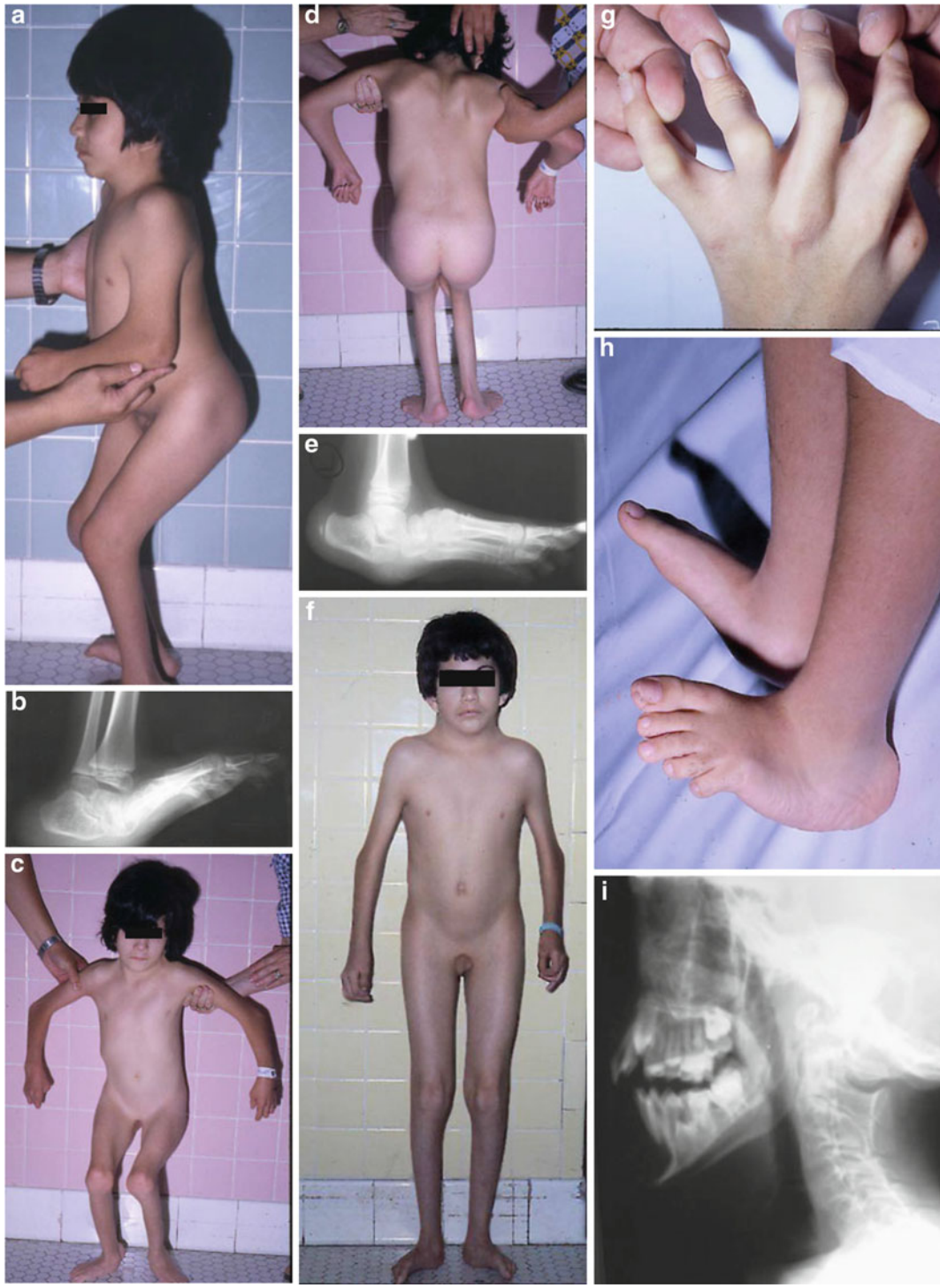

Fig. 2 (**a**–**i**) Three Nicaraguan siblings (parents are third cousins) with multiple pterygium syndrome showing similar features. Radiographs showed rocker-bottom feet with vertical talus (**b**, **e**) and the fusion of cervical vertebrae (**i**). Patient 1 (**a**) (a 7-year-old boy) had motionless facial appearance, cleft palate, multiple flexion contractures, and severe webbing at the antecubital and popliteal fossae, and interphalangeal regions. He also had severe foot

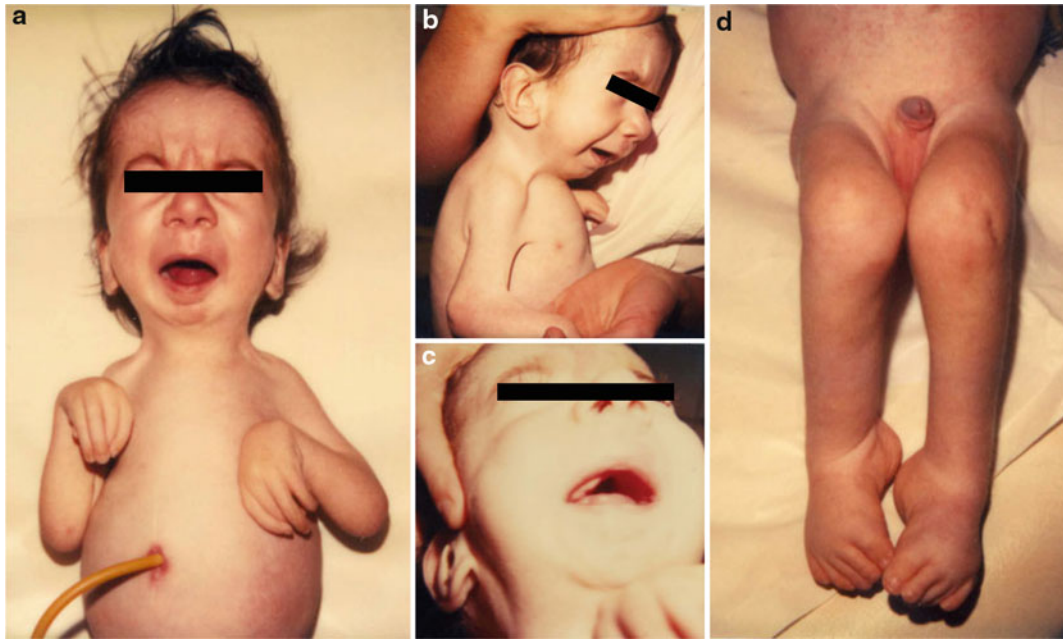

Fig. 3 (**a**–**d**) A boy with a sporadic case of multiple pterygium syndrome showing multiple pterygia, long philtrum, receding chin, cleft palate, low-set ears, and multiple contractures

Fig. 2 (continued) deformities with calcaneus heels and vertical talus (**b**). Patient 2 (**c**, **d**) (a 9-year-old girl) crawled at 4 years of age but had never walked. She was much more severely affected. Patient 3 (**f**–**i**) (an 11-year-old boy) walked with difficulty but much less severely affected than younger brother and sister. Digital deformities were addressed surgically with some recurrence of original deformities. Hip flexion contractures were addressed with an active stretching program and prone positioning, resulting in satisfactory resolution. Popliteal webbing was treated by either physiotherapy alone and/or operative procedures. Bilateral congenital tali were treated by either bilateral talectomy or arthodesis with partial talectomies

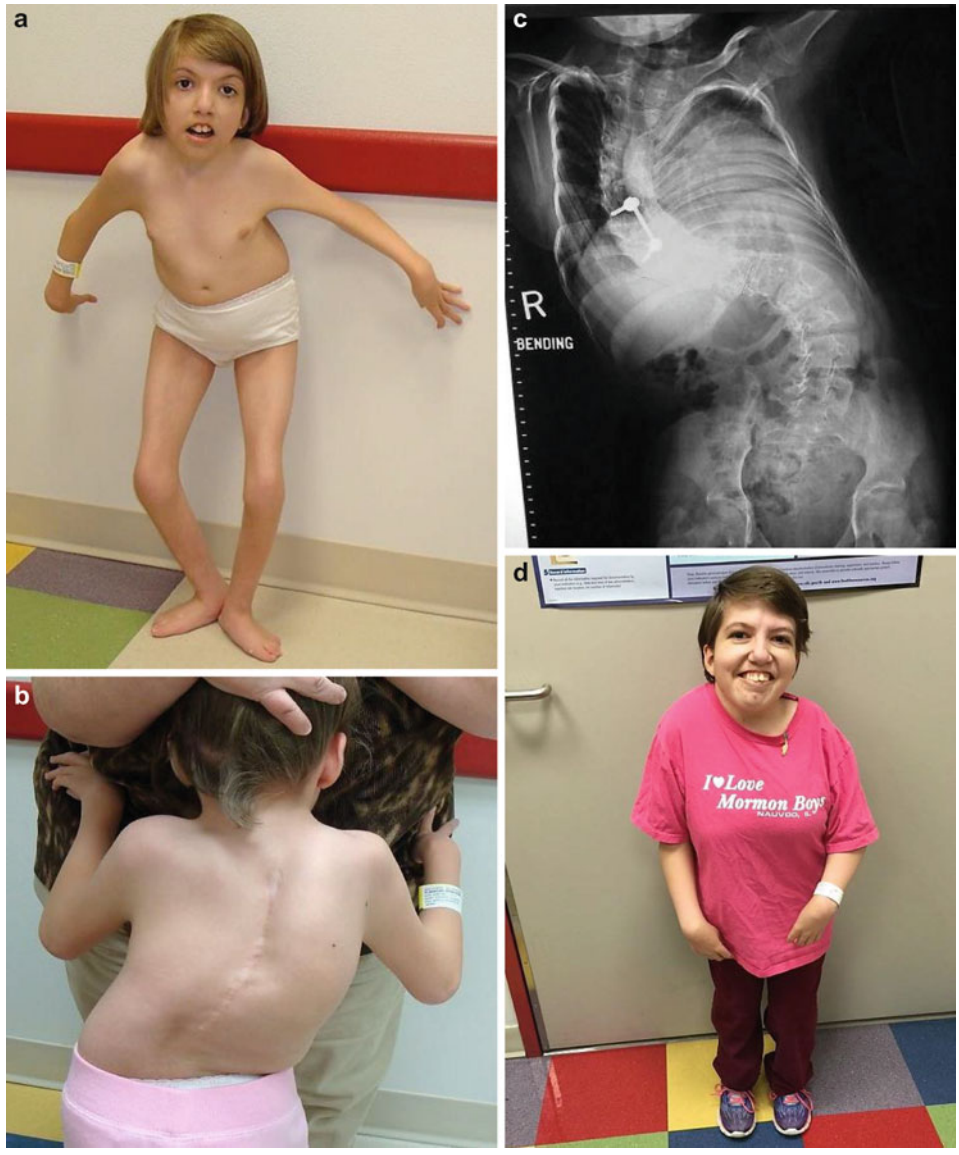

Fig. 4 (**a**–**c**) An 11-year-old girl with typical Escobar syndrome (**a**) with severe kyphoscoliosis (**b**), illustrated by radiograph (**c**). She was seen recently at 18 years of age (**d**)

Myotonic Dystrophy Type 1

Contents

Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy affecting adults with an estimated incidence of 1 in 8,000 among Caucasians (Brook et al. 1992).

Synonyms and Related Disorders

Myotonic dystrophy type 1 (dystrophia myotonica 1; Steinert disease); Myotonic dystrophy type 2 (dystrophia myotonica 2, proximal myotonic myopathy, proximal Ricker syndrome)

Genetics/Basic Defects

1. Inheritance: autosomal dominant with an anticipation phenomenon (Harley et al. 1993)
2. Molecular genetic perspective (Brook et al. 1992)
    1. Considerable variability of phenotype between affected individuals even within the same family
    2. An association of myotonic dystrophy with specific haplotypes in the population, indicating that most cases have resulted from a small number of genetic events
    3. Multisystemic nature of the phenotype
    4. An apparent increase in severity of symptoms and reduction in age at onset that is observed during transmission of the gene within families
3. Genetic defect: caused by an expanded CTG (cytosine-thymine-guanine) repeat in the dystrophia myotonica phosphokinase (*DMPK*) gene (Thornton 1999)
    1. Encodes for a serine-threonine protein kinase
    2. Mapped on chromosome 19q13.3
4. CTG triplet repeat (Gennarelli et al. 1996; Gharehbaghi-Schnell et al. 1998)
    1. Transcribed and located in the 3′ untranslated region of an mRNA that is expressed in tissues affected by myotonic dystrophy
    2. Repeat size
        1. Highly variable in the normal population (5–36 triplets)
        2. Undergoing expansion in myotonic dystrophy patients (50 to several thousand copies)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Expansion of at least 50 repeats in patients who are minimally affected
2. Expansion of up to several thousands of such repeat in more severely affected patients

3. Intergenerational instability (unstable CTG expansion at mitotic and meiotic levels with a bias toward length increase in the successive generations)
   1. Accounting for anticipation (the CTG repeat size increases in successive generations in parallel with increasing severity of the disease)
   2. Accounting for somatic instability and mosaicism (the CTG repeat size varies considerably among different tissues and organs with coexistence in the same subject of cell lines with different CTG repeats)
4. Genotype-phenotype correlations (Finsterer et al. 2001)
   1. Size of the CTG trinucleotide repeats generally correlated with the age of onset and clinical severity of the disease.
   2. Longer CTG repeat expansions correlate, in general, with an earlier age of onset and more severe disease.
   3. Relation of cardiac abnormalities and CTG repeat size in myotonic dystrophy.
      1. Increased cardiac involvement with increasing CTG repeat size in patients age 21–50.
      2. The number of CTG repeats needed to develop a reasonable cardiac involvement is higher in young patients than in older patients.
      4. Occasionally difficult to diagnose: the pleomorphic manifestations, due to a dynamic mutation in the length of CTG repeat, lead to difficulty in clinical identification of asymptomatic or mildly affected patients.

Clinical Features

1. Highly variable phenotypic expression and age of onset.
   1. The mildest form
      1. Seen in middle or old age (>50).
      2. Characterized by cataracts and baldness with little or no muscle involvement.
      3. CTG repeats: 50–100.
   2. The classic (juvenile or adult) form
      1. The more common form
      2. Usually becoming evident between the ages of 15 and 35 years
      3. CTG repeats: 100–1,000
      4. Phenotypically variable
      5. Characteristic clinical features
         1. Myotonia (sustained muscle contraction)
         2. Muscle weakness
         3. Cardiac arrhythmias
         4. Male balding (frontoparietal alopecia)
         5. Hypogonadism
         6. Psychocognitive dysfunction
         7. Glucose intolerance
   3. The childhood form
      1. Age at onset: 1–10
      2. CTG repeats: 50 $\geq$ 2,000
      3. Clinical manifestations
         1. Hypotonia
         2. Learning difficulties
         3. Limited motor skills
   4. The most severe (congenital) form (CMD) (Harper 1975a; Pearse and Howeler 1979; Hageman et al. 1993)
      1. Recognized at birth or in the neonatal period
      2. CTG length: >1,000
      3. Pregnancy
         1. Maternal polyhydramnios
         2. Reduced fetal movement
         3. Breech presentation
         4. Prematurity
      4. Associated with generalized muscular hypotonia
      5. Respiratory distress
         1. Aspiration pneumonia
         2. Recurrent bronchitis
         3. Hypoventilation
         4. Sleep apnea
         5. Bronchiectasis

6. Feeding difficulties
7. Dysphagia
8. Nasal regurgitation
9. Facial diplegia with a "tented-shaped" mouth
10. Delayed motor development
11. Joint deformities
12. Mental retardation
13. High neonatal mortality
14. Those survived invariably exhibiting the classical form of the disease in late childhood or adolescence
15. Almost all congenital cases are exclusively maternally transmitted (Harper 1975b; Dufour et al. 1997)
16. CTG repeats: 1,000–5,000
17. The phenomenon of anticipation often most strikingly manifested in a family producing a congenitally affected child

2. Neurologic manifestations.
    1. Myotonia (100%) (Miller 2008)
        1. Delayed relaxation of muscles after an initial voluntary contraction or percussion.
        2. Muscle stiffness that improves with repeated use of the muscle, the so-called warm-up phenomenon.
        3. On examination, myotonia may be apparent from the first handshake, presenting with inability to quickly release a handgrip (grip myotonia). This can also be appreciated by asking the patient to repeatedly grip and release the examiner's fingers. Another helpful maneuver is to ask the patient to repeatedly close the eyes tightly. After the first closure, there may be lag in opening the eyes, but this will improve with repeated efforts.
        4. Myotonia may be provoked by percussion of muscle, e.g., by percussion of the thenar eminence with a reflex hammer (percussion myotonia). The muscle stiffens, often adducting the thumb.
    2. Muscle weakness and atrophy
        1. Muscles most prominently affected
            1. Superficial facial muscles
            2. Levator palpebrae superioris
            3. Temporalis
            4. Sternocleidomastoids
            5. Distal muscles of forearm
            6. Dorsiflexors of foot
        2. Other muscles commonly affected
            1. Quadriceps
            2. Diaphragm and intercostals
            3. Intrinsic muscles of hand and feet
            4. Palate and pharyngeal muscles
            5. Tongue
            6. External ocular muscles
    3. Percussion myotonia and voluntary myotonia aggravated by cold
    4. Dysarthria
    5. Slow nasal indistinct speech
    6. Foot drop
    7. Step page gait
    8. Contractures of the Achilles tendon
    9. Diminished deep tendon reflexes
    10. Cognitive and behavioral abnormalities
3. Craniofacial appearance.
    1. Long thin face
    2. Flat, sagging, sad, and expressionless face
    3. Frontal bossing
    4. Hollow temple secondary to atrophy of temporalis
    5. Bilateral facial weakness (facial diplegia)
    6. Tented mouth
    7. Micrognathia
    8. Swan neck appearance (sternocleidomastoid muscle wasting)
4. Ocular findings.
    1. Cataracts (>85%)
    2. Ptosis
    3. Extraocular weakness
    4. Peripheral retinal changes
    5. Coloboma of retina/choroid
    6. Optic atrophy
    7. Blepharospasms
    8. Decreased ocular pressure
5. Cardiac involvement (76%).
    1. An integral part of myotonic dystrophy targeting
        1. Almost selectively the conduction system
        2. Less specifically the myocardium
    2. Electrocardiographic conduction abnormalities

1. Manifesting with or without ventricular tachyarrhythmias or bradyarrhythmias
2. The first-degree atrioventricular (AV) block (most common)
3. Intraventricular conduction abnormalities (premature ventricular complexes like couplets and triplets)
4. Atrial arrhythmias (atrial fibrillation and flutter)

3. A high incidence of sudden death
4. Possible cardiomyopathy
5. Congestive heart failure (6%)

6. Gastrointestinal findings.
   1. Achalasia
   2. Gastroparesis
   3. Constipation
   4. Megacolon
   5. Gallstones
7. Genitourinary findings.
   1. Dysuria
   2. Urinary retention
   3. Polycystic kidneys
   4. Testicular atrophy
8. Endocrine findings.
   1. Hypogonadism
   2. Male infertility secondary to testicular atrophy
   3. Hypothyroidism
   4. Goiter/hyperparathyroidism
   5. Multiple endocrine neoplasia type 2A (pheochromocytoma and amyloid-producing medullary thyroid carcinoma)
   6. Dysmenorrhea
   7. Postprandial hyperinsulinemia
9. Orthopedic problems.
   1. Arthrogryposis
   2. Talipes
   3. Kyphoscoliosis
10. Female patients.
    1. Decreased total reproductive rate
    2. Obstetrical complications (Dufour et al. 1997; Rudnik-Schöneborn and Zerres 2004)
       1. Higher rate of spontaneous abortions
       2. Ectopic pregnancies
       3. Abnormal placentation
       4. Urinary tract infections
       5. Premature delivery
       6. Hydrops
       7. In utero demise
       8. Difficulty in expulsion
       9. Hemorrhage during delivery
       10. Anesthetic accidents
11. Occasional accompanying benign or malignant neoplasms.
    1. Pilomatrixoma
    2. Parathyroid adenoma
    3. Small bowel carcinoma
    4. Neurofibromatosis
    5. Thymoma
    6. Pleomorphic adenoma of the parotid gland
    7. Pituitary adenoma
    8. Ovarian cancer
    9. Ovarian cyst
    10. Laryngeal cancer (Osanai et al. 2000)
12. Natural history (Mathieu et al. 1999).
    1. Usually progressive
    2. Usually leading to severe disability within 15–20 years
    3. Greatly reduced life expectancy, particularly in the case of an early disease onset and proximal muscle involvement
    4. The high mortality rate reflecting an increase in deaths due to
       1. Respiratory diseases
       2. Cardiovascular diseases
       3. Neoplasms
       4. Sudden deaths induced by cardiac arrhythmias
13. Consensus for the new nomenclatures (International Myotonic Dystrophy Consortium (IDMC) 2000): all multisystemic myotonic disorders including myotonic dystrophy, proximal myotonic myopathy, proximal myotonic dystrophy, and myotonic dystrophy type 2 are collectively called "myotonic dystrophies."
14. Differential diagnosis of myotonic disorders (Meola 2000; Miller 2008; Bird 2013).
    1. Myotonic dystrophy type 2 (DM2) (Day et al. 2003; Dalton et al. 2013)
       1. Clinical characteristics similar to those of DM1 but more benign: an adult-onset muscular dystrophy associated with

1. Myotonia (90% of affected individuals)
2. Muscle dysfunction: weakness, pain, and stiffness
3. Iridescent posterior subcapsular cataracts
4. Cardiac conduction defects or progressive dilated cardiomyopathy
5. Facial and respiratory muscles: relatively spared
6. Insulin-insensitive type 2 diabetes mellitus
7. Infertility of males (testicular failure)
8. Hypogammaglobulinemia
9. Absence of congenital form of DM2 comparable with DM1

2. Molecular basis of DM2: caused by a *CNBP* expansion of a cytosine-cytosine-thymine-guanine (CCTG) repeats in the zinc finger protein 9 (*ZNF9*) gene on chromosome 3q21 (Day et al. 1999; Liquori et al. 2001)

2. Myotonia congenita
   1. Myotonia: prominent clinical symptom.
      1. Stiffness especially when first starting an activity in severe classic myotonia
      2. Perform activities at a normal or advanced level, including competitive sports, once warmed up.
      3. Presents in early childhood, described by the parents as weakness and clumsiness in addition to or instead of stiffness.
      4. Despite the reported difficulties, affected children appear "athletic," with increased muscle bulk, presumably because of the sustained muscle activity.
      5. The myotonic symptoms often improve with age but do not completely disappear.
   2. Caused by a mutation in the gene encoding skeletal muscle chloride channel-1 (*CLCN1*) (Renner and Ptacek 2002). The chloride channel defect leads to an elevation of the resting membrane potential and thus a tendency toward repeated muscle contractions.
   3. Inheritance: either autosomal dominant (Thomsen myotonia congenita) or autosomal recessive (Becker myotonia congenita).
3. Schwartz-Jampel syndrome (chondrodystrophic myotonia)
   1. Caused by loss-of-function mutation in the *HSPG2* gene, which encodes perlecan, a heparan sulfate proteoglycans secreted into basement membranes (Nicole et al. 2000)
   2. Clinical manifestations
      1. Severe myotonia: one of the first symptoms present in childhood. No warm-up phenomenon for the myotonia
      2. Short stature
      3. Muscular hypertrophy
      4. Diffuse bone disease
      5. Ocular and facial abnormalities
      6. Joint contractures
4. Proximal myotonic myopathy: characterized by early involvement of proximal limb muscles with long-term survival more favorable than that of patients with myotonic dystrophy (Meola and Sansone 1996; Udd et al. 1997; Thornton 1999)

Diagnostic Investigations

1. Clinical examination to search muscle and nonmuscle manifestations (Meola 2000)
2. Lab: mildly elevated serum creatine kinase in affected individuals but normal in asymptomatic individuals
3. Electromyography to identify subclinical myotonia (Day et al. 1999)
4. Slit-lamp examination to detect characteristic posterior subcapsular cataracts (red and green iridescent opacities)
5. Muscle biopsy
   1. Diagnostic but not indicated or useful for routine clinical evaluation

2. Atrophic small type I fibers
3. An increase in central nuclei
4. Ringed fibers
5. Fibrosis and fatty infiltration

6. Light microscopy of hairs (Amorosi et al. 1999)
   1. Hair twisting
   2. Hair swelling
   3. Trichoschisis (presence of broken or split hairs)
7. Radiography
   1. Kyphosis of cervical spine
   2. Thin ribs observed in neonates suffering from myotonic dystrophy
8. Electrocardiogram abnormalities (60–70%) (Finsterer et al. 2001)
   1. ST abnormalities
   2. AV block I
   3. Increased QTC interval
   4. Tall R and/or S waves
   5. Left anterior hemiblock
   6. Supraventricular ectopic beats
   7. T wave abnormalities
   8. Pacemaker
   9. Missing R progression
   10. Abnormal U wave
   11. Left bundle branch block
9. Echocardiography (Finsterer et al. 2001)
   1. Septal thickness >11 mm
   2. Posterior wall thickness >11 mm
   3. Fractional shortening <30%
   4. E/A ratio >1
   5. Left ventricular end-diastolic diameter >57 mm
   6. Valve abnormalities
10. DNA testing for CTG repeat size: detects mutations in nearly 100% of affected individuals and is clinically available (Bird 2013)
    1. Gold standard for the diagnosis of DM1.
    2. CTG repeat size
       1. Normal alleles: 5–34 CTG repeats
       2. Premutation (mutable normal alleles): 35–49 CTG repeats. Individuals with premutation range are asymptomatic but their children are at increased risk of inheriting a larger repeat size and thus having symptoms (Martorell et al. 2001).
       3. Full penetrance alleles (associated with disease manifestations): >50 CTG repeats.
    3. Clinical testing by targeted mutation analysis
11. Presymptomatic carrier testing
    1. Leukocyte DNA analysis: provides an earlier opportunity to diagnose DM1 in family members at risk who are clinically asymptomatic
    2. Providing more aggressive monitoring program to detect
       1. Early cardiac conduction disturbance
       2. Cataract formation
       3. Respiratory difficulties
       4. At risk of developing anesthetic complications, especially delayed-onset apnea
12. Reporting guidelines for DM1 genetic testing according to Kamsteeg et al. (2012) with the influence of gender of the transmitting parent (Pavicevic et al. 2013)
    1. No expansion homozygous or heterozygous for allele in the size range of 5–35 repeats (normal alleles)
       1. DM1 diagnosis is excluded.
       2. When it concerns a fetus, it is not affected.
    2. A heterozygous expansion in the size range of 36–50 repeats (premutation alleles)
       1. DM1 diagnosis is excluded; when it concerns a fetus, it is not affected.
       2. Premutations may or may not expand in next generations.
       3. Transmission by female mostly results in stable inheritance or small changes in repeat copy number, while when transmitted by men, they are more prone to expand, even reaching the disease-associated mutation in a single generation, thus raising the risk of having affected child.
       4. Relatives (including offspring) of the counselee may be at risk of developing DM1 and should be offered counseling. An offer of repeat-length analysis to those relatives is warranted.

3. A heterozygous expansion in the size range of 51–150 repeats
    1. When symptoms are evident, the diagnosis of DM1 is confirmed. When symptoms of DM1 are not evident (asymptomatic family member or fetus), the individual is at risk of developing DM1, although individuals with a repeat expansion of this size may also remain symptomless.
    2. Counselees in the reproductive age are warranted. Smaller repeat expansion of this size range can be stably transmitted by female, while larger repeat expansion of this size range raising the risk of having a child with even congenital form of DM1.
    3. When transmitted by male repeat expansion of this size range almost invariably results in a large increase into the disease-associated mutation, raising the risk of having affected offspring.
    4. Relatives (including offspring) of the counselee may be at risk of developing DM1. Due to anticipation in DM1, offspring may be more severely affected. Relatives should therefore be offered counseling. An offer of repeat-length analysis to those relatives is warranted.
4. A heterozygous expansion in the size over 50 repeats
    1. When symptoms are evident, the diagnosis of DM1 is confirmed.
    2. When symptoms of DM1 are not evident (asymptomatic family member), the individual is at risk of developing DM1, although individuals with a repeat expansion of this size range may rarely remain symptomless.
    3. When it concerns a fetus, it is very likely to be affected and has a high risk to be more severely affected than the affected parent.
    4. Counselees in the reproductive age are warranted. Women are, especially, at risk of having children with the congenital form of DM1.
    5. Relatives (including offspring) of the counselee may be at risk of developing DM1. Due to anticipation in DM1, the offspring may be more severely affected. Therefore, relatives should be offered counseling. An offer of repeat-length analysis to those relatives is warranted.

Genetic Counseling

1. Recurrence risk (Koch et al. 1991; Magee et al. 2002; Bird 2013)
    1. General principle for genetic counseling
        1. A normal molecular analysis excludes the risk of developing or transmitting myotonic dystrophy in essentially all situations.
        2. For women who have had a child with congenital myotonic dystrophy, almost all subsequently affected pregnancies are likely to be severely affected.
        3. Clinically affected women, in general, have around a 30% chance that an affected child would have congenital or severe childhood myotonic dystrophy. The risk of a congenitally affected child is related to maternal repeat size.
        4. The risk for the healthy sib of a congenitally affected patient developing the disorder after childhood is low.
        5. For the adult healthy sib of an adult-onset case, the risk of carrying the mutation is also low (around 10%), with about half of this developing clinically significant disease.
    2. Patient's sib: recurrence risk depending on the genetic status of the parents
        1. Not increased if both parents are normal
        2. Fifty percent risk if one parent has an expanded *DMPK* allele
    3. Patient's offspring
        1. Offspring of an individual with an expanded allele (>34 CTG repeats) have a 50% chance of inheriting the mutant allele.

2. Disease-causing alleles may expand in length during gametogenesis, resulting in the transmission of longer CTG trinucleotide repeat alleles that may be associated with earlier onset and more severe disease than that observed in the parent.

2. Prenatal diagnosis (Geifman-Holtzman and Fay 1998)
   1. Prenatal ultrasonography in congenital myotonic dystrophy
      1. Polyhydramnios
      2. Talipes
      3. Decreased fetal movements reflecting the neuromuscular failure of swallowing and movement
   2. Prenatal diagnosis of CMD (Geifman-Holtzman and Fay 1998)
      1. Based on history and clinical symptoms during pregnancy in addition to the fetal and maternal CTG repeat sizes (>300 repeats and 600 repeats, respectively)
      2. Using 30–4,300 repeat size in amniocytes or villi to anticipate (to exclude as well as to identify severe risk in the fetus with CMD) (Redman et al. 1993)
   3. Prenatal diagnosis: possible by using mutation analysis (requires prior confirmation of the diagnosis of DM1 by molecular genetic testing of DMPK in an affected family member) and detection of the CTG repeat expansion with the *DMPK* gene in amniocytes or chorionic villi
   4. More challenging by using the CTG repeat test to determine whether the fetus is at risk for the severe form of myotonic dystrophy
      1. Generally, in amniocytes, congenital myotonic dystrophy is associated with CTG repeat expansion larger than that of the affected mother.
      2. CTG repeat size may change over time in CVS or amniocentesis, providing different CTG repeat size at different gestational ages.
   5. Counseling of pregnant patients affected with myotonic dystrophy
      1. An explanation of the risk associated with anticipation, which is the tendency toward large intergenerational expansion of the CTG repeat during maternal transmission, resulting in offspring with congenital myotonic dystrophy.
      2. CTG repeat number provides only an approximate guide to prognosis or to pregnancy outcome. Most cases with over 2,000 repeats will have congenital or severe childhood-onset disease; most individuals with 50–100 repeats will not have significant neuromuscular disease.
      3. An intergenerational contraction of the CTG fragment observed in approximately 7% of cases. Clinical anticipation was seen despite the reduced CTG repeat size, resulting in congenital myotonic dystrophy in the offspring.
      4. Prenatal diagnosis (PND) is available; however, the decision to terminate affected pregnancies is difficult as the extent of disability is hard to predict from the size of the expansion.
   6. Preimplantation genetic diagnosis (PGD) genetic analysis: available and is carried out before the establishment of pregnancy (Kakourou et al. 2008)

3. Management
   1. No specific treatment available for the progressive weakness that is responsible for most of the disability in patients with myotonic dystrophy.
   2. Patients with myotonic dystrophy usually do not seek treatment for the myotonia per se, or they are not compliant with medication regimens to treat it, either because myotonia is much milder than their other symptoms or because they avoid medical treatment as part of their personality (Conravey and Santana-Gould 2010).
   3. To alleviate myotonia by drugs.
      1. Quinine, quinidine, dilantin, carbamazepine, procainamide, diamox to alleviate myopia not universally successful
      2. Encouraging results with mexiletine (Logigian et al. 2010) and tocainide
   4. Avoid cold which may induce myotonia.
   5. Prescription for orthoses, wheelchairs, or other assisted devices.

6. Treat cataracts, diabetes mellitus, hypothyroidism, and sleep apnea.
7. Avoid surgery and anesthesia (sensitive to narcotics and sedatives) (Mathieu et al. 1997).

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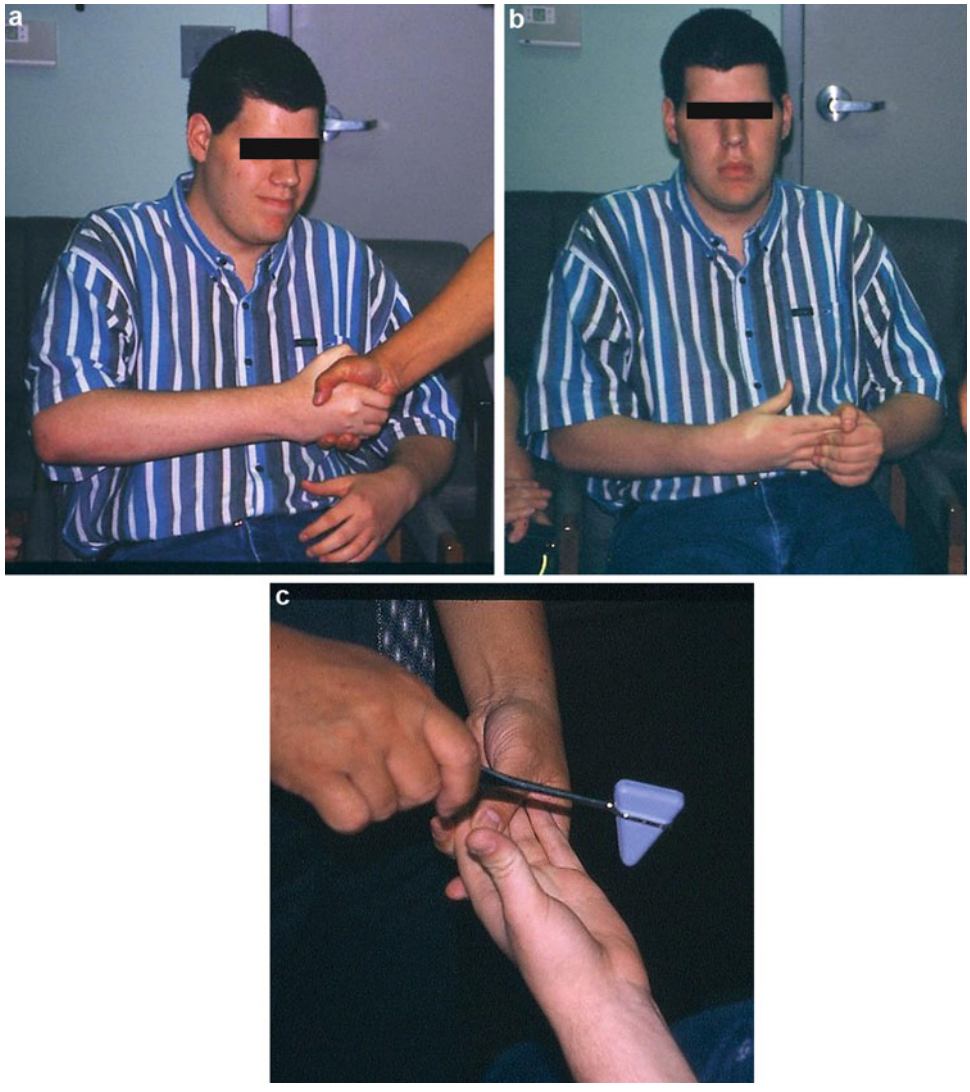

Fig. 1 An adult (**a**) with myotonic dystrophy showing hard to release after shaking hand (**b**) and thenar myotonia after tapping (**c**)

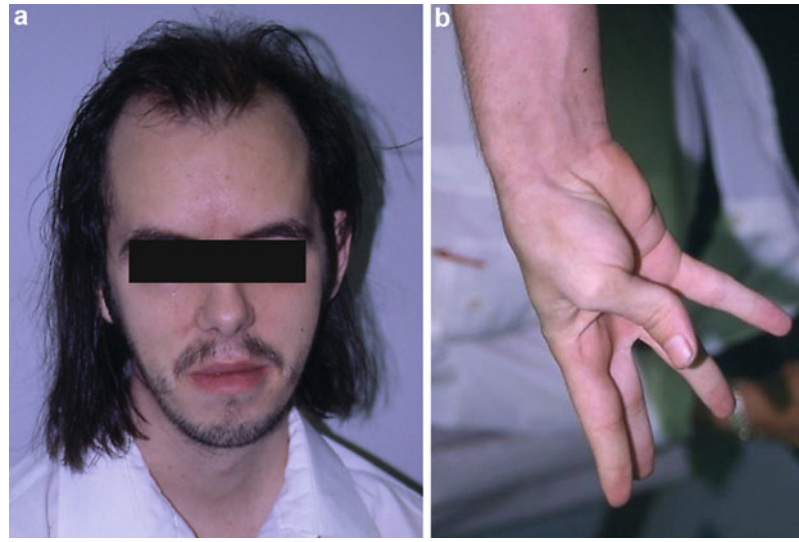

Fig. 2 An adult with myotonia dystrophy showing long thin face with frontal bossing (**a**) and thenar myotonia after tapping (**b**)

Fig. 3 A 23-year-old mother and her 21-month-old daughter with myotonia congenita type 1 (**a**). The mother has myotonia (hard to relax after shaking hand) (**b**), thenar myotonia after tapping (**c**), and absent tendon reflexes. The pregnancy was complicated by polyhydramnios, feeble fetal movement, and breech presentation. After scheduled cesarean section, the baby breathed only once and needed intubation for 5 days. She was very floppy and just started to walk about 2 months prior to the clinic visit. She chokes easily and does not chew and talk. On physical examination, in addition to hypotonia, there is a long and sagging face with marked tented mouth (**a**). Molecular genetic testing of the daughter showed CTG repeats of 1,050

Möbius Syndrome

Contents

Möbius syndrome (MBS) (Möbius 1988) is a rare congenital disorder characterized by complete or partial facial diplegia accompanied by other cranial nerve palsies and musculoskeletal anomalies.

Synonyms and Related Disorders

Möbius sequence; Poland anomaly; Poland syndrome

Genetics/Basic Defects

1. Multifactorial etiology
    1. The term "Möbius sequence" represents a pattern of multiple anomalies due to multiple etiologies, compared with the designation "syndrome" which implies a single cause.
2. It is usually a sporadic occurrence, but familial descriptions have been rarely reported (Briegel 2006; Graziadio et al. 2010).
3. Genetic heterogeneity (Legum et al. 1981)
    1. Familial cases usually without associated anomalies
    2. Low incidence of familial cases with associated anomalies such as limb defects and mental retardation
    3. Autosomal dominant inheritance (Verzijl et al. 1999)
        1. Autosomal dominant Möbius syndrome has been linked to markers on 3q21–q22 in a large Dutch family (Kremer et al. 1996).
        2. A second gene for autosomal dominant Möbius syndrome is localized to chromosome 10q in a second large Dutch family.
    4. Autosomal recessive inheritance (Criado and Aytes 1999)
    5. X-linked recessive inheritance
4. Four genetic loci for MBS have been described to date (Van Der Zwaag et al. 2002).
    1. MBS1 on chromosome 13q12.2–q13 (Ziter et al. 1977; Slee et al. 1991), based on the following observations:
        1. A reciprocal translocation of 13q12.2–q13 cosegregating with the disease in a three-generation MBS family

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2. An MBS patient with a deletion of chromosome 13q12.2
2. MBS2 on chromosome 3q21–q22 (Kremer et al. 1996)
3. MBS3 on chromosome 10q21.3–22.1 (Verzijl et al. 1999)
4. MBS4 on chromosome 1p22 (Donahue et al. 1993; Nishikawa et al. 1997), based on
   1. A t(1;11)(p22;p13) in a patient with Möbius syndrome
   2. A t(1;2)(p22.3;q21.1) in a patient with Möbius-like syndrome
5. *HOXA1* mutations are not a common cause of sporadic Möbius syndrome in the general population (Rankin et al. 2010).
   1. The *HOXA1*-related syndromes result from autosomal recessive truncating mutations in the homeobox transcription factor, *HOXA1*.
   2. Limited horizontal gaze and sensorineural deafness are the most common features.
   3. Affected individuals can also have facial weakness, mental retardation, autism, motor disabilities, central hypoventilation, and carotid artery and/or conotruncal heart defects.
   4. Möbius syndrome is also phenotypically heterogeneous, with minimal diagnostic criteria of nonprogressive facial weakness and impaired ocular abduction; mental retardation, autism, motor disabilities, additional eye movement restrictions, hearing loss, hypoventilation, and craniofacial, lingual, and limb abnormalities also occur.
6. *PLXND1* and *REV3L* mutations (Tomas-Rocas et al. 2015)
   1. De novo mutations in *PLXND1* and *REV3L* cause Möbius syndrome.
   2. PLXND1 and REV3L represent totally unrelated pathways involved in hindbrain development: neural migration and DNA translesion synthesis, essential for the replication of endogenously damaged DNA, respectively.
7. Chromosome abnormalities (Verzijl et al. 1999)
8. Ischemia: vascular disruption in the subclavian artery territory (Bavinck and Weaver 1986; Bouwes-Bavinck and Weaver 1986; Charles et al. 1993)
9. Teratogens
   1. Thalidomide
   2. Alcohol
   3. Benzodiazepines
   4. Cocaine
   5. Ergotamine
   6. Infections
   7. Hyperthermia
   8. Trauma
   9. Misoprostol (a synthetic prostaglandin analogue used in the therapy of upper gastrointestinal ulceration or self-administered by the mothers in Brazil as an abortifacient) (Blanchard et al. 1998; Pastuszak et al. 1998; Strömland et al. 2002; Guedes 2014)

2. Pathogenesis (Van Der Zwaag et al. 2002; Graziadio et al. 2010)
   1. A primary metameric defect in the brain stem nuclei in the region of the tegmentum
   2. An ischemic process resulting from an interruption of the vascular supply of the brain stem (Ghabrial et al. 1998)
   3. Disruption of the developing vascular system, affecting vasculogenesis (in situ differentiation of endothelial cells) and/or angiogenesis (sprouting of new capillaries from preexisting ones) (Bouwes-Bavinck and Weaver 1986; Abramson et al. 1998)
3. An etiopathologic classification (Towfighi et al. 1979; Pedraza et al. 2000)
   1. Type or group I (central lesion in the brain stem nuclei due to congenital origin)
   2. Type or group II (primary peripheral nerve involvement)
   3. Type or group III (central lesion in the brain stem nuclei due to an anoxic-infectious cause)
   4. Type or group IV (without CNS or cranial nerve lesions who had wasting of

skeletal muscle tissue due to myopathic cause)

Clinical Features

1. Congenital onset
2. Complete or partial facial diplegia (essential for the diagnosis of Möbius syndrome), often accompanied by other cranial nerve palsies (Palmer 2014)
    1. Signs and symptoms
        1. Incomplete eyelid closure during sleep
        2. Drooling
        3. Difficulty in sucking
        4. Inability to smile
        5. Lack of facial movement when crying (masklike facies)
        6. Asymmetry of the angles of the mouth
        7. Indistinct speech secondary to the inability to close the lips leading to labial sounds
    2. Involved cranial nerves (Kumar 1990)
        1. Facial nerve (VII) palsy (all cases), resulting in masklike facies and flattened facial expression
        2. Abducens nerve (VI) palsy (75%), less commonly oculomotor (III) and trochlear (IV) nerve palsies, resulting in marked internal strabismus, lateral gaze paralysis, and ophthalmoplegia
        3. Hypoglossal nerve (XII) palsy (25%), leading to paralysis, hypoplasia, and atrophy of the tongue
        4. Paresis of cranial nerves V (trigeminal), IX (glossopharyngeal), and X (vagus), leading to bulbar weakness (swallowing and speech difficulties due to velopharyngeal insufficiency)
3. Involvement of cerebellum, hypothalamus, and pituitary gland
4. Oculofacial abnormalities (Strömland et al. 2002)
    1. Masklike facial appearance: may create profound difficulties in social interactions with other people, especially strangers who are unfamiliar with the syndrome
    2. Epicanthal folds
    3. Ptosis
    4. Refractive error (Cronemberger et al. 2001)
        1. Astigmatism
        2. Lagophthalmos
        3. Amyopia
    5. Strabismus
    6. Nystagmus
    7. Micrognathia
    8. Tongue abnormalities
        1. A common anomaly
        2. A small asymmetric tongue with irregular atrophic areas: characteristic of Möbius syndrome
        3. Impaired motility and fasciculations
    9. At risk for caries and periodontal disease
    10. Impaired speech (Meyerson and Foushee 1978)
        1. A severe and disabling condition
        2. Factors affecting speech development
            1. Cognitive and language skills
            2. Hearing
            3. Communication ability
            4. Orofacial anatomy
            5. Oral motor function
        3. Dysarthria caused by cranial nerve dysfunction, worsened by orofacial anomalies, mental retardation, and autism
5. Frequent occurrence of limb malformations
    1. Reduction malformation of limbs
    2. Hypoplasia to aplasia of digits
    3. Brachydactyly
    4. Syndactyly
    5. Ectrodactyly
    6. Talipes deformities (clubfoot)
    7. Clinodactyly
    8. Polydactyly
    9. Joint contractures
6. Other musculoskeletal features
    1. Rib defects
    2. Klippel-Feil anomaly
    3. Aplasia of muscles
7. Mental retardation (10%)
8. Autistic behavior (30–40%) (Gillberg and Steffenburg 1989; Johansson et al. 2001)
9. Association with other anomalies or syndromes

1. Poland anomaly/syndrome (Sugarman and Stark 1973; Gadoth et al. 1979)
    1. Hypoplasia/aplasia of pectoralis major muscle.
    2. Ipsilateral symbrachydactyly.
    3. Generally unilateral.
    4. Associated with mammary hypoplasia of the same side.
    5. Poland syndrome, Möbius syndrome, and Möbius-Poland syndrome may be a spectrum of the same condition.
2. Hypoglossia-hypodactyly
3. Arthrogryposis multiplex congenita
4. Dextrocardia
5. Robin syndrome
6. Carey-Fineman-Ziter syndrome (congenital nonprogressive myopathy with Möbius and Robin sequence)
7. Kallmann syndrome (association with anosmia and hypogonadotropic hypogonadism)

10. Several similar syndromes (Strömland et al. 2002)
    1. Oromandibular limb hypogenesis syndrome
        1. Characteristic features
            1. Micrognathia
            2. Cranial nerve palsies
            3. Limb anomalies
            4. Sometimes combined with aplasia of the pectoral muscle (Poland anomaly)
        2. Entities included:
            1. Möbius syndrome
            2. Hanhart syndrome
            3. Hypoglossia-hypodactyly (aglossia/adactyly)
            4. Glossopalatine ankylosis
    2. Terminal transverse defects with orofacial malformations
        1. Orofacial features
            1. Micrognathia
            2. Cleft palate
            3. Tongue anomalies
            4. Ear anomalies
            5. Dental anomalies
        2. Limb malformations
            1. Syndactyly
            2. Clubfeet
            3. Toe deformities
            4. Symbrachydactyly
            5. Absent digits (ectrodactyly)
            6. Amputation-type defects of the limbs

Diagnostic Investigations

1. CT of the head: normal in most patients (Beerbower et al. 1986; Kuhn et al. 1990; Pedraza et al. 2000).
    1. Medial deviation of the eyes
    2. Hypoplastic or dysplastic brain stem
    3. Hypoplastic cerebellum consistent with Dandy-Walker variant malformation
    4. Bilateral calcifications adjacent to the fourth ventricle floor at the level of the VIth cranial nerve nuclei
2. Autopsies in patients with normal CT studies (D'Cruz et al. 1993).
    1. Focal necrosis and calcifications
    2. Hypoplasia to agenesis of the respective cranial nerve nuclei
3. MRI of the brain.
    1. Calcification in the pons within the abducens nuclei
    2. Hypoplasia of the brain stem
    3. Hypoplasia of the cerebellum
4. Neurophysiological studies may be helpful in locating the site of the lesion.
    1. Abnormal nerve conduction studies
    2. Electromyography (EMG) of facial muscles (Jaradeh et al. 1996):
        1. Reveals multifocal chronic neurogenic changes
        2. Indicates a brain stem process predominantly affecting the facial nuclei and their internuclear connections rather than a supranuclear or muscular site of involvement

3. Abnormal brain stem evoked potential
5. Array-CGH analysis of familial Poland anomaly identified three maternally inherited copy number variants in three patients (1p31.1, Xp11.22, and 16q23.1 duplication). These results do not allow any conclusive remarks on the probable molecular basis of the disease, mainly due to the small number of tested families (Baban et al. 2012).

Genetic Counseling

1. Recurrence risk
   1. Lower recurrence risk (2%) for Möbius syndrome with congenital sixth and seventh nerve paralysis with skeletal defects (MacDermot et al. 1991)
   2. Higher recurrence risk (25–30%) for Möbius syndrome with isolated facial palsy, deafness, ophthalmoplegia, and digital contractures without skeletal defects (MacDermot et al. 1991)
   3. Autosomal recessive inheritance
      1. Patient's sib: 25%
      2. Patient's offspring: not increased unless the spouse is a carrier
   4. Autosomal dominant inheritance
      1. Patient's sib: 50% if a parent is affected; otherwise not increased
      2. Patient's offspring: 50%
   5. X-linked recessive inheritance
      1. Patient's sib: 50% affected in the brothers if the mother is a carrier; otherwise not increased
      2. Patient's offspring: 50% carrier risk in the daughters
2. Prenatal diagnosis possible in the Möbius-Poland spectrum (Sherer and Spafford 1994)
3. Management
   1. Supportive care
   2. Intervention programs
      1. Physical therapy useful for congenital orthopedic problems or postoperative orthopedic intervention
      2. Occupational therapy to help activities of daily living, especially in patients with absent hands or digits
      3. Speech therapy for patients affected by severe facial nerve paralysis or lower cranial nerve deficit
   3. Dental hygiene
   4. Treat corneal ulcerations or abrasions secondary to exposure keratitis and conjunctivitis secondary to incomplete eyelid closure
   5. Splints and prostheses for congenital limb anomalies
   6. Surgical care
      1. Clubfoot.
      2. Tracheotomy to support the airway and permit tracheobronchial clearing when airway functions are compromised.
      3. Feeding gastrostomy tube required in some cases.
      4. Ocular surgical procedures in some cases.
      5. Combinations of microsurgical procedures and aesthetic techniques are being used to restore some movement to the expressionless face of these patients by nerve and muscle transplantation (Terzis and Noah 2003).

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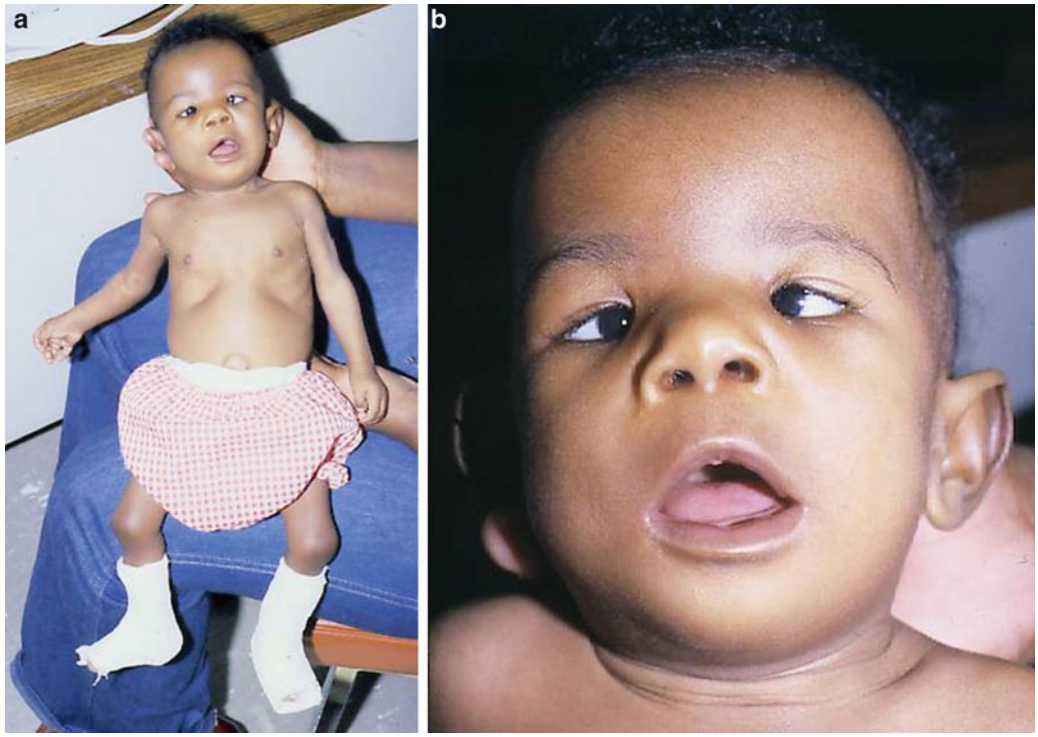

Fig. 1 (**a**, **b**) A child with Möbius syndrome showing masklike facies, epicanthal folds, strabismus, and facial palsy (**a**, **b**)

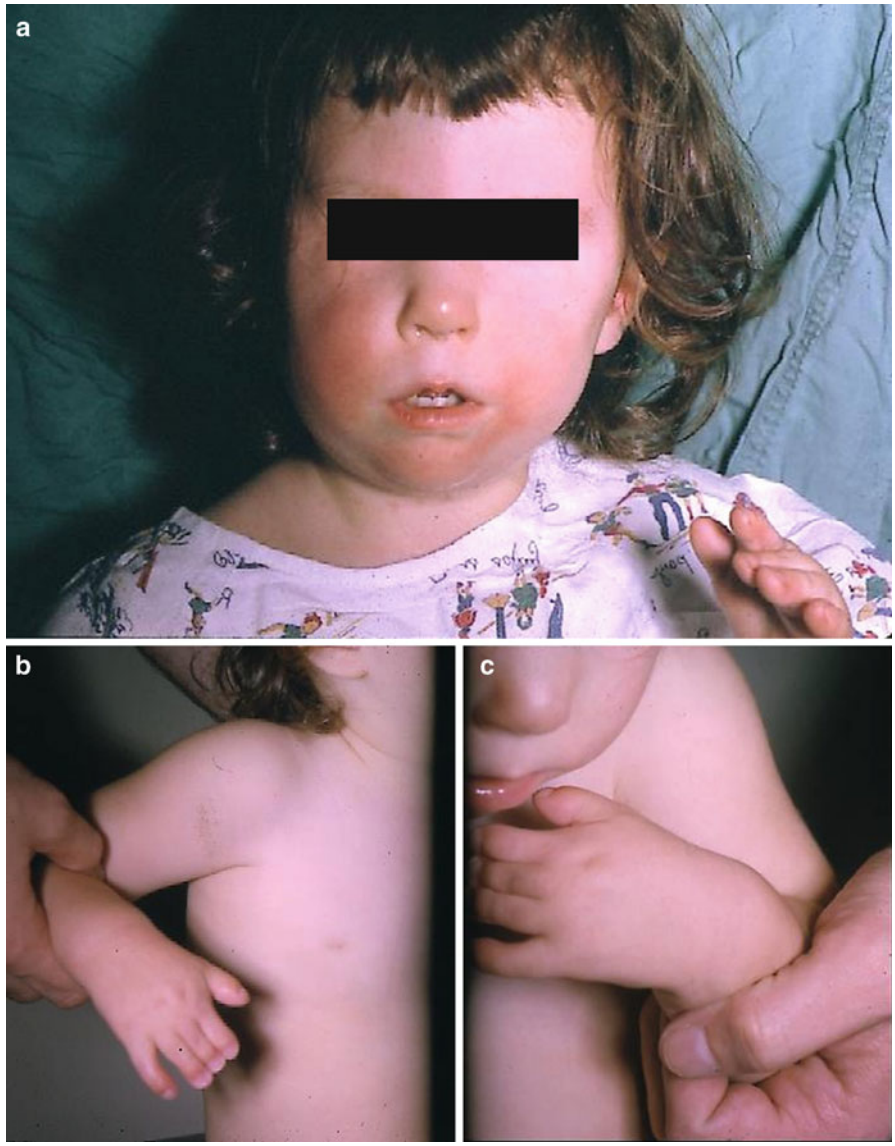

Fig. 2 (**a**–**c**) A child with Möbius syndrome showing masklike facies, epicanthal folds, strabismus, and limb defect

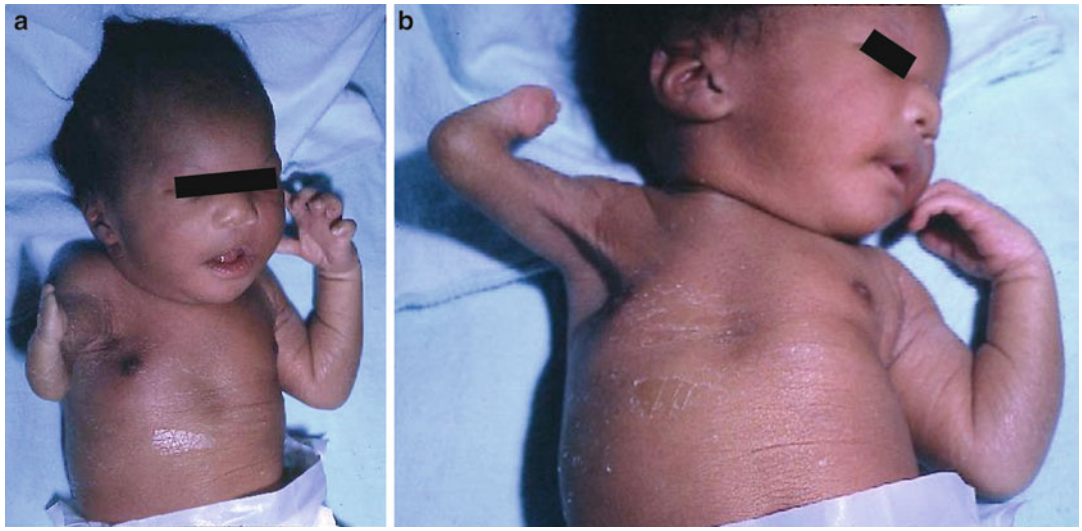

Fig. 3 (**a**, **b**) A child with Möbius-Poland syndrome (**a**, **b**) showing masklike facies, strabismus, and ptosis, associated with right arm defect and absence of right pectoralis major muscle

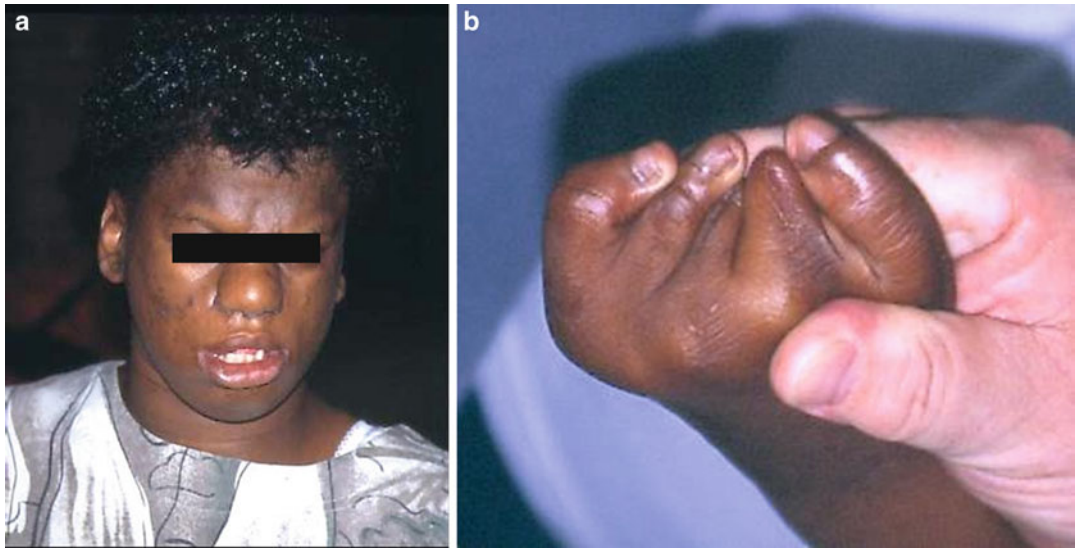

Fig. 4 (**a**, **b**) An adult with Möbius syndrome showing masklike facies, ptosis, strabismus (**a**), and digital anomaly (**b**)

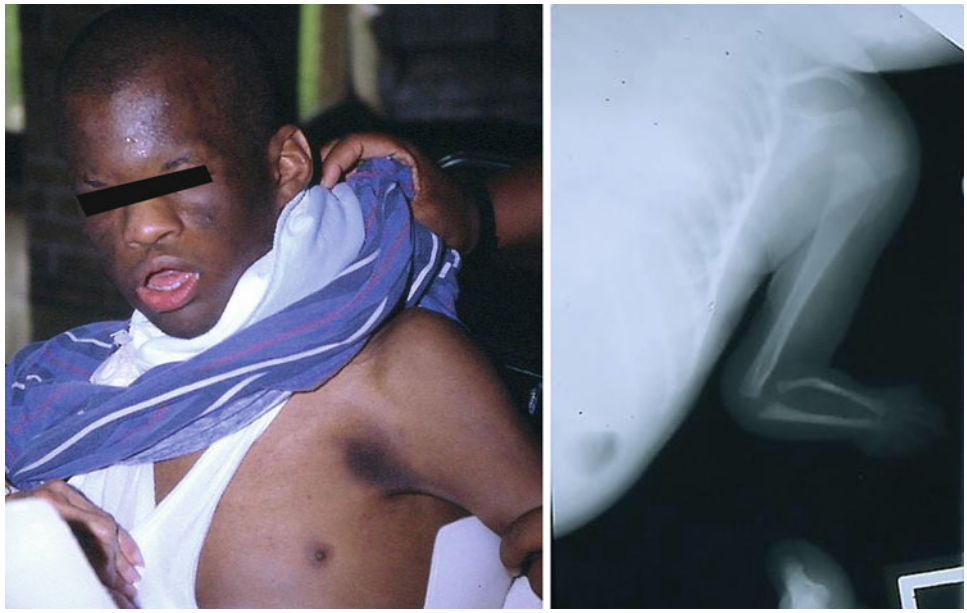

Fig. 5 (**a**, **b**) An adult with Möbius-Poland syndrome showing masklike facies, ptosis, absence of left pectoralis major muscle, and limb defect (**a**), which were illustrated in the patient's earlier radiograph (**b**)

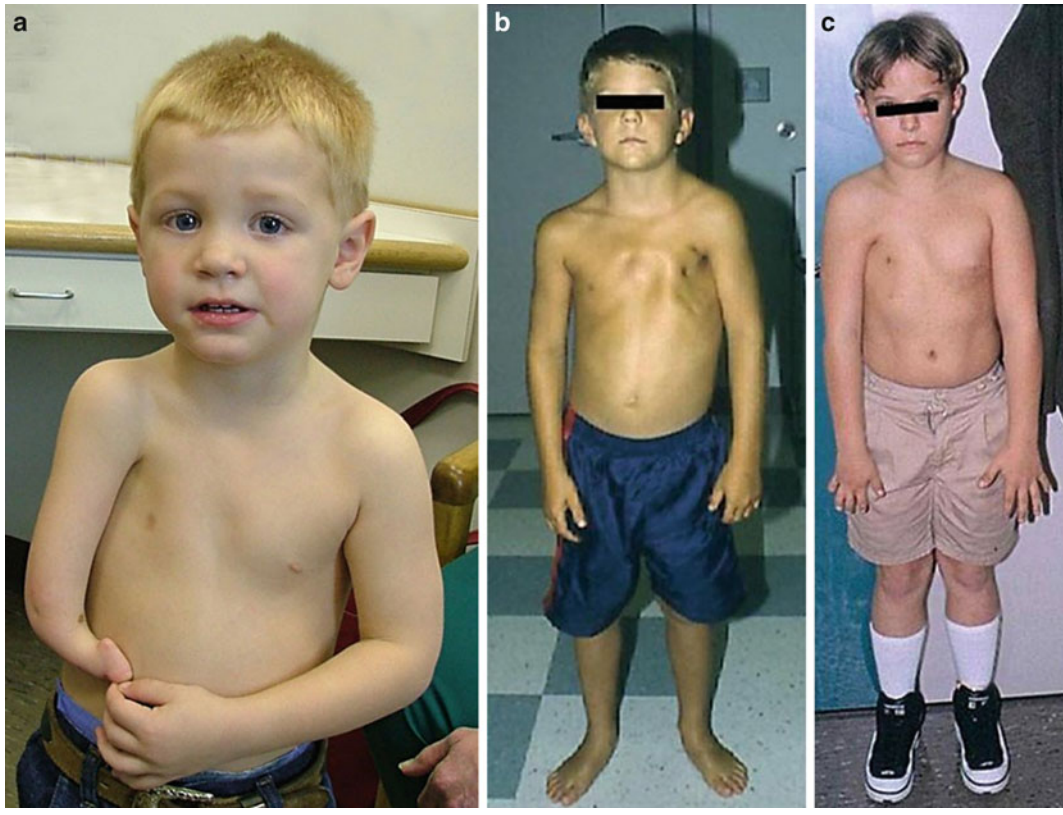

Fig. 6 (**a**–**c**) Three children (**a**–**c**) with Poland anomaly showing unilateral absence of pectoralis major muscle associated with ipsilateral limb defect

Nager Acrofacial Dysostosis

Contents

Nager acrofacial dysostosis, described by Nager and deRenier in 1948, is a mandibulofacial dysostosis associated with preaxial limb abnormalities. It is a very rare disorder with <100 reported cases by 2009 (Ansart-Franquet et al. 2009).

Synonyms and Related Disorders

Nager syndrome; Preaxial acrofacial dysostosis

Genetics/Basic Defects

1. Heterogeneous causes
    1. Most cases are sporadic
    2. Autosomal recessive inheritance (Chemke et al. 1988; Kennedy and Teebi 2004)
    3. Autosomal dominant inheritance (Hall 1989; Aylsworth et al. 1991; McDonald and Gorski 1993)
2. Del(1q12-q21.1 or q21.3), which encompasses *SF3B4*, was observed in a child characteristic of Nager syndrome (Waggoner et al. 1999)
3. Whole-exome sequencing recently identified mutations in the *SF3B4* gene as causative mutations underlying the etiology of Nager syndrome (Bernier et al. 2012)
4. Whole-exome sequencing study confirmed the *SF3B4* gene is mutated in about 50% of patients with clinical diagnosis of Nager syndrome (Czeschik et al. 2013)

Clinical Features

1. Craniofacial features
    1. Downward slanting of the palpebral fissures
    2. Midface retrusion (malar hypoplasia)
    3. Absent medial lower lid eyelashes
    4. Retromicrognathia
    5. Glossoptosis
    6. Cleft palate
    7. External ear anomalies including microtia and atresia of external auditory canal, leading to bilateral conductive hearing loss
    8. Intelligence: typically normal
    9. Speech difficulties and upper airway obstruction: common secondary to otologic and oral/mandibular abnormalities
2. Preaxial limb defects
    1. Usually affecting radial elements of the forelimbs
        1. Hypoplasia or agenesis of the radius

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Proximal radioulnar synostosis
3. Hypoplasia or agenesis of the thumbs
4. Duplication of thumbs
5. Triphalangeal thumbs
6. Symphalangism

2. Phocomelia of the upper limbs
3. Occasional lower-limb defects (Le Merrer et al. 1989)

3. Skeletal anomalies and other malformations (McDonald and Gorski 1993)
   1. Skeletal anomalies
      1. Thoracolumbar scoliosis
      2. Cervical vertebral and rib anomalies
   2. Genitourinary abnormalities
      1. Vesicoureteral reflux
      2. Unilateral renal agenesis
      3. External genital hypoplasia
      4. Duplicated ureter
      5. Bicornuate uterus
   3. Gastrointestinal abnormalities
      1. Gastroschisis
      2. Hirschsprung disease
   4. Cardiovascular malformations
      1. Tetralogy of Fallot
      2. Ventricular septal defect
      3. Subvalvular muscular obstruction of the right ventricular outflow tract
   5. Central nervous system anomalies
   6. Microcephaly
   7. Aqueduct stenosis resulting in hydrocephalus
   8. Polymicrogyria
4. Differential diagnosis:
   1. Treacher Collins syndrome: Please see the chapter on ▶ "Treacher-Collins Syndrome"
   2. At least 18 different forms of acrofacial dysostoses have been described (Wieczorek 2013)
   3. Miller syndrome(Trainor and Andrews 2013)
      1. The presentation of anterior forelimb anomalies as opposed to posterior forelimb anomalies and the general lack of hind limb malformations distinguishes Nager syndrome from Miller syndrome, another rare acrofacial disorder
      2. Craniofacial anomalies similar to Treacher Collins syndrome
         1. Micrognathia
         2. Orofacial clefts
         3. Malar hypoplasia
         4. Aplasia of the medial lower lid eyelashes
         5. Coloboma of the lower eyelid
         6. Cup-shaped ears
      3. Postaxial limb deformities (Genee 1969; Wiedemann 1973; Miller et al. 1979)
         1. Apparent absence of either the fifth or both the fourth and fifth rays of the hands and feet
         2. With or without ulnar and fibular hypoplasia
      4. Molecular basis was identified via
         1. Whole-exome sequencing shown to correlate with mutations in dihydroorotate dehydrogenase (*DHODH*) (Ng et al. 2010)
         2. Recently additional biallelic mutations in *DHODH* were identified in four unrelated families with typical clinical features of Miller syndrome (Rainger et al. 2012)

Diagnostic Investigations

1. Radiography
   1. Craniofacial anomalies
      1. Malar hypoplasia
      2. Retro/micrognathia
      3. External ear anomalies
   2. Preaxial limb anomalies: variable often asymmetric
      1. Hypoplasia or aplasia of the thumb
      2. Duplicated thumb
      3. Symphalangism
      4. Radial hypoplasia or aplasia often associated with proximal radioulnar synostosis
      5. Lower-limb involvement usually mild and rare: phocomelia, talipes equinovarus, metatarsus varus, absent tibia/fibula, and toe abnormalities
   3. Abnormalities of the axial skeleton
      1. Thoracolumbar scoliosis
      2. Cervical vertebral and rib anomalies

2. Facial CT
   1. Micrognathia
   2. Mandibular hypoplasia
   3. Absence or near-complete absence of zygomatic arch
   4. Atresia of bony external auditory canals
3. Molecular genetic analysis of *SF3B4*
   1. Deletion/duplication analysis
   2. Sequence analysis of the entire coding region

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal recessive: 25%
      2. Autosomal dominant: recurrence risk not increased unless one of the parents is affected
   2. Patient's offspring
      1. Autosomal recessive: recurrence risk not increased unless the spouse is a carrier or affected
      2. Autosomal dominant: a 50% risk
2. Prenatal diagnosis
   1. Ultrasonography (Couyoumjian et al. 2008)
      1. Marked micrognathia
      2. Abnormal ears: low set and posteriorly rotated
      3. Short humerus with pronounced shortening of radius and ulna
      4. Abnormally appearing thumb
   2. Molecular genetic analysis: Prenatal testing for pregnancies at increased risk is possible if the family specific disease-causing mutation is known
3. Management (Opitz et al. 2000)
   1. Tracheostomy or mandibular advancement for severe airway obstruction shortly after birth
   2. Primary velopharyngoplasty
   3. Bronchoscopic intubation
   4. Surgical cleft repair
   5. Early correction of micrognathia by surgical distraction of the mandible, a means of improving facial esthetics relatively early in order to enhance the patient's chances regarding his psychosocial quality of life
   6. Mandibular elongation and remodeling by distraction
   7. Speech and language management must be focused on receptive and expressive language skills and linguistic conceptualization, correct phonetic placement, and the modification of hypernasality and nasal emission
   8. Multidisciplinary team approach to speech and hearing problems
   9. Amplification through the use of a properly fitted hearing aid, preferred therapy for conductive and mixed hearing loss (Herrmann et al. 2005)

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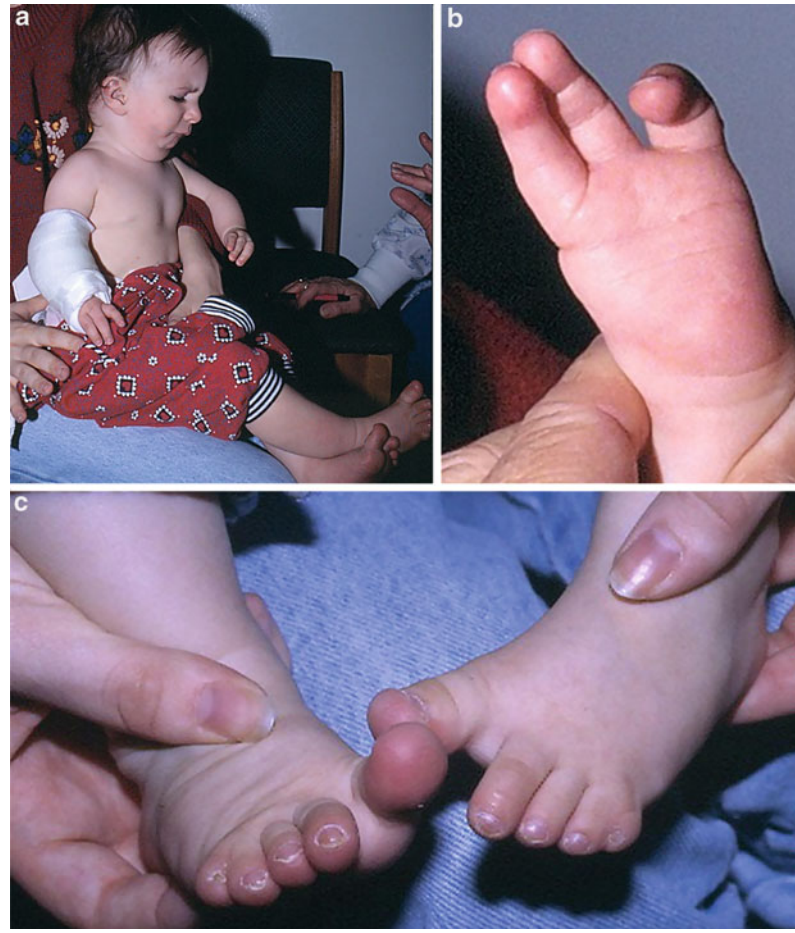

Fig. 1 (**a**–**c**) A 13-month-old girl was evaluated for Nager acrofacial dysostosis. Facial features (**a**) were characterized by antimongoloid slant of the palpebral fissures, ptosis of lower lids, hypoplasia of lower lid eyelashes, malar hypoplasia, and mandibular hypoplasia with severe microretrognathia. She also had multiple limb abnormalities including short forearms, radioulnar synostosis, limited elbow extension, three fingers on both hands with absent thumbs and presence of transverse palmar crease on the left (**a**, **b**), and partial syndactyly of the 5th toes (**c**)

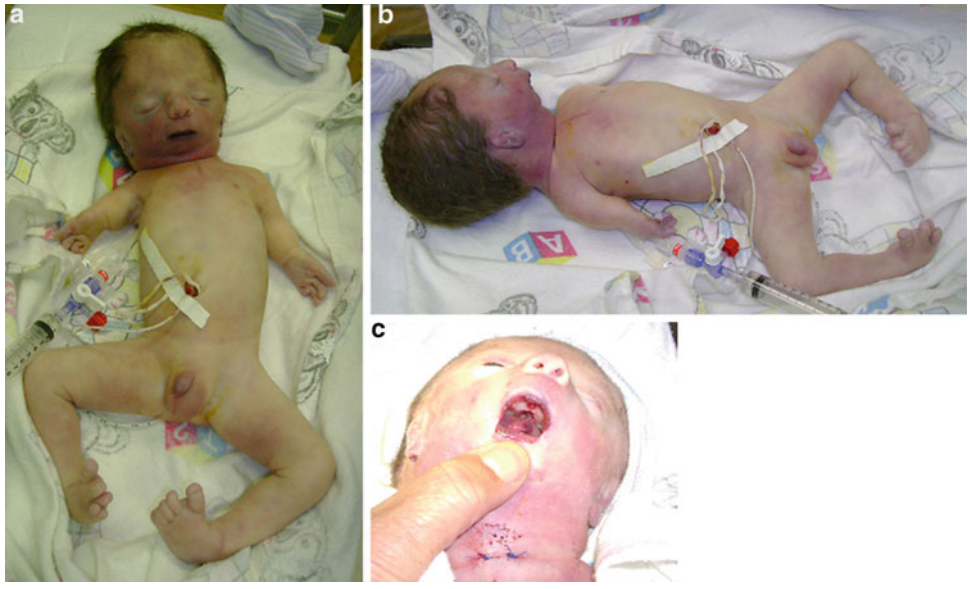

Fig. 2 (**a**–**c**) A newborn boy was evaluated for Nager acrofacial dysostosis. Craniofacial anomalies (**a**, **b**) were much more severe than the previous case. In addition, he had cleft palate (**c**), short neck, short upper extremities with near phocomelia on the right, missing thumb and camptodactyly on both hands, and bilateral talipes equinovarus

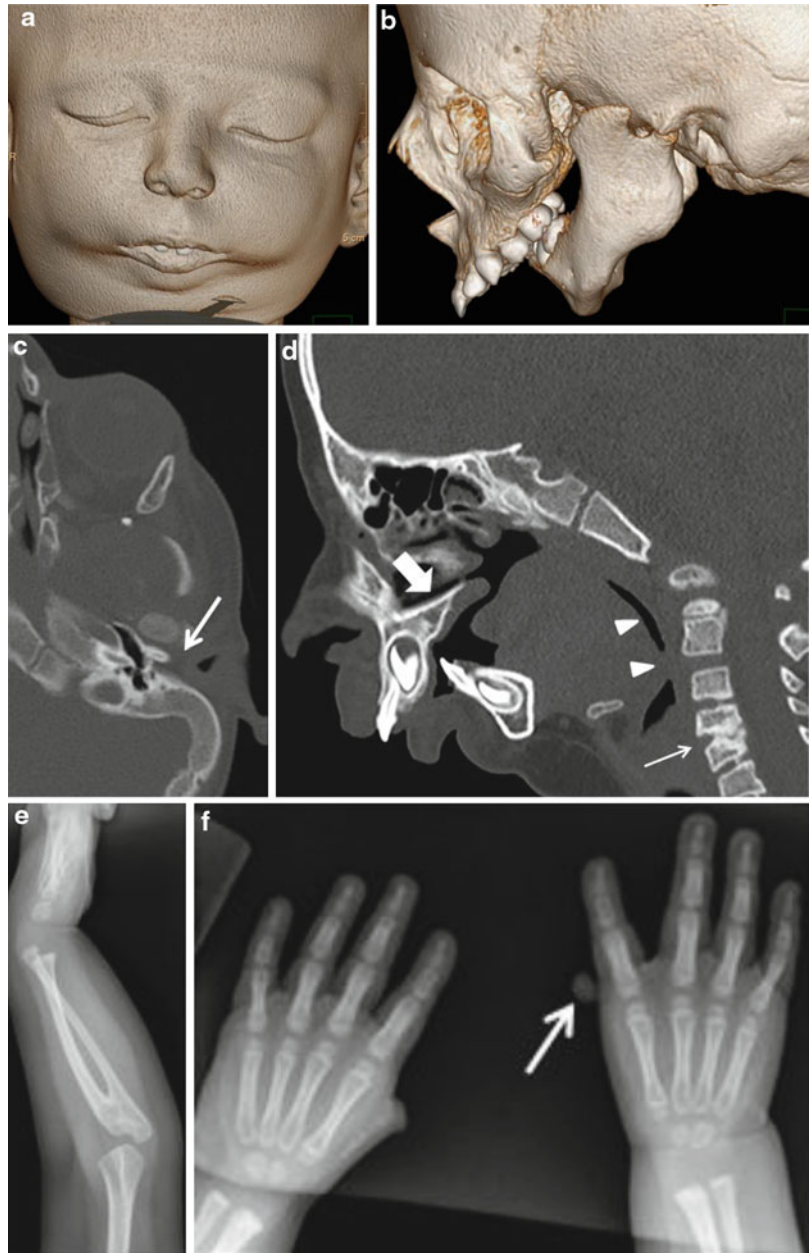

Fig. 3 (**a**–**f**) The 2-year-old girl (**a**) was evaluated for Nager acrofacial dysostosis. 3D reconstruction images of facial CT show marked symmetric mandibular hypoplasia and an increased angle of the body and ramus of the mandible. The mandibular condyles and mandibular fossa are present bilaterally with dysmorphic coronoid processes. There is absence of right zygomatic arch and near-complete absence on the left (**b**). CT images of bilateral temporal bones show bilateral bony external auditory canal atresia (**c**) (*arrows*). Sagittal CT image (**d**) demonstrates again micrognathia with foreshortened hard palate (*large arrow*), posterior displacement of the tongue compatible with glossoptosis (*arrow heads*), and cervical anomaly with fusion of C4–5 (*small arrow*). Radiography of the both forearms demonstrates proximal radioulnar synostosis with dysmorphic radius (only left side was shown here) (**e**). Radiography of bilateral hands (**f**) shows severely hypoplastic left thumb with tiny metacarpal and a phalanx and absent right thumb with only a small soft tissue remnant (*arrow*) (Courtesy of Dr. Grace Guo)

Nail-Patella Syndrome

Contents

In 1820, Chatelain (1951) first observed the nail-patella syndrome in a patient with a triad of abnormal nails, elbows, and knees. The hereditary nature of the syndrome was first described by Pye-Smith in 1883 in the English literature. The presence of iliac horns was first noted by Kieser (1939) in 1939 and later by Fong (1946) in 1946. In 1948, Mino et al. described the tetrad of abnormal nails, elbows, knees, and iliac horns for which the name hereditary onycho-osteodysplasia was coined by Duncan and Souter in 1963.

Synonyms and Related Disorders

Hereditary onycho-osteodysplasia (Duncan and Souter 1963; Carbonara and Alpert 1964)

Genetics/Basic Defects

1. Genetic heterogeneity (Ghoumid et al. 2015)
2. An autosomal dominant disorder with complete penetrance (Lucas and Opitz 1966; Beals and Eckhardt 1969; Figueroa-Silva et al. 2016)
3. An autosomal recessive inheritance: reported in a Saudi Arab family with nail-patella syndrome (Al-Dawsari et al. 2015). Genetic analysis of the *LMX1B* gene detected a previously reported homozygous mutation (c.268C > TP. Leu90Phen) in exon 2 of the *LMX1B* gene in both of the affected sisters. Both of the parents were confirmed to be heterozygous for the same mutation
4. Case reports of donor insemination, embryo donation (Figueroa-Silva et al. 2016)
5. *LMX1B*
    1. The only gene known to be associated with nail-patella syndrome (NPS)
    2. A LIM-homeodomain transcription factor involved in normal patterning of the dorsoventral axis of the limb during development and early morphogenesis of the glomerular basement membrane (Bongers et al. 2002)
    3. Targeted disruption of *Lmx1b* results in skeletal defects, including hypoplastic nails, absent patellae, and a unique form of renal dysplasia (Chen et al. 1998)
    4. *LMX1B* gene maps to 9q in the same region as the NPS locus by fluorescence in situ hybridization. Three unrelated NPS patients carried *de novo* heterozygous mutations in this gene (Dreyer et al. 1998)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_172

6. A microdeletion of chromosome 9q33.3 encompassing the entire *LMX1B* gene have been reported in a Chinese family with nail-patella syndrome (Jiang et al. 2014)
7. Demonstration of association between the haplotype of the mutant allele and the variability in the nail score ($p = 0.024$) (Dunston et al. 2005a)
8. Genotype/phenotype correlations (Bongers et al. 2005a)
    1. Individuals with an *LMXB1* mutation located in the homeodomain showed significantly more frequent and higher values of proteinuria than subjects with mutations in the LIM domains
    2. No clear genotype-phenotype association was apparent for extrarenal manifestations (McIntosh et al. 1998)

Clinical Features

1. Inter- and intrafamilial phenotypic variabilities (Lee et al. 2009)
2. Classic clinical tetrad
    1. Onychodysplasia (Sweeney et al. 2003): the most constant feature of the syndrome (approximately 98% of cases)
        1. Variable
        2. Absent, hypoplastic, or dystrophic nails usually noted at birth
        3. Spoon-shaped nails (Koilonychia)
        4. Pitting, discoloration, thin/thick nails
        5. Often bilateral or symmetrically involved
        6. Longitudinally or horizontally ridged (grooved) nails
        7. Thin or less often thickened nails
        8. Triangular lunules (lunulae): a characteristic feature of the syndrome
        9. Most pronounced involvement in thumbnails, decreases in severity ulnarward
        10. Dysplasia of toenails usually less marked, often affecting little toenails, and less frequent than that of the fingernails
        11. Report of nail changes in the mother and son (Neri et al. 2015)
            1. Mother: missing ulnar half of the first fingernail, triangular lunula associated with pseudopterygium/fissure/furrow
            2. Son: anonychia of the first fingernail, koilonychia of the third fingernail, triangular lunula associated with pseudopterygium/fissure/furrow
    2. Knee dysplasia (approximately 74% of cases)
        1. Small, irregularly shaped, or absent patella that is prone to dislocate
        2. May be asymmetrically involved
        3. Hypoplastic patella often located laterally and superiorly, even though not actually dislocated
        4. May be associated with prominent medial femoral condyles, hypoplastic lateral femoral condyles, and prominent tibial tuberosities
        5. Appearance of flattened profile of knee joints
    3. Elbow dysplasia (approximately 70% of cases)
        1. May be asymmetrical
        2. The deformity is characterized by hypoplasia of the capitellum, commonly by secondary dysplasia and dislocation, usually posteriorly, of the radial head, associated with limitation of rotation (pronation and supination) of variable degree
        3. Triceps hypoplasia with antecubital pterygia, a frequent accompaniment of the syndrome, further limiting extension resulting in cubitus valgus
    4. "Iliac horns" (Cottereill and Jacobs 1961)
        1. Clinically palpable
        2. Generally symmetrical
        3. Known to develop a secondary center of ossification
        4. The iliac horns can be present at birth by X-ray examination
    5. To the classical clinical tetrad of involvement of the nails, knees, and elbows and

presence of iliac horns, kidney disease, and glaucoma had been added as recognized parts of the syndrome (McIntosh et al. 2005)

3. Other skeletal abnormalities
    1. Talipes equinovarus, talipes calcaneovalgus deformities, and flat feet
    2. Mild short stature
    3. Adults with nail-patella syndrome have a bone mineral density (BMD) that is 8–20% lower than controls, which is associated with an increase in the prevalence of fractures and scoliosis (Towers et al. 2005)
4. Associated nephropathy (Darlington and Hawkins 1967; Eisenberg et al. 1972; Bennett et al. 1973) (30–50% of cases) (renal failure in approximately 5% of cases)
    1. Proteinuria
        1. Usually the first sign of renal involvement
        2. With or without hematuria
        3. May present at any age from birth onward
        4. May be intermittent
        5. May remit spontaneously, remain asymmetric, progress to nephritic syndrome, and occasionally to renal failure
        6. May be exacerbated during pregnancy
    2. Relatively benign although fatality at a young age from this complication has been described (Leahy 1966)
    3. Progression to chronic glomerulonephritis leading rarely to renal failure
        1. May occur rapidly
        2. May occur after many years of asymptomatic proteinuria
5. Eye involvement
    1. Primary open-angle glaucoma
    2. Ocular hypertension
    3. Iris pigmentary changes: frequent observation of a zone of darker pigmentation shaped like a cloverleaf or flower around the central part of the iris (Lester's sign)
6. Gastrointestinal involvement (about one third of cases)
    1. Constipation
    2. Irritable bowel syndrome
7. Neurologic and vasomotor symptoms are also part of the NPS phenotype (Sweeney et al. 2003)
    1. Neurological involvement
        1. Intermittent numbness, tingling, and burning sensations in the hands and feet in some cases
        2. Epilepsy (6% of cases)
        3. Neurologic symptoms: considered particularly interesting in light of the role of Lmx1b in neuronal migration in the mouse and in the developing brain (Dunston et al. 2005b)
    2. Vasomotor problems in some cases
        1. Poor peripheral circulation, presenting as very cold hands and feet even in warm weather
        2. Raynaud's phenomenon
8. Dental problems
    1. Weak, crumbling teeth
    2. Thin dental enamel
9. Differential diagnoses (Bongers et al. 2005b; Sweeney et al. 2014)
    1. Small patella syndrome (ischiopatellar dysplasia, coxo-podo-patellar syndrome, Scott-Taor syndrome) (Bongers et al. 2004)
        1. Similarities: small or absent patellae, recurrent patella dislocations, pelvic anomalies
        2. Differences, defective ossification at the ischiopubic junction, ischial hypoplasia, infra-acetabular "axe-cut" notch, no nail changes, no elbow changes, no renal involvement, no ocular involvement
    2. Patella aplasia-hypoplasia
        1. Familial occurrence (Bernhang and Levine 1973; Braun 1978)
        2. A family segregating PTLAS mapping to 17q21-q22 (Mangino et al. 1999)
        3. Similarities: isolated aplasia or hypoplasia of the patella
        4. Differences: no nail changes, no elbow changes, no renal involvement, no ocular involvement
    3. Familial recurrent dislocation of the patella (Carter and Sweetnam 1960; Miller 1978; Borochowitz et al. 1988)

1. Similarities: familial tendency toward patella dislocation (autosomal dominant inheritance)
2. Differences: absence of other NPS features

4. Meier-Gorlin syndrome (ear-patella-short stature syndrome) (Shalev and Hall 2003; Bicknell et al. 2011)
   1. Caused by homozygous or compound heterozygous mutation in the ORC1 gene on chromosome 1p32
   2. Similarities: Absent patellae, dislocation of the radial head
   3. Differences: microtia, markedly short stature, delayed bone age, characteristic facial appearance, autosomal recessive inheritance
5. Genitopatellar syndrome (Cormier-Daire et al. 2000; Sankararaman et al. 2012) (please see the chapter on "► Genitopatellar Syndrome")
   1. Similarities: absent patellae, renal anomalies, flexion deformities of the knees and hips, club foot
   2. Differences: hypoplasia of the ischia and iliac bones, genital anomalies, facial dysmorphism, microcephaly, intellectual disability, structural (multicystic kidneys or hydronephrosis) rather than functional abnormalities, renal manifestations
6. DOOR syndrome (deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures syndrome) (Cantwell 1975; Nevin et al. 1982; James et al. 2007)
   1. Caused by homozygous or compound heterozygous mutation in the *TBC1D24* gene on chromosome 16p13 (Campeau et al. 2014)
   2. Similarities: absent or poorly formed nails
   3. Differences: long thumbs and big toes, often with triphalangy, other fingers and toes short as the result of an absent or hypoplastic distal phalanx, bilateral ptosis, short broad nose with a broad nasal tip and large nostrils, structural renal tract abnormalities, cataracts, optic atrophy, Dandy-Walker malformation, seizures, autosomal recessive inheritance
7. Trisomy 8 mosaicism (Jones 1997) (please see the chapter on "► Trisomy 8 Mosaicism Syndrome")
   1. Similarities: absent or hypoplastic patellae, limited elbow supination, abnormal nails
   2. Differences: significant learning difficulties, variable facial dysmorphism, camptodactyly, and progressive joint restriction, usually of the fingers and toes
8. Coffin-Siris syndrome (Vergano and Deardorff 2014)
   1. Caused by heterozygous mutation in the *ARID1B* gene on chromosome 6q25 (Wieczorek et al. 2013)
   2. Similarities: absence or hypoplasia of the nails and patellae, elbow dislocation
   3. Differences: nail hypoplasia, usually affecting the little finger nails, facial dysmorphism
9. RAPADILINO syndrome (Kääriäinen et al. 1989)
   1. The acronym RAPADILINO stands for the characteristic main features: RAdial and PAtellar aplasia or hypoplasia, cleft or highly arched PAlate, infantile DIarrhea and DIslocated joints, LIttle size and LImb malformation, and long slender NOse and NOrmal intelligence
   2. Caused by homozygous or compound heterozygous mutation in the DNA helicase gene *RECQL4* on chromosome 8q24 (Siitonen et al. 2009)
   3. Similarities: absent or hypoplastic patellae, dislocated joints
   4. Differences: cleft palate, facial dysmorphism, short stature, radial defects, including absent or hypoplastic thumbs and radii, autosomal recessive inheritance
10. Senior syndrome (Brachymorphism-onychodysplasia-dysphalangism syndrome) (Senior 1971; Verloes et al. 1993)
    1. Similarities: small nails

2. Differences: characteristic facial appearance, short stature, mild intellectual impairment

Diagnostic Investigations

1. Diagnosis based on clinical and radiographic findings
2. Laboratory studies
    1. Urinalysis: proteinuria, hematuria
    2. Plasma urea, BUN, creatinine concentrations
3. Radiologic features
    1. The characteristic "NPS knee" consists of a combination of easily recognizable malformations (Tigchelaar et al. 2016)
        1. A small or absent patella and a number of malformations of the femoral condyles, encompassing shortening of the lateral femoral condyle, a prominent anterior surface of the lateral femoral condyle and a flat anterior surface of the medial femoral condyle
        2. At least one of these malformations is observed in all patients with NPS and at least three of them are observed in the majority of cases
    2. Elbow involvement
        1. Dysplasia of the radial head
        2. Hypoplasia of the lateral epicondyle and capitellum
        3. Prominence of the medial epicondyle
        4. Dislocation of the radial head, usually posteriorly
    3. Iliac horns
        1. Bilateral, conical, bony processes that project posteriorly and laterally from the central part of the iliac bones of the pelvis
        2. Present in about 70% of cases
        3. Considered pathognomonic of the syndrome (Goshen et al. 2000)
        4. Pelvic X-ray
            1. Usually necessary for detection of iliac horns, but large horns may be palpable clinically
            2. Iliac horns: may be observed at birth
            3. An epiphysis at the apex of iliac horns: may be present in children
    4. MRI
        1. For possible bone/soft tissue abnormalities
        2. For a subluxated or dislocated patella (Konrads et al. 2016)
    5. Ultrastructural (electron microscopic) abnormalities (Morita et al. 1973): the most specific histologic changes seen in nail-patella syndrome
        1. Collagen fibril deposition within the basement membrane and the mesangial matrix
        2. Irregular thickening of the glomerular basement membrane with electron-lucent areas giving a mottled "moth-eaten" appearance
        3. The skin revealed epidermal basement membrane thickening and redundancy in addition to significant perivascular basal lamina reduplication by electron microscopy (Burkhart et al. 1980)
    6. Renal histopathology (Browning et al. 1988)
        1. Characteristic changes in the glomeruli at age 27 months
        2. Strong immunofluorescent staining, particularly for IgM, raised the possibility of superimposed immune complex disease
    7. Molecular genetic testing: *LMX1B* gene mutation analysis available clinically

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. An affected parent: a 50% risk
        2. Clinically unaffected parents
            1. A low risk in a case of de novo mutation in the proband
            2. An increased risk if germline mosaicism exists in a parent (not been reported)
    2. Patient's offspring
        1. A 50% risk
        2. Affected person has a risk of about 1 in 4 of having a child with nail-patella syndrome nephropathy and a risk of about 1 in 10 of having a child in whom renal failure will develop (Looij et al. 1988)

2. Prenatal diagnosis
    1. Use of ultrasound in 3rd trimester diagnosis of NPS (Feingold et al. 1998)
    2. Use of five DNA markers flanking the LMX1B locus demonstrated that a fetus was affected (McIntosh et al. 1999). The pregnancy was terminated at 15 weeks
    3. Demonstration of the disease-causing mutation previously identified in the proband on fetal DNA obtained from amniocentesis or CVS
    4. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the LMX1B pathogenic variant has been identified (Sweeney et al. 2014)
3. Management
    1. Patella dysplasia: most patients asymptomatic, rarely require surgical treatment
    2. Physiotherapy for orthopedic complaints
    3. Surgical treatment
        1. Bilateral elbow soft tissue release
        2. Bilateral radial head excisions
        3. Foot and ankle reconstructive procedures for equinus, pes cavus, calcaneovalgus, congenital vertical talus, and clubfoot deformities
        4. Knee extensor realignments and foot posteromedial releases had overall good results. Knee flexion contractures required full posterior capsular releases. Elbow reconstructive procedures were rarely indicated (Guidera et al. 1991)
        5. Occurrence of secondary patella dislocation is common in NPS. The most likely cause is a medial patellofemoral ligament (MPFL) tear and corrective surgery should be aimed at reconstructing the ligament. Reconstruction using gracilis tendon is a safe and effective method and can be used in NPS cases caused by an MPFL tear (Gong et al. 2016)
        6. Subluxated or dislocated patella (Konrads et al. 2016): early surgical treatment via resection of the trochlear septum and soft tissue balancing of the patella. When the septum displaces the patella and prevents physiological articulation of the patella with the trochlea femoris, early septum resection is likely to be important for a good functional outcome and proper development of the patellofemoral joint during growth
    4. Screening for proteinuria
    5. Screening for glaucoma
    6. Course of pregnancy: complicated by further deterioration of renal function with superimposed pre-eclampsia resulting in early delivery. Such pregnancies should be regarded as high risk and managed jointly with the renal physician in a tertiary care center to ensure an optimal outcome to the mother and baby (Chua et al. 2002)

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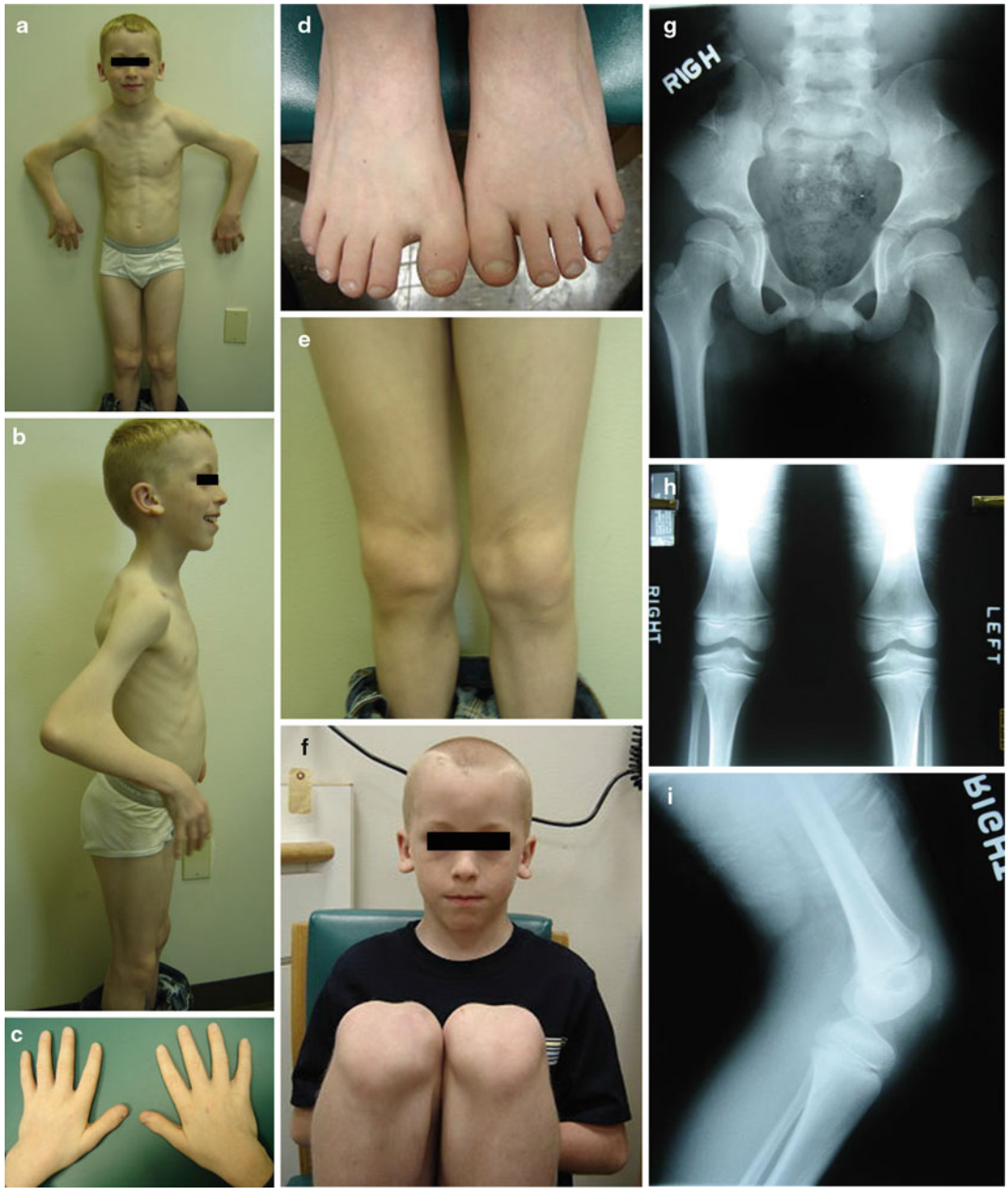

Fig. 1 (**a**–**i**) A 10-year-old boy (**a**, **b**) has classic nail-patellar syndrome. Note webbings of the neck and the elbows causing marked elbow contractures, abnormal muscle distribution of the upper extremities, nail hypoplasia (**c**, **d**), and absent patella (**e**, **f**). The radiographs show "iliac horn" sign of the pelvis (**g**) and patella agenesis (**h**, **i**)

Nasal Obstruction in Neonates and Children

Contents

Nasal obstruction in the neonate may lead to serious consequences including respiratory distress or failure to thrive. While bilateral nasal obstruction often presents in the neonatal period, unilateral nasal obstruction may not present until much later in life, with chronic nasal drainage, skin irritation, and congestion (Gnagi and Schraff 2013).

Synonyms and Related Disorders

Choanal atresia; Nasal dermoid; Nasal encephalocele; Nasal Glioma; Nasal obstruction; Nasolacrimal duct cyst; Pyriform aperture stenosis

Genetics/Basic Defects

1. Congenital malformations secondary to aberrant embryogenesis of both the internal and external nose potentially causing nasal obstruction include the following but not limited to (Gnagi and Schraff 2013):
    1. Midfacial hypoplasia
    2. Craniosynostosis
    3. Arhinia (complete absence of the nose)
    4. Nasal hypoplasia (congenitally absent nasal bones)
    5. Complete or partial nasal duplication
    6. Single centrally placed nostril
    7. Supernumerary teeth in the nose
    8. Thornwaldt cyst (a common incidental benign midline nasopharyngeal mucosal cyst)
    9. Nasopharyngeal stenosis (incomplete separation of the soft palate and posterior pharyngeal wall)
    10. Others
2. The most common and clinically significant congenital anomalies: please see the differential diagnosis section.

Clinical Features

1. Signs and symptoms of nasal obstruction (Gnagi and Schraff 2013):
    1. Stuffy nose
    2. Rhinorrhea
    3. Mucus
    4. Stertor
    5. Snoring/snorting
    6. External deformity
    7. Nasal flaring

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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8. Chest retractions
9. Cyanosis (+/− cyclical nature)
10. Feeding difficulties
11. Hyponasal cry
12. Failure to thrive
13. Dyspnea/apnea
14. Aerophagia with abdominal distention
15. Difficulty sleeping
16. Epiphora

2. Differential diagnosis (Adil et al. 2012; Gnagi and Schraff 2013):
    1. The most common and clinically significant congenital anomalies:
        1. Choanal atresia:
            1. The most common congenital nasal anomaly
            2. Most commonly associated with CHARGE syndrome (please see the chapter)
            3. Can also be seen with Apert, Crouzon, and Treacher Collins syndromes (please see the chapters)
        2. Congenital nasal pyriform aperture stenosis:
            1. Pyriform aperture: the pear-shaped, bony opening of the nasal cavity
            2. Pyriform aperture stenosis: caused by a bony overgrowth of the medial nasal processes of the maxilla, usually bilateral causing nasal obstruction in neonates
            3. May occur as an isolated anomaly or in association with the absence of the anterior pituitary, diabetes insipidus, submucous cleft palate, and hypoplastic maxillary sinuses or as part of the holoprosencephaly sequence
        3. Midnasal stenosis;
            1. A rare clinical entity secondary to bilateral bony overgrowth midway through the nasal cavity
            2. Usually occurs in children with midfacial hypoplasia
        4. Nasolacrimal duct cysts (dacryocystoceles) (Brugger et al. 2010):
            1. Fluid accumulation and distension of the nasolacrimal duct.
            2. Unilaterally in 50.6% or bilaterally in 49.4%.
            3. Can resolve spontaneously during intrauterine life.
            4. Bilateral involvement with substantial intranasal extension may develop respiratory distress syndrome (Bachelard-Serra et al. 2013).
            5. Usually seen as an isolated abnormality but can be associated with other congenital anomalies (Yazici et al. 2010).
        5. Midline nasal masses:
            1. Nasal/nasopharyngeal dermoid: the most common of the congenital midline nasal mass
            2. Glioma (neuroglial heterotopia)
            3. Encephalocele/meningocele: caused by defective development of the skull and herniation of intracranial contents/meninges
            4. Thornwaldt cyst
    2. Neoplasms:
        1. Teratoma
            1. Histologically containing all three germ cell layers.
            2. Tumors: composed of immature cells carrying a higher risk of malignancy with a worse prognosis.
            3. Alpha-fetoprotein and beta-hCG tumor markers may be elevated.
        2. Hamartoma
        3. Vascular lesions (hemangiomas, arteriovenous malformations, vascular malformations)
        4. Lymphangioma
        5. Lipoma
        6. Neurofibroma
        7. Rhabdomyosarcoma
        8. Lymphoma
    3. Infectious:
        1. Upper respiratory infection
        2. Respiratory syncytial virus
        3. Sexually transmitted diseases:
            1. Chlamydia
            2. Gonorrhea
            3. Syphilis

4. Foreign body:
5. Traumatic/iatrogenic:
    1. Septal dislocation
    2. Septal hematoma
    3. Nasal tip depression
    4. Rhinitis medicamentosa
    5. Instrumentations: suction trauma, nasogastric tube, CPAP, and nasal prongs
2. Inflammatory:
    1. Allergic rhinitis (cow's milk, soy)
    2. Gastroesophageal reflux
    3. Recurrent emesis
    4. Idiopathic
3. Metabolic: hypothyroidism
4. Maternal:
    1. Estrogenic stimuli
    2. Drug ingestion (methimazole, methyldopa, opiates, tricyclic antidepressants, propranolol)
5. Associated syndromes:
    1. Cystic fibrosis
    2. Kartagener syndrome
    3. Charge association
    4. Apert syndrome
    5. Crouzon syndrome
    6. Treacher Collins syndrome
    7. Fetal alcohol syndrome
    8. Down syndrome

Diagnostic Investigations

1. Clinical procedures (Gnagi and Schraff 2013):
    1. Anterior rhinoscopy with an otoscope: help visualize anterior stenosis, masses, or obstructive mucus.
    2. Gently passing a small (5 or 6 French) catheter through the nose into the nasopharynx to confirm an open communication:
        1. Obstruction at the anterior inlet may suggest pyriform aperture stenosis, while obstruction posteriorly (approximately 32 mm) may suggest choanal atresia (Myer and Cotton 1983).
        2. Visualizing or palpating the tube through the mouth confirms that the tube is not coiled in the nose to prevent misdiagnosis. In infants with craniofacial abnormalities or visible nasal masses, care must be taken when attempting to pass a nasal catheter, as these may be associated with skull base defects and risk intracranial passage of the catheter (Ramsden et al. 2009).
    3. Additional studies to assess nasal patency include the use of a tympanometer placed at the nares to confirm or exclude a closed cavity (Effat 2005).
    4. Nasal endoscopy:
        1. A simple and minimally invasive diagnostic procedure.
        2. When a nasal mass is identified on endoscopy, it should be assumed to have intracranial extent until proven otherwise. Therefore, no biopsy of a mass should be performed until appropriate imaging has been undertaken (Jaffe 1981).
2. Radiologic imagings (Adil et al. 2012; Gnagi and Schraff 2013):
    1. Plain radiographs with radiopaque contrast in the nasal cavity: rarely employed because of poor sensitivity and specificity
    2. CT scans: best allow bony definition and typically the test of choice to assess choanal atresia and pyriform aperture stenosis
    3. MRI: better choice to evaluate nasal masses to delineate intracranial involvement and extent

Genetic Counseling

1. Recurrence risk: Recurrence risk depends on the etiology of the nasal obstruction:
    1. Patient's sib:
        1. Autosomal recessive: 25%
        2. Autosomal dominant: not increased unless a parent is affected or having gonadal mosaicism
        3. Sporadic: unknown, probably not increased
    2. Patient's offspring:
        1. Autosomal recessive: not increased unless the spouse is also a carrier

2. Autosomal dominant: 50%
3. Sporadic: unknown, probably not increased

2. Prenatal diagnosis:
   1. Ultrasonography:
      1. Nasal gliomas detected at mid-trimester (De Basio et al. 2006; Grzegorczyk et al. 2010; Tonni et al. 2011; Beegun et al. 2012).
      2. A huge fetal facial mass protruded through the left nostril at 33 weeks of gestation: computed tomography of the neonate suggested a transethmoidal encephalocele. However, MRI showed a huge mass occupying the nasopharynx and the nasal cavity and protruding externally to the face without any intracranial connection. Pathologic examination revealed intranasal glioma (Okumura et al. 2012).
      3. Dacryocystocele: anechogenic cystic masses located anteromedially in the orbits and centered on the medial canthus (Bianchini et al. 2004).
   2. Fetal MRI has been used to confirm the diagnosis of dacryocystoceles with the following triad (Bianchini et al. 2004):
      1. Paraocular cystic mass in the medial canthus region
      2. Nasolacrimal duct enlargement
      3. Intranasal cyst
3. Management (Adil et al. 2012; Gnagi and Schraff 2013): secure an adequate airway (the first goal of therapy):
   1. Choanal atresia:
      1. Delay repair of unilateral atresia until school age to allow the nasal cavity to mature.
      2. Transnasal endoscopic repair: most popular technique today.
      3. Transpalatal approach may also be used.
   2. Congenital nasal pyriform aperture stenosis:
      1. Bilateral balloon dilation
      2. Short-term stenting of the nasal pyriform apertures
      3. May require surgical intervention to drill and widen the pyriform aperture
   3. Nasolacrimal duct cysts:
      1. May resolve spontaneously within the first year of life (Peterson and Robb 1978)
      2. Conservative management: warm compresses and gentle massage for simple dacryocystoceles without intranasal extension
      3. Probing the duct and/or surgical marsupialization of the intranasal cyst (Leonard et al.. 2008)
   4. Congenital frontonasal masses (nasal dermoid, encephalocele, glioma, other neoplasms): surgical intervention with multiple surgical subspecialties
   5. Infectious etiologies: treat the underlying cause
   6. Iatrogenic etiologies: treat the underlying cause
   7. Inflammatory, systemic, and other etiologies: treat the underlying cause
   8. Syndrome associations: treat according to the underlying syndrome

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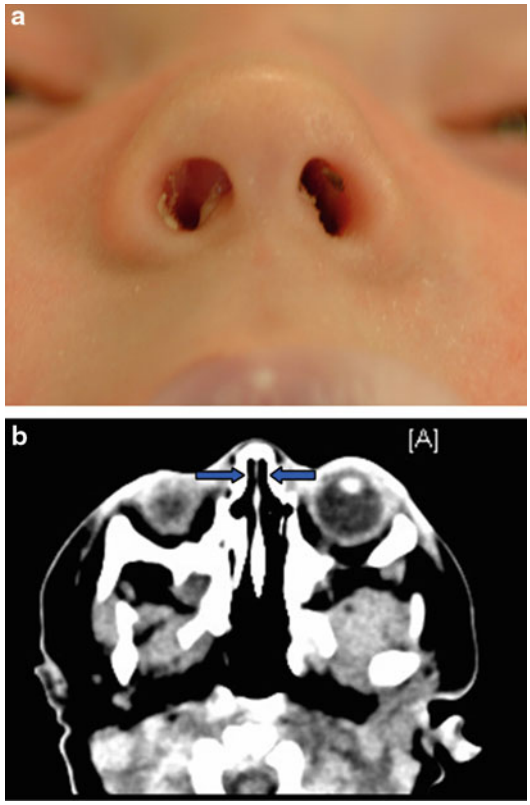

Fig. 1 (**a**, **b**) A 3-week-old Caucasian boy was seen for respiratory distress and inability to feed. Nasal catheters could not be passed on either nasal side and he was referred for evaluation of possible choanal atresia (**a**). He struggled with breathing and desaturated every time he ate. Nasal obstruction was persistent. A flexible pediatric (2.4 mm diameter) endoscope was unable to insert beyond the nasal vestibule on either side. Rigid pediatric endoscope (2 mm Hopkins rod) could not be passed through either nasal passage. A non-contrast axial CT scan (**b**) showed CNPAS with a bilateral combined nasal vestibular aperture width of 5.03 mm (*arrows*) and normal choanae. He underwent bilateral balloon dilation and short-term stenting of the nasal pyriform apertures without the need for additional procedures and remained patent after 12 months at follow-up (Gungor and Reiersen 2014) (Courtesy of Dr. Anil Gungor)

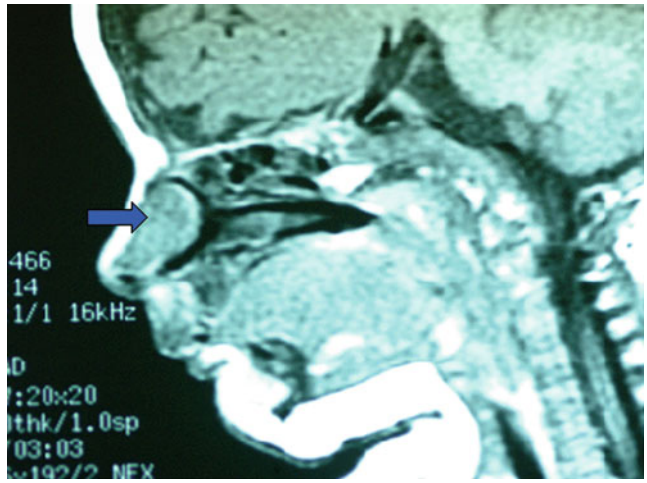

Fig. 2 A 3-month-old boy was seen for a nasal mass present since birth. The mass grew slowly bigger in size, causing nasal obstruction and difficulty in his nasal breathing, accompanied by occasional snoring and intermittent episodic epistaxis. Anterior rhinoscopy showed a large mass originating from the lower lateral cartilage and completely obstructing the right nostril. It appeared to extend to the superior part of the vestibule, but the extent of the entire lesion could not be determined by anterior rhinoscopy alone. Palpation of the mass showed a smooth, rubbery lesion that did not blanche with direct pressure. The lesion was nonpulsatile and did not change in size when the patient cried. A computed tomographic scan and a magnetic resonance imaging scan showed a $0.7 \times 1.8 \times 1.1$ cm soft tissue mass in the anterior right nasal cavity (*arrow*), without extension into the bony nasal framework, nasopharynx, paranasal sinuses, or skull base. No bony erosion was observed. A transnasal excision of the mass was performed with endoscopic guidance. The mass was excised from vestibular skin without difficulty, and a small mucosal attachment from the inferior turbinate was freed with electrocautery. Grossly, the lesion, which was dense and glistening, was a small, tan, white, and focally red mass. Histologically, the mass was a heterotopic neuroglial tissue (nasal glioma) (Roy and Gungor 2014) (Courtesy of Dr. Anil Gungor)

Neonatal Herpes Simplex Infection

Contents

Hass (1935) in *1935* described a fatal case of neonatal herpes simplex virus (HSV) infection with hepatoadrenal necrosis and intranuclear inclusion bodies. Neonatal herpes is defined as the diagnosis of HSV infection in an infant within the first 28 days of life.

Synonyms and Related Disorders

Fetal/intrauterine herpes simplex infection; HSV-1 infection; HSV-2 infection; Maternal genital herpes infection

Genetics/Basic Defects

1. HSV-1 and HSV-2 (Kimberlin 2004)
    1. Belong to Herpesvirus family
        1. Herpes simplex viruses
            1. Enveloped, double-stranded DNA viruses
            2. Exist as two serotypes, 1 and 2 (HSV-1 and HSV-2)
    2. Infections with HSV-1 generally involve the face and skin "above the waist" and are associated with orolabial disease. Most infections occur during childhood. HSV-1 also can cause genital infection, resulting more frequently from oral-genital contact.
    3. Infections with HSV-2 usually involve the genitalia and skin "below the waist" in sexually active adolescents and adults, usually resulting from sexual intercourse. Most HSV disease in neonates is due to HSV-2. HSV-2 also causes oral lesions in approximately 25% of the infected population.
2. Viruses are transmitted from infected to susceptible individuals during close personal contact.
3. Recurrent HSV infections occur in over one third of the world's population due to the rare fatal nature of the infection and a latency period.
4. Infections in children and nonpregnant adults.
    1. Recurrent herpes labialis: the largest reservoir of HSV infections in the community
    2. Genital herpes
        1. A first-episode primary infection occurs in a person with no prior HSV-1 or HSV-2 antibody.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. A first-episode nonprimary infection occurs in a person with preexisting HSV-1 antibody acquiring HSV-2 genital infection.
3. Recurrent infections can result from viral reactivation from latency and subsequent antegrade translocation of virus back to the skin and mucosal surfaces.

5. Maternal genital infections (Kimberlin 2004; Brown et al. 2005; Pinninti and Kimberlin 2014; James and Kimberlin 2015).
   1. Genital herpes infections are caused by either HSV-1 or HSV-2, and the majority of infections are asymptomatic.
   2. Twenty-two percent of pregnant women are seropositive for herpes simplex virus (HSV)-2, and more than 2% of women acquire genital herpes during pregnancy.
   3. Recurrent genital herpes infections: the most common form of genital HSV infections during gestation.
   4. The most devastating complication of genital HSV is infection of the neonate caused by contact with infected genital secretions at the time of delivery.
   5. Woman with primary genital HSV disease: at highest risk of transmitting the virus to her baby.
   6. Neonatal transmission occurs in the peripartum period, provided the gravid woman is shedding virus, either symptomatically or asymptomatically, at the time of delivery.
   7. Factors influencing transmission from mother to neonate.
      1. Type of maternal infection (primary versus recurrent): Mothers with a first episode of genital HSV infection near term are at much greater risk of developing neonatal herpes than those whose mothers have recurrent genital herpes.
      2. Maternal antibody status.
      3. Duration of rupture of membranes: Cesarean delivery within 4 h of membrane rupture in a woman with active genital lesions can reduce the infant's risk of acquiring HSV.
      4. Integrity of mucocutaneous barriers (e.g., use of fetal scalp electrodes).
      5. Mode of delivery (cesarean section versus vaginal): effective in the prevention of HSV transmission to the neonate from a mother actively shedding virus from the genital tract. Neonatal infection has occurred in spite of cesarean delivery performed prior to the rupture of membranes.
   6. Incidence of neonatal disease: estimated at approximately 1 in 3,200 deliveries (an estimated 1,500 cases of neonatal HSV infection annually in the United States).
   7. Transmission of HSV disease to neonates occurs in the following three distinct time intervals (Pinninti and Kimberlin 2014).
      1. Intrauterine (in utero): 5% infected with HSV in utero
      2. Peripartum (perinatal): overwhelming majority (85%) of infected neonates
      3. Postpartum (postnatal): an additional 10% of infected neonates
   8. Disease classification of HSV infections acquired either peripartum or postpartum: predictive of both morbidity and mortality.
      1. Disease localized to the skin, eyes, and/or mouth (SEM disease, accounting for 45% of cases of neonatal HSV)
      2. Encephalitis, with or without SEM involvement (CNS disease, accounting for 30% of cases of neonatal HSV)
      3. Disseminated infection involving multiple organs, including the CNS, lungs, liver, adrenal glands, skin, eyes, and/or mouth (disseminated disease, accounting for 25% of cases of neonatal HSV)
2. Two biologic properties of HSV that directly influence human diseases
   1. Latency: a period of reactivation of virus multiplication, resulting in clinically apparent disease (lesions) or clinically inapparent (asymptomatic, or subclinical) infection.
   2. Neurovirulence: an affinity with which HSV is drawn to and propagated in neuronal

tissue, resulting in profound disease with severe neurologic sequelae.
    1. Neonatal HSV central nervous system (CNS) disease
    2. Herpes simplex encephalitis in older children and adults
3. Epidemiology (James and Kimberlin 2015)
    1. Humans are the only known natural reservoir of HSV.
    2. Seroprevalence studies indicate that HSV-1 and HSV-2 infections are common worldwide, in both developed and undeveloped countries (Smith and Robinson 2002).
    3. Acquisition of HSV results in lifelong infection, with periodic clinical or subclinical viral reactivation.
    4. Interaction of herpes simplex virus types 1 and 2: Combining data from prospective studies show a trend towards a protective effect for previous HSV-1 infection against infection with HSV-2 (Looker and Garnett 2005).

Clinical Features

1. Intrauterine infection (Hutto et al. 1987; Baldwin and Whitley 1989; Kimberlin 2004)
    1. Incidence: approximately 1 in 300,000 deliveries.
    2. Intrauterine HSV infection can occur as a consequence of either primary or recurrent maternal infection and has severe consequences for the fetus.
    3. In utero disease unlikely to be missed due to the extent of involvement of affected babies.
    4. A triad of clinical findings.
        1. Cutaneous manifestations
            1. Scarring
            2. Active lesions
            3. Hypo-/hyperpigmentation
            4. Aplasia cutis
            5. Erythematous macular exanthem
        2. Ophthalmologic findings
            1. Microphthalmia
            2. Retinal dysplasia
            3. Optic atrophy
            4. Chorioretinitis
        3. Neurologic involvement
            1. Microcephaly
            2. Encephalomalacia
            3. Hydranencephaly
            4. Intracranial calcification
2. Neonatal HSV infection (Waggoner-Fountain and Grossman 2004)
    1. May occur between birth and 4 weeks of age.
    2. Neonatal disease may present as:
        1. Disseminated disease involving multiple organs, most prominently the liver and lungs and possibly with a central nervous system (CNS) component
        2. Disease localized to any area of the skin, eyes, and mouth (SEM)
        3. Localized CNS disease
    3. When HSV infection occurs within the first several weeks of life, viral replication is poorly controlled and the majority of infants will die without treatment. However, acquisition of HSV after this period is typically mild or even asymptomatic (Gantt and Muller 2013).
3. Initial presentation of neonatal presentation of neonatal herpes simplex virus infection (Pinninti and Kimberlin 2014; Curfman et al. 2016)
    1. Disseminated disease (Kimberlin 2004) involving multiple organs, most prominently the liver and lungs and possibly with a central nervous system (CNS) component
        1. Incidence: approximately 25% of all children with neonatal HSV disease.
        2. Has the earliest age of onset, often during the first postnatal week.
        3. Encephalitis: about 60–75% of infants with disseminated disease.
        4. Vesicular rash: over 20% of neonates with disseminated HSV disease do not develop cutaneous vesicles during the course of their illness.
        5. Hepatitis: alanine aminotransferase (ALT) ($\geq \times 1.5$ normal) (McGoogan et al. 2011).

6. HSV pneumonitis: severe respiratory distress or failure with radiographic evidence of opacities in the setting of HSV disease.
7. Disseminated intravascular coagulation: defined as decreased platelets and clotting factors as evidenced by platelets $<$150,000/μL or prothrombin time, international normalized ratio, or partial thromboplastin time above normal range.
8. Death relates primarily to the severe coagulopathy, liver dysfunction, and pulmonary involvement of the disease.

2. Localized CNS disease with or without SEM involvement (Kimberlin 2004; Pinninti and Kimberlin 2014): observed in almost one third of all neonates with HSV infection and has the latest age of onset, usually between the second and third weeks after birth
   1. Account for one third of cases of neonatal herpes disease
   2. Clinical manifestations
      1. Hypotonia
      2. Seizures (both focal and generalized)
      3. Lethargy
      4. Irritability
      5. Tremors
      6. Poor feeding
      7. Temperature instability
      8. Bulging fontanelle
      9. Associated skin vesicles in 60% and 70% of babies classified as having CNS disease
      10. Death usually caused by devastating brain destruction, with resulting acute neurologic and autonomic dysfunction
3. SEM disease
   1. Incidence: approximately 45% of all cases of neonatal HSV disease
   2. Infection confined to the skin, eye, and/or mouth of newborn
   3. Since the introduction of antiviral therapy, ~45% of infants with neonatal HSV disease present with SEM disease (Whitley et al. 1988)
   4. Infants present around day 10–12 of life
   5. 80% of infants with SEM disease present with a vesicular rash
4. Factors affecting the severity of neonatal disease
   1. Prompt diagnosis: PCR assay to detect HSV DNA in neonates has improved early diagnosis of disease.
   2. Initiation of antiviral (intravenous acyclovir) therapy.
      1. Reduces mortality and morbidity among neonates with skin, eye, and mouth disease
      2. Unable to reduce morbidity associated with disseminated or CNS disease
5. Despite early intervention with high-dose antiviral therapy, 30% of infants with disseminated disease die, and 40% of survivors of CNS disease have severe neurologic damage. Therefore, prevention of neonatal infection is critical.

Diagnostic Investigations

1. Clinical diagnosis based on:
   1. Typical findings (HSV culture not necessary):
      1. Herpes labialis
      2. Gingivostomatitis
      3. Genital herpes
   2. Atypical HSV infections (culture and antiviral susceptibility testing needed to guide antiviral therapy)
      1. Immunocompromised patients
      2. HSV conjunctivitis and keratitis: need an ophthalmologist consultation
2. Diagnostic evaluations obtained prior to initiation of acyclovir therapy
   1. HSV cultures: remains the definitive diagnostic method of establishing HSV disease
      1. Skin vesicles, if present
      2. Oropharynx
      3. Conjunctivae
      4. Urine
      5. Blood
      6. Stool

7. Rectum
8. Cerebrospinal fluid (CSF)

2. Liver transaminase: Elevated levels suggest disseminated HSV infection.

3. Serologic testings
   1. Type-specific antibody assays to distinguish between HSV-1 and HSV-2 antibodies.
   2. Identifies only past infection but cannot identify the site of HSV infection.
   3. Patients with cold sores due to HSV-1 will test HSV-1 seropositive regardless of presence or absence of genital HSV-1 infection.
   4. Possible to identify serodiscordant couples in which the woman is HSV-2 seronegative and the partner is seropositive. Women in such couples are at risk for acquiring primary genital HSV infection during pregnancy and are thus at higher risk of transmitting the virus to their babies during birth.
   5. Serologic studies, in general, play no role in the diagnosis of neonatal HSV disease.
4. Cytological examination (Tzanck test) of material obtained from the base of the vesicles becomes extremely important as it can reveal giant multinucleated epithelial cells (Bittencourt et al. 2016)
5. Classification of genital HSV based on serologic and viral detection test results: important in pregnancy because the risk of perinatal HSV transmission varies accordingly
   1. Primary first episode: characterized by isolation of HSV-1 or HSV-2 from genital secretions in the absence of HSV antibodies in serum
   2. Nonprimary first episode: characterized by isolation of HSV-2 from genital secretions in the presence of HSV-1 antibodies in serum
   3. Reactivation disease: characterized by isolation of HSV-1 or HSV-2 from the genital tract in the presence of HSV antibodies of the same serotype as the isolate
6. PCR amplification
   1. Able to correctly diagnose neonatal HSV disease, especially in patients without overt manifestations such as skin vesicles
   2. Able to assess the response to therapy
      1. Having HSV DNA detected in CSF at or after the completion of intravenous therapy is associated with poor outcomes.
      2. Repeat lumbar puncture of all patients with CNS HSV involvement is indicated at the end of intravenous acyclovir therapy to determine that the specimen is PCR negative in a reliable laboratory and to document the end-of-therapy CSF indices. Persons who remain PCR positive should continue to receive intravenous antiviral therapy until PCR negativity is achieved.
7. Canadian Paediatric Society Position Statement: laboratory diagnostics for NHSV (Allen et al. 2014)
   1. Whenever a diagnosis of NHSV is being considered, it is essential to order laboratory testing for HSV in addition to performing skin and mucous membrane examinations:
      1. The standard tests for HSV include CSF PCR and swabs of vesicular lesions and mucous membranes (tested by the method recommended by the local laboratory). Also, blood for HSV PCR may be tested, if available.
      2. Serum hepatic transaminase levels should be measured to provide supporting evidence for disseminated HSV infection.
   2. When evaluating NHSV infection in exposed asymptomatic infants, mucous membrane swabs should be obtained from the mouth, nasopharynx and conjunctivae at least 24 h after delivery. Additional swabs may be obtained (e.g., from sites of scalp electrodes, if present).
   3. PCR testing for CSF HSV DNA is the diagnostic method of choice for CNS HSV.
   4. For all the above tests, clinicians and laboratory staff should work together to minimize the turn-around time for test results.
   5. Direct immunofluorescent antibody staining of skin lesions.
   6. Enzyme immunoassays for HSV antigens in skin lesion.
8. Patients with CNS disease (Curfman et al. 2016) have either

1. Positive HSV CSF PCR or viral culture, with or without CSF or neurologic abnormalities or
2. Positive HSV PCR of blood or skin lesion accompanied by neurologic abnormality and CSF pleocytosis

9. SEM disease (Curfman et al. 2016): characterized by
   1. PCR or viral culture positive for HSV from the skin, conjunctiva, and/or mouth, with or without a positive blood HSV PCR, and
   2. No evidence of other end organ involvement
10. Neuroimaging (Bajaj et al. 2014): a significant correlation between early diffusion-weighted imaging and neurologic sequelae, suggesting that MRI is the most valuable imaging modality in neonatal HSV.

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Unknown
      2. No cases in siblings reported
   2. Patient's offspring
      1. Unknown
2. Prenatal diagnosis
   1. Genetic counseling complicated due to:
      1. Fetal infection may follow primary or recurrent disease.
      2. Fetal infection can occur at any time in gestation.
      3. Only approximately one third of cases have a history suggestive of maternal herpes infection during pregnancy.
   2. Isolation of the virus from amniotic fluid obtained at amniocentesis does not necessarily imply fetal infection (Zervoudakis et al. 1980)
   3. Currently no accurate risk estimate available for congenital malformations following maternal herpes infection during pregnancy
      1. Appears to be small
      2. Highest risk for women with primary infection during the first trimester
3. Management (Kimberlin 2004)
   1. Antiviral drugs
      1. Vidarabine (1-β-D-arabinofuranosyladenine): the first systemically administered antiviral medication with activity against HSV for which the therapeutic efficacy outweighed its toxicity
         1. Administered over prolonged infusion times and in large volumes of fluid
         2. Management of life-threatening HSV and varicella zoster virus infections, HSV encephalitis, and herpesvirus infections in immunocompromised patients
      2. Acyclovir
         1. Lower dose: lower toxicity and improved ease of administration
         2. Higher dose: improved outcome in mortality and morbidity achieved with use of higher-dose acyclovir
   2. Antibody therapy
      1. Use of passive immunotherapy as an adjuvant to active antiviral interventions.
      2. Neonates with higher neutralizing antibody titers: less likely to become infected with HSV following perinatal exposure and being more likely to have localized disease (and less likely to have disseminated disease) once they are infected.
      3. Intravenous gamma globulin currently not recommended for the management of neonates with HSV disease due to variable amount of anti-HSV antibodies present in conventional intravenous gamma globulin preparations.
      4. A monoclonal antibody directed against γD may be available for clinical investigation as an adjuvant therapeutic agent by the NIAID Collaborative Antiviral Study Group in the future.
   3. Prevention of neonatal HSV infections (Pinninti and Kimberlin 2014)
      1. Prevention strategies
         1. Identification of women at risk for HSV acquisition during pregnancy by testing women and possibly their partners for HSV antibodies

2. Provide counseling to prevent transmission to women in late pregnancy
2. Cesarean section
   1. Reduces the infant's risk of acquiring HSV in women with active genital lesions present at the time of delivery.
   2. Limitations: 60–80% of babies who develop neonatal HSV disease are born to women without a history of genital herpes, and thus, infection in these babies may not be prevented by this approach, and women with recurrent infections who are shedding virus at the time of delivery are at low risk of their babies developing neonatal HSV disease.
3. Antiviral therapy during pregnancy
   1. Oral acyclovir near the end of pregnancy to suppress genital HSV recurrences becoming increasingly common in clinical practice.
   2. Additional studies are needed to more definitively establish the effectiveness and safety of late-pregnancy maternal HSV suppression.
4. Vaccine development for genital herpes
   1. Currently, no vaccine has proven to be effective for preventing acquisition of HSV-1 or HSV-2.
   2. A candidate HSV-2 gD subunit vaccine adjuvanted with alum combined with 3-deacylated monophosphoryl lipid A has recently demonstrated promising results in preventing HSV-1 or HSV-2 genital herpes disease and HSV-2 infection, efficacy limited only to women who were HSV-1 and HSV-2 seronegative prior to vaccination.

4. Avoid unnecessary invasive procedures in labor.
   1. Vaginal delivery in women with genital herpes but without lesions or symptoms at the time of labor
   2. Avoid the following procedures to lessen the risk of HSV transmission, except when critical to obstetric care:
      1. Artificial rupture of membranes
      2. Fetal scalp electrodes
      3. Vacuum or forceps delivery
5. HSV infections of the CNS are devastating and require prompt diagnosis and institution of therapy. Heightened awareness of the disease is essential regardless of whether in a newborn or in an adult (Whitley 2015).

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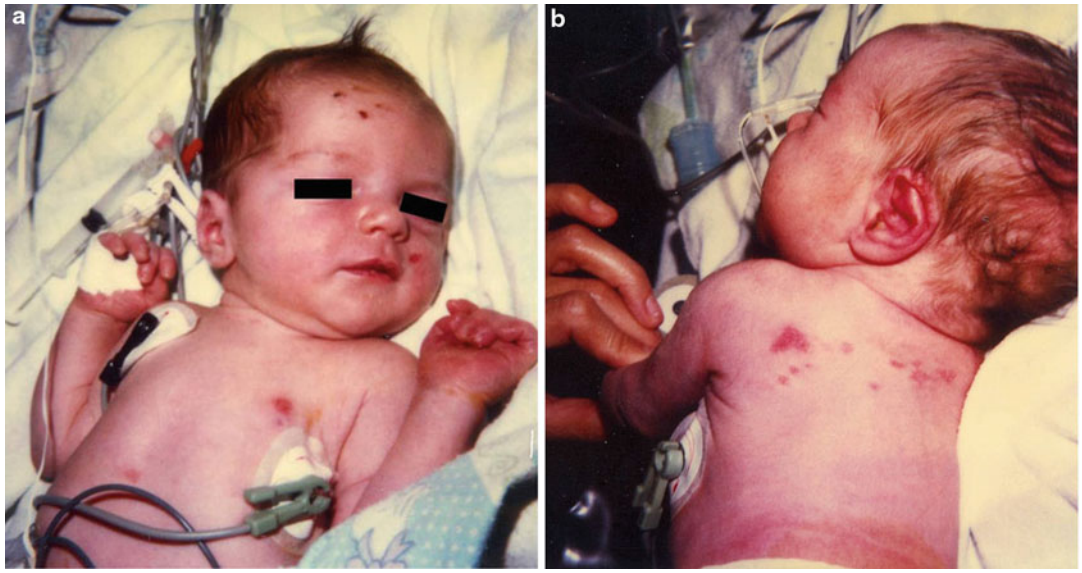

Fig. 1 (**a**, **b**) A neonate born with congenital herpes simplex infection showing generalized vesicular rash

Nephrogenic Diabetes Insipidus

Contents

Hereditary nephrogenic diabetes insipidus (NDI) is a rare disorder of defective vasopressin-stimulated water reabsorption via the luminal water channels in the cortical and medullary collecting ducts (Knoers and Deen 2001). In other words, NDI is caused by inability of the kidneys to concentrate urine by reabsorbing water in the collecting duct (Bockenhauer and Bichet 2015).

Synonyms and Related Disorders

Aquaporin 2 diabetes insipidus; Congenital nephrogenic diabetes insipidus

Genetics/Basic Defects

1. Causes of diabetes insipidus (Linshaw 2007; Robertson 2016)
    1. Central: hypothalamic/pituitary lesions leading to insufficient production or release of antidiuretic hormone (ADH)
        1. Postoperative brain surgery
        2. Intracranial lesions (cysts, aneurysms, tumors of pituitary, brainstem)
        3. Infiltrative malignancies (lymphoma, leukemia)
        4. Infections, including encephalitis, meningitis, abscess
        5. Head trauma
        6. Hypoxic injury
        7. Congenital, inherited as an autosomal dominant disorder
    2. Nephrogenic: renal resistance (lack of response of the distal nephron) to ADH from lesions interfering with the renal concentrating mechanism
        1. Acquired metabolic aberrations
            1. Hypokalemia (chronic, Bartter syndrome)
            2. Hypercalcemia
            3. Hypercalciuria (rare)
            4. Diabetes mellitus
        2. Medullary damage
            1. Chronic pyelonephritis
            2. Infiltrative disease (leukemia, lymphoma, amyloidosis)
            3. Sickle cell disease
            4. Cystinosis
            5. Other forms of chronic renal failure
            6. Obstructive uropathy

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3. Drugs
    1. Lithium
    2. Demeclocycline
    3. Amphotericin B
    4. Diphenylhydantoin
4. Inherited
    1. X-linked recessive: approximately 90% of cases of hereditary nephrogenic diabetes insipidus
    2. Autosomal recessive: approximately about 9% of cases
    3. Autosomal dominant: about 1% of cases

2. Adult patients can develop acquired NDI (Sands and Bichet 2006). The most common cause is lithium therapy for bipolar disorders. Other causes of acquired NDI are prolonged hypokalemia, hypercalcemia, protein malnourishment, and the release of bilateral or unilateral ureteral obstruction. In addition, normal aging can result in partial NDI
3. X-linked inheritance
    1. Caused by mutations in the arginine vasopressin V2 receptor (*AVPR2*) gene (Vargas-Poussou et al. 1997) on the X chromosome (mapped on Xq28), encoding the arginine vasopressin receptor type 2 (VR2): molecular basis for lack of concentration of urine
    2. The spectrum of mutations varies from rare gene variants or polymorphisms not causing NDI to rare mutations causing NDI, among which arginine and tyrosine are the most common missense (Spanakis et al. 2008)
    3. Novel large deletion in AVPR2 gene causing copy number variation in a patient with X-linked nephrogenic diabetes insipidus (Cho et al. 2016)
    4. Males who carry the defective gene
        1. Do not concentrate urine after administration of arginine vasopressin (AVP): defined as the excretion of increased (>30 ml/kg/day) volumes of diluted urine (<250 mmol/kg) (Fujiwara and Bichet 2005)
        2. Tend to have more serious symptoms
            1. Polydipsia (excessive thirst)
            2. Polyuria (excessive urine production)
    5. Females who carry the defective gene: can have variable (rarely severe) degrees of polydipsia and polyuria because of skewed X chromosome inactivation (Arthus et al. 2000)
4. Autosomal recessive inheritance (Hochberg et al. 1997)
    1. Caused by aquaporin 2 (*AQP2*, mapped on 12q13) mutations (Hoekstra et al. 1996; Vargas-Poussou et al. 1997; Fujiwara and Bichet 2005; Bircan et al. 2008; Duzenli et al. 2012; Sasaki et al. 2013)
    2. Polyuria and polydipsia are usually present at, or shortly after, birth
    3. Disease tends to be more severe, with urine osmolality generally not exceeding approximately 200 mOsm/kg water
5. Autosomal dominant inheritance
    1. A few *AQP2* mutations have been described to cause autosomal dominant disease (Vargas-Poussou et al. 1997; Mulders et al. 1998; Kuwahara et al. 2001; Marr et al. 2002; Kamsteeg et al. 2003)
    2. Clinical expression
        1. Tends to become noticeable after 6–12 months or even later
        2. May not be as severe (urine osmolality may be higher)
        3. Transient response to ADH may be present
    3. AQP2-R254W is associated with a partial nephrogenic DI phenotype with some ability to concentrate urine when dehydrated (Dollerup et al. 2015)

Clinical Features

1. Medical history (Linshaw 2007)
    1. Failure to thrive
    2. Extreme thirst
    3. Unexplained fever
    4. Irritability
    5. Constipation
    6. Impressive polyuria
    7. Vomiting
    8. Seizures

2. Physical features
   1. Dry mouth and eyes
   2. Poor skin turgor
   3. Sunken eyes and anterior fontanelle
   4. Mottled skin
   5. Decreased peripheral pulses
   6. Low blood pressure
   7. Multiple abdominal masses/fecaliths
   8. Low cognitive and psychosocial functioning: current prevalence considerably lower than suggested in literature (Hoekstra et al. 1996)
3. Urologic complications in patients with NDI ($n = 173$) (Fujimoto et al. 2014)
   1. Hydronephrosis 47
   2. Hydroureter 24
   3. Renal failure 11
   4. Vesicoureteral reflux 11
   5. Slightly dilatation of renal pelvic 7
   6. Dilatation of bladder 3
   7. Renal atrophy/dwarf kidney 3
   8. Neurogenic bladder 2
   9. Acidosis 1
4. Four different types of diabetes insipidus: differential diagnosis and management (Babey et al. 2011; Robertson 2016)
   1. Pituitary DI (neurohypophyseal)
      1. Basic defect: deficient production and secretion of AVP
      2. Causes: acquired or genetic
      3. Treatment: antidiuretic hormone, arginine vasopressin (AVP), desmopressin, chlorpropamide, tegretol
   2. Primary polydipsia
      1. Basic defect: suppressed secretion of AVP due to excessive fluid intake
      2. Causes: abnormal thirst (dipsogenic) or abnormal cognition (psychogenic)
      3. Treatment: education, psychotherapy?
   3. Gestational diabetes insipidus
      1. Basic defect: increased degradation of AVP during pregnancy
      2. Causes: placental vasopressinase
      3. Treatment: Management of DI of pregnancy depends on the pathophysiology of the disease; forms of DI that lack AVP can be treated with desmopressin (DDAVP), while forms of DI that involve resistance to AVP require evaluation of the underlying causes (Ananthakrishnan 2016)
   4. Nephrogenic diabetes insipidus
      1. Basic defect: renal insensitivity to antidiuretic effect of AVP
      2. Causes: acquired or genetic
      3. Treatment: thiazide and/or amiloride with or without Indomethacin

Diagnostic Investigations

1. Laboratory features (Knoers 2012; Linshaw 2007)
   1. Hypernatremia: serum sodium concentration >143 mEq/L in the presence of a low urine specific gravity and in the absence of excessive sodium intake: highly suggestive of diabetes insipidus
   2. Failure to concentrate the urine in the presence of high plasma vasopressin concentration and in the presence of parenteral administration of vasopressin or desmopressin: diagnostic of NDI
   3. Hyperchloremia
   4. Metabolic acidosis
   5. Normal potassium concentration
   6. Hyperuricemia
   7. High serum and low urine osmolality
2. DDAVP (vasopressin analogue 1-desamino-8-D-arginine vasopressin) test (Bockenhauer and Bichet 2015): upon administration of the DDAVP, phosphorylation of AQP2 at Ser256, Ser264, and Ser269 is abundantly increased, whereas phosphorylation at Ser261 is decreased (Kortenoeven and Fenton 2014)
3. All families with hereditary diabetes insipidus should have their molecular defect identified (Bichet and Bockenhauer 2016)
4. Molecular identification underlying X-linked NDI (*AVPR2*): immediate clinical significance because early diagnosis and treatment of affected infants can avert the physical and mental retardation that results from repeated episodes of dehydration (Fujiwara and Bichet 2005)

5. Molecular identification underlying autosomal recessive and autosomal dominant NDI (*AQP2*)

Genetic Counseling

1. Recurrence risk (Knoers 2012)
    1. Patient's sib
        1. X-linked recessive: risks of sibs depending on the genetic status of the proband's mother
            1. If the mother is a carrier: 50% of male sibs will be affected (inheriting the maternal *AVPR2* mutation); 50% of female sibs will be carriers
            2. A low recurrence risk but not zero due to possible germline mosaicism if the proband is the only one affected in the family and the disease-causing mutation cannot be detected in the DNA of the mother
        2. Autosomal recessive inheritance: risk of recurrence 25%
        3. Autosomal dominant inheritance
            1. Recurrence risk of 50% if a parent is affected
            2. A low recurrence risk if both parents are normal
    2. Patient's offspring
        1. X-linked recessive: All daughters of affected males will be carriers. All sons of an affected male will be normal
        2. Autosomal recessive inheritance
            1. Obligatory carriers for a disease-causing mutation in the *AQP2* gene
            2. A low recurrence risk unless the spouse is affected or a carrier
        3. Autosomal dominant inheritance: a 50% risk of offspring affected (inheriting the *AQP2* mutation)
2. Prenatal diagnosis
    1. X-linked recessive: available for pregnancies at increased risk if the *AVPR2* mutation has been identified in an affected family member by amniocentesis of CVS if the fetal karyotype is 46,XY
    2. Autosomal recessive and autosomal dominant: available for pregnancies at increased risk for the *AQP2* mutation
    3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation(s) has/have been identified.
3. Management (Linshaw 2007; Bockenhauer and Bichet 2015)
    1. Current treatment approaches for congenital NDI focus on ameliorating the symptoms rather than curing the disease
    2. If possible, treatment of acquired NDI should target the underlying cause, such as relief of urinary obstruction or amiloride therapy in lithium-associated NDI (Batlle et al. 1985)
    3. Patients with NDI should be treated with hypotonic fluids, either enterally (using water or milk) or if necessary intravenously (using 5% dextrose in water). Hypotonic fluids must never be administered as an intravenous bolus; instead, the infusion rate should only slightly exceed the urine output. The aim is to provide just enough water to safely normalize plasma sodium concentration at a rate of <0.5 mmol/l per h (<10–12 mmol/l per day). The main risk of a rapid decrease in plasma sodium is cerebral edema and potentially death (Kahn et al. 1979; Cansick et al. 2009; Fang et al. 2010; Sterns 2015)
    4. The usual prescription of overnight dehydration should not be used in patients, and especially children, with severe polyuria and polydipsia. Great care should be taken to avoid any severe hypertonic state, arbitrarily defined as a plasma sodium of >155 mEq/l
    5. Sufficient water to maintain normal electrolytes
    6. Low renal solute load to minimize water loss
    7. Adequate calories to support growth
    8. Pharmacotherapy
        1. Prostaglandin synthesis inhibitors have become essential components in the treatment of NDI, particularly in the

first years of life when management is the most complicated. The effect of these drugs can be quite marked when first initiated. Indeed, hyponatremic seizures associated with rapid lowering of plasma sodium levels as a result of commencing indomethacin and hydrochlorothiazide have been reported (Boussemart et al. 2009)

2. Thiazide
    1. Hydrochlorothiazide: 1–3 mg/kg/day bid
    2. Hypokalemia
    3. Hyponatremia
    4. Alkalosis
    5. Hypercalcemia
    6. Hyperglycemia
    7. Hyperuricemia
    8. Hepatitis
    9. Intestinal symptoms
    10. Bone marrow suppression
3. Indomethacin
    1. 1.5–2.5 mg/kg/day tid
    2. Gastrointestinal discomfort
    3. Gastrointestinal bleeding
    4. Headaches
4. Amiloride
    1. 20 mg/1.73 m^2/day bid-tid
    2. Hyperkalemia
    3. Headaches
    4. Gastrointestinal discomfort
    5. Renal toxicity
    6. Hematopoietic adverse effects

9. With appropriate treatment, complications of NDI, such as failure to thrive and mental retardation resulting from repeated hypernatremic dehydration, can be avoided

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Fig. 1 A 3-year-old girl was evaluated because her father has nephrogenic diabetes insipidus. He has problems with dehydration, polyuria, and polydipsia. His mother is a carrier and his maternal grandfather died of nephrogenic diabetes insipidus. The girl was found to have a mutation in the *AVPR2* gene. The mutation detected is g692-693delCT where two bases (CT) in codon 111 are deleted. The deletion causes a frameshift mutation that begins with a change of the amino acid at position 111 and results in a premature termination of protein synthesis at codon 190. This mutation has been reported to cause nephrogenic diabetes insipidus (NDI). The genetic data along with the family history are consistent with this female being a carrier of X-linked NDI

Netherton Syndrome

Contents

Netherton syndrome is a rare hereditary disorder of keratinization. It was described by Comèl (1949) in 1949 and Netherton (1958) in 1958. The syndrome is sometimes called Comèl-Netherton syndrome (De Felipe et al. 1997). The incidence is about 1 in 200,000 (Bitoun et al. 2002b).

Synonyms and Related Disorders

Comel-Netherton syndrome; Ichthyosis linearis circumflexa; Netherton disease; Trichorrhexis invaginata

Genetics/Basic Defects

1. Inheritance: autosomal recessive (Bitoun et al. 2002b)
2. Defective gene in Netherton syndrome
    1. Serine protease inhibitor, Kazal type 5 (*SPINK5*) mapped on chromosome 5q31-32 (Chavanas et al. 2000a, b).
    2. The protein encoded by *SPINK5* is highly expressed in thymus and mucous epithelia, thereby termed LEKTI for lymphoepithelial Kazal type-related inhibitor (Bitoun et al. 2003).
        1. LEKTI possibly plays a role in anti-inflammatory and/or antimicrobial protection of mucous epithelia.
        2. LEKTI possibly have similar function in the epidermis.
    3. Compound heterozygous mutation of the SPINK5 gene inherited from both parents (Chao et al. 2003).
    4. A compound synonymous mutation c.474G>A with p.Arg578X mutation in *SPINK5* causes splicing disorder and mild phenotype in Netherton syndrome (Numata et al. 2016).
    5. Lethal Netherton syndrome due to homozygous p.Arg371X mutation in *SPINK5* (Diociaiuti et al. 2013).
    6. Severe lethal phenotype of a Japanese case of Netherton syndrome with homozygous founder mutations of SPINK5 c.375_376delAT (Itoh et al. 2015).
    7. Complete maternal isodisomy of chromosome 5 with a pathogenic SPINK5 mutation in a Japanese patient with Netherton syndrome was reported (Numata et al. 2014). The most likely cause of UPD in this patient

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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is fertilization of a normal egg by a nullisomic sperm with subsequent salvage of a monosomy by post-fertilization duplication of the maternal chromosome 5, resulting in homozygosity for the *SPINK5* locus containing the mutation p. Arg578X (Kotzot and Utermann 2005). The other case of Netherton syndrome reported previously by Lin et al. (2007) was caused by a homozygous missense mutation p.Arg267Glu in *SPINK5*, resulting from a de novo mutation in combination with segmental maternal isodisomy.

Clinical Features

1. Clinical triad.
    1. Congenital ichthyosis
        1. Extent of involvement: highly variable
        2. Natural course
            1. At birth: usually normal-appearing skin.
            2. Within a few weeks of age: the skin becomes erythematous and develops serpiginous double-edged scales typical of ichthyosis linearis circumflexa or ichthyosiform erythroderma.
        3. Severe congenital generalized exfoliative erythroderma in newborns and infants: a possible sign of Netherton syndrome (Hausser and Anton-Lamprecht 1996)
    2. Hair abnormality (Stevanovic 1969)
        1. Trichorrhexis invaginata/nodosa.
            1. Sparse and brittle scalp hair with a characteristic “bamboo” shape under light microscope due to invagination of the distal part of the hair shaft to its proximal part
            2. The major diagnostic sign (considered pathognomonic) but may be difficult to detect in infancy and early childhood (Ansai et al. 1999)
            3. May not affect all hair and can be limited to the lateral part of the eyebrows
        2. Pili torti.
        3. Eyelashes and eyebrows (Powell 2000) may be affected.
    3. Atopic manifestations (Bitoun et al. 2002b)
        1. Eczema-like rashes
        2. Atopic dermatitis
        3. Pruritus
        4. Allergic rhinitis
        5. Asthma
        6. Urticaria/angioedema
        7. Mimicking pustular psoriasis (Small and Cordoro 2016)
2. Prognosis: poor (Bitoun et al. 2002b).
    1. Frequent life-threatening complications during the neonatal period
        1. Hypernatremic dehydration (Jones et al. 1986; Stoll et al. 2001)
        2. Hypothermia
        3. Extreme weight loss
        4. Recurrent infections
        5. Bronchopneumonia
        6. Sepsis
    2. Failure to thrive common during childhood resulting from:
        1. Malnutrition
        2. Metabolic disorders
        3. Chronic erythroderma
        4. Persistent cutaneous infections
        5. Severe enteropathy with villous atrophy
        6. Growth retardation
    3. Other abnormalities
        1. Renal failure
        2. Aminoaciduria
        3. Congenital heart defects
        4. Hydroureter
        5. Infantile pyloric stenosis
        6. Increased susceptibility to skin cancer (Krasagakis et al. 2003)
            1. Squamous cell carcinoma (Sahari et al. 2002)
            2. Vulvar cancer
3. Intrafamily and interfamilial phenotype variation and immature immunity in patients with Netherton syndrome and Finnish *SPINK5* founder mutation (Hannula-Jouppi et al. 2016).
4. Genotype-phenotype correlations suggested that homozygous nucleotide changes resulting

in early truncation of LEKT1 are associated with a severe phenotype (Sprecher et al. 2001).

5. Differential diagnosis of Netherton syndrome with neonatal presentations of selected ichthyoses (Craiglow 2013).
    1. Collodion baby (please see the chapter of "► Collodion Baby")
    2. Harlequin ichthyosis (please see the chapter of "► Harlequin Ichthyosis")
    3. X-linked ichthyosis (please see the chapter of "► X-Linked Ichthyosis")
    4. Epidermolytic ichthyosis (EI) (also known as bullous congenital ichthyosiform erythroderma or epidermolytic hyperkeratosis)
        1. An autosomal dominant disorder caused by mutations in the genes *KRT1* and *KRT10*, encoding keratin 1 and keratin 10, respectively (Rothnagel et al. 1992).
        2. Presents at birth with blistering and areas of denuded skin: This presentation may initially be confused with epidermolysis bullosa, staphylococcal scalded skin syndrome, or toxic epidermal necrolysis.
        3. A similar but milder presentation can be seen in infants with ichthyosis bullosa of Siemens, where blisters tend to be smaller and arise at sites of trauma. Over time, the blistering and denudation seen in EI diminishes, and hyperkeratosis becomes the prominent cutaneous manifestation, with dark, thick scales, often in a corrugated or ridged pattern.
6. Differential diagnosis of Netherton syndrome with syndromic forms of inherited ichthyosis (Yoneda 2016).
    1. Sjögren-Larsson syndrome: an autosomal recessive disorder characterized by congenital ichthyosiform exanthema, spastic paralysis of the limbs, and mental retardation.
    2. Refsum syndrome: an autosomal recessive disorder characterized by pigmentous retinitis, peripheral neuritis, cerebellar ataxia, and an increase in the cerebrospinal fluid level of protein. In addition, symptoms, such as anosmia, hemeralopia, vision disorder, cataract, muscular atrophy, cardiomyopathy, bone disorder, progressive myelin degeneration, functional disorder of the nervous system, cochlear hearing loss, ichthyosis, and renal failure, are observed.
    3. Multiple sulfatase deficiency ichthyosis.
        1. Caused by homozygous or compound heterozygous mutation in the sulfatase-modifying factor-1 (*SUMF1*) gene.
        2. Patients show symptoms related to the concomitant development of three disease groups:
            1. Metachromatic leukodystrophy with the deposition of sulfatide in the nerve tissue or kidney, resulting from abnormalities in arylsulfatase A
            2. Acidic mucopolysaccharidosis with the accumulation of heparan sulfate or dermatan sulfate in a large number of cells, including fibroblasts, resulting from abnormalities in arylsulfatase B
            3. Ichthyosis related to steroid sulfatase abnormalities
    4. Keratitis-ichthyosis-deafness syndrome (please see the chapter of "► KID Syndrome").
    5. Congenital hemidysplasia, ichthyosiform erythroderma or nevus, and limb defects syndrome.
        1. X-linked recessive or X-linked dominant inheritance (male lethal)
        2. Caused by *NSDHL* gene (3-β-hydroxysteroid dehydrogenase) mutations
    6. Ichthyosis, brittle hair, impaired intelligence, decreased fertility, and short stature.
        1. An autosomal recessive disorder
        2. Classified into three types:
            1. Trichothiodystrophy (TTD)/XPD, in which excision-repair, complementing defective, in Chinese hamster, 2 (ERCC2)/xeroderma pigmentosum, complementation group D (XPD) gene mutations are detected
            2. TTD/XPB, in which ERCC3/XPB gene mutations are detected
            3. TTD-A

7. Conradi-Hünermann-Happle syndrome (please see the chapter of "▶ Chondrodysplasia Punctata"
8. Dorfman-Chanarin syndrome.
    1. An autosomal recessive disorder.
    2. Caused by homozygous mutation in the comparative gene identification-58 (CGI58) gene.
    3. Clinical symptoms resemble those of non-bleb-type congenital ichthyosiform erythroderma (patients are not collodion babies at the time of birth), severe pruritus, decreased sweat volume, liver dysfunction, muscular weakness, cataract, renal dysfunction, deafness, mental retardation, nervous diseases, and a short stature.
9. Ichthyosis follicularis with alopecia and photophobia.
    1. X-linked recessive inheritance is suggested.
    2. Caused by mutation in the *MBTPS2* gene on chromosome Xp22.
10. Hystrix-like ichthyosis with deafness: caused by heterozygous mutation in the connexin-26 gene, *GJB2*, located at human chromosome 13q12.11.

Diagnostic Investigations

1. Clinical laboratory
    1. Increased serum immunoglobulin E levels (Smith et al. 1995).
    2. Hypereosinophilia.
    3. No consistent or significant abnormalities of immune function (Judge et al. 1994).
    4. IgG abnormalities (both hypo- and hyper-IgG).
    5. T-cell and neutrophil defects may also occur.
    6. Selective humoral deficiency to bacterial polysaccharide antigens has been described (Stryk et al. 1999).
    7. Specific IgE antibodies against airborne and food allergens frequently present.
2. Dermatoscopy (trichoscopy) (Sun and Linden 2005; Burk et al. 2008; Rakowska et al. 2009; Akkurt et al. 2014; Bittencourt et al. 2015)
    1. Trichorrhexis invaginata (bamboo hairs).
        1. A focal defect of the hair shaft that produces development of torsion nodules and invaginated nodules.
        2. The proximal element of the node overlaps the distal portion, causing an intussusception.
    2. Golf tee-like endings of hair shafts: If hair is pulled distally from this focal defect, a golf tee-like deformity is left. Hence, any hairs examined should be cut, rather than plucked.
    3. The hair shaft nodules caused by this defect are sometimes able to be seen by the naked eye. These hair defects can be found in scalp, eyebrow, or eyelash hairs. Grossly, scalp hair is described to be sparse and brittle.
    4. The hair shaft abnormality was reported to be secondary to intermittent incomplete formation of disulfide bonds in the keratogenous zone (Ito et al. 1984).
    5. Other hair shaft abnormalities.
        1. Pili torti
        2. Trichorrhexis nodosa
        3. Helical hairs (Lurie and Garty 1995)
        4. "Matchstick" eyebrow hairs: a dermoscopic clue to the diagnosis of Netherton syndrome (Goujon et al. 2010)
3. Classic histological criteria of Netherton syndrome (Berthold et al. 2016)
    1. Trichorrhexis invaginata
    2. Parakeratosis
    3. Acanthosis
    4. Lack of stratum granulosum
    5. Increased dermal vascularization
    6. Sparse perivascular inflammatory infiltrate
4. Immunohistochemistry using anti-LEKTI antibodies: shows a complete absence of LEKTI in the skin samples (Shimomura et al. 2005)
5. Histology and ultrastructural studies of skin sections
    1. Incomplete keratinization or defective cornification of the epidermis
    2. Dermal lymphocytic infiltrate
    3. Ultrastructure of the stratum corneum: characterized by premature degradation of

corneodesmosomes with separation of corneocytes (Chao et al. 2005)

6. Molecular genetic testing of *SPINK5*: clinically available
   1. Mutation analysis of patients
   2. Carrier testing

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25 %
   2. Patient's offspring: not increased unless the spouse is a carrier of the gene
2. Prenatal diagnosis (Bitoun et al. 2002a)
   1. Ultrastructural examination of fetal skin biopsies for defective cornification of the epidermis is not reliable, since fetal skin keratinization does not begin until the 24th week of gestation, whereas in utero, fetal skin biopsy is usually performed between 19 and 22 weeks.
   2. DNA-based prenatal diagnosis on fetal DNA obtained from amniocentesis or CVS.
      1. *SPINK5* mutation detection
         1. First case of prenatal diagnosis by mutation detection (Sprecher et al. 2001).
         2. A recurrent homozygous mononucleotide deletion (153delT) in exon 3 of *SPINK5* gene, resulting in a severe case of Netherton syndrome exhibiting exfoliative erythroderma with lethal outcome at the age of 4 months and its application in prenatal testing in a subsequent pregnancy of the mother (Müller et al. 2002).
         3. Two consanguineous Turkish families (two sisters married with two brothers) for prenatal diagnosis of Netherton syndrome and successful intracytoplasmic sperm injection (ICSI) pregnancies using planned prenatal genetic diagnosis (Bingol et al. 2011). Homozygous mutation was found in exon 4 as 238 insG, and this mutation was confirmed by direct sequencing analysis with DNA samples from father and mother (Bingol et al. 2011).
      2. Indirect genotype analysis at the *SPINK5* locus using linkage analysis
         1. This approach is reliable since there is no evidence of locus heterogeneity.
         2. Presence of a large number of SPINK5 intragenic restriction fragment length polymorphisms (RFLPs) showing a high percentage of heterozygosity.
3. Management
   1. No specific treatment available.
   2. Emollients.
   3. Keratolytics.
   4. Antibiotics for recurrent infections.
   5. Topical corticosteroids.
   6. Topical tacrolimus and pimecrolimus with good control of skin disease without toxic effect (Saif and Al-Khenizan 2007).
   7. Medium dose of psoralen-UVA1 phototherapy may be effective and tolerated in adult (Capezzera et al. 2004).
   8. NS is a complex disorder, where defects in epidermal integrity and cohesion may induce the appearance of aggressive skin cancers. Strict surveillance for human papillomavirus-related lesions and skin malignancies and caution in administrating immunosuppressive drugs or phototherapy are strongly recommended for these patients (Guerra et al. 2015).
   9. A trial of intravenous immunoglobulin (the TNF-α inhibitor infliximab) is a rational treatment approach for patients with severe disease (Small and Cordoro 2016).

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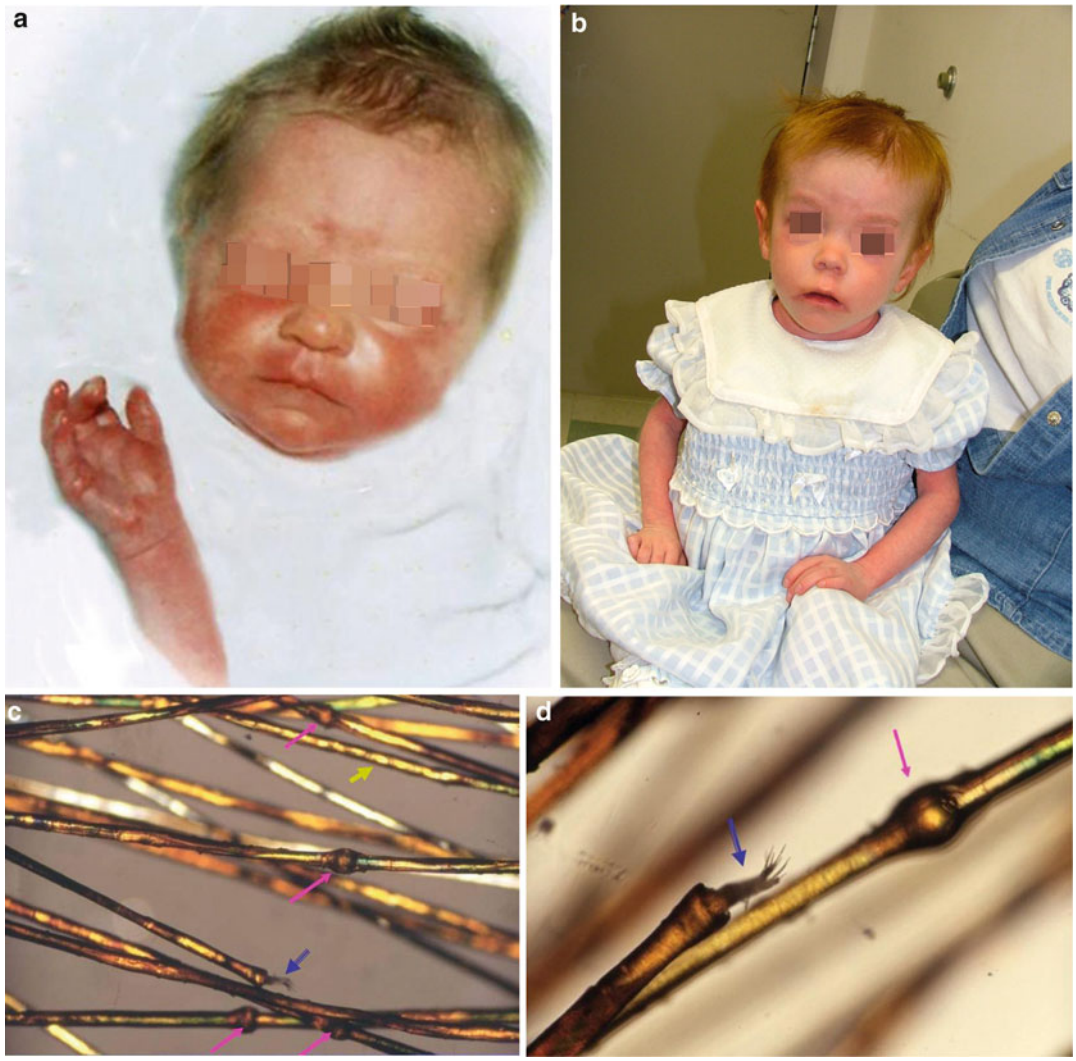

Fig. 1 A neonate (**a**) with Netherton syndrome showing erythroderma. The patient had markedly elevated serum total IgE levels of 409 IU/mL at age 8 months and 285 IU/mL at 14 months of age. Molecular genetic analysis of *SPINK5* showed a compound heterozygote with a mutation 316DelGA in exon 5 inherited from the mother and a mutation 2441+1delGTGA in exon 25 inherited from the father. The same patient at age 3 years (**b**) showed generalized erythroderma and marked growth retardation (height age of 7 months and weight age of 4 months). Microscopic analysis of the hair (**c** and **d**, lower and higher magnification) showed trichorrhexis invaginata/nodosa (*bamboo hair*) (*pink arrows*), pili torti (*yellow arrow*), and fractured hair shaft at the site of invagination (*blue arrow*)

Neu-Laxova Syndrome

Contents

The Neu-Laxova syndrome (NLS) is a lethal disorder characterized by multiple congenital malformations. Microcephaly, lissencephaly, absence of corpus callosum, facial anomalies (notably absent eyelids), short broad neck, peripheral edema, ichthyosis, limb anomalies, and other malformations are common findings. The syndrome was described first by Neu et al. in 1971 and Laxova et al. in 1972 (Neu et al. 1971; Laxova et al. 1972).

Genetics/Basic Defects

1. Inheritance: autosomal recessive inheritance (Abdel Meguid and Temtamy 1991; King et al. 1995; Badakali et al. 2012; Mattos et al. 2015).
2. Genetic heterogeneity: can be caused by mutations in all three genes (*PHGDH*, *PSAT1*, and *PSPH*) encoding enzymes of the L-serine biosynthesis pathway (Acuna-Hidalgo et al. 2014).
    1. *PHGDH* missense mutations were identified in three unrelated families (Shaheen et al. 2014).
    2. Furthermore, an overlapping homozygous chromosome 9 region containing *PSAT1* was mapped in four consanguineous families. This gene encodes phosphoserine aminotransferase, the enzyme for the second step in L-serine biosynthesis. Six families with three different missense and frameshift *PSAT1* mutations fully segregating with the disease were also identified.
    3. In another family, a homozygous frameshift mutation in *PSPH*, the gene encoding phosphoserine phosphatase, which catalyzes the last step of L-serine biosynthesis, was identified.
    4. Interestingly, all three identified genes have been previously implicated in serine-deficiency disorders, characterized by variable neurological manifestations. The findings expand our understanding of NLS as a disorder of the L-serine biosynthesis pathway and suggest that NLS represents the severe end of serine-deficiency disorders, demonstrating that certain complex syndromes characterized by early lethality could indeed be the extreme end of the phenotypic spectrum of already known disorders.
    5. Serine biosynthesis defects present in a broad phenotypic spectrum that includes, at the severe end, Neu-Laxova syndrome,

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a lethal multiple congenital anomaly disease; intermediately, infantile serine biosynthesis defects with severe neurological manifestations and growth deficiency; and at the mild end, the childhood disease with intellectual disability (El-Hattab 2016; El-Hattab et al. 2016). A serine transport defect resulting from deficiency of the ASCT1, the main transporter for serine in the central nervous system, has been recently described in children with neurological manifestations that overlap with those observed in serine biosynthesis defects. L-serine therapy may be beneficial in preventing or ameliorating symptoms in serine biosynthesis and transport defects.

3. Based on previous associations of mutations in the *PHGDH* with a milder NLS phenotype, as well as cases of serine deficiency, these observations lend further support to a genotype-phenotype correlation between the degree of *PHGDH* inactivation and disease severity (Mattos et al. 2015).
4. Pathogenesis (Coto-Puckett et al. 2010): remains unknown and differing etiologies have been postulated.
    1. A form of neuroectodermal dysplasia given the CNS and skin findings (Lazjuk et al. 1979; Ejeckam et al. 1986; Muller et al. 1987; Naveed and Sreenivas 1990)
    2. CNS pathology described as a neuronal migration defect with arrest of development early at 12–14 weeks of embryogenesis (Muller et al. 1987; Ostrovskaya and Lazjuk 1988)
    3. A neurodegenerative disorder with abnormal cell death causing neuronal atrophy and depletion (Allias et al. 2004)
    4. Limb deformities: caused by failure of muscle, bone, nerve, and arterial development in early embryogenesis (Shved et al. 1985)
    5. Contractures: secondary to reduced fetal movements or fetal akinesia/hypokinesia (Fitch et al. 1982; Russo et al. 1989)
    6. Ichthyotic skin changes: the cause of the deformed limbs, reduced movement, massive edema, and IUGR (Karimi-Nejad et al. 1987; Russo et al. 1989)
    7. Mechanism of ichthyosis proposed as hypoproteinemia caused by protein leakage through skin fissures as the primary pathogenesis of Neu-Laxova syndrome (Karimi-Nejad et al. 1987)
    8. It is the restrictive dermopathy that leads the various authors to characterize Neu-Laxova syndrome as a malformation sequence

Clinical Features

1. Considerable intrafamilial and interfamilial variation in clinical features
2. Prenatal history
    1. Severe intrauterine growth retardation
    2. Polyhydramnios
3. Clinical characteristics (Manning et al. 2004; Badakali et al. 2012; Mattos et al. 2015)
    1. Spectrum of skin lesions
        1. Edema over the dorsum of the foot and hand, often associated with hypoplastic phalanges
        2. Thick, waxy, and stretched in appearance
        3. Peeling of skin, scaling, and extensive plaque formation over the scalp, face, neck, back, and arm
        4. Translucent flexible membrane covering most of the skin
        5. Varying degrees of lamellar ichthyosis
        6. Absence of scalp hair
    2. Craniofacial features
        1. Receding forehead
        2. Ocular hypertelorism
        3. Exophthalmos (protruding eyes)
        4. Absence of the eyelids
        5. Flat, abnormal nose
        6. Ectropion: abnormal eversion (turning outward) of the lower eyelid margin away from the eye globe
        7. Eclabium: turning outward of the lip
        8. Cataract
        9. Micrognathia
        10. Cleft palate/lip
        11. Hypodontia
        12. Low-set, malformed ears

3. CNS abnormalities
    1. Microcephaly
    2. Lissencephaly
    3. Hypoplastic or abnormal cerebellum
    4. Agenesis or dysgenesis of the corpus callosum
    5. Decreased or absent gyri
    6. Dilatation or abnormal ventricles
    7. Dandy-Walker malformation
    8. Choroid plexus cysts
4. Limb anomalies
    1. Deformed digits
    2. Deformed limbs
    3. Flexion deformity
    4. Severe edema of the hands with short, spaced fingers (rubber glove appearance) (AL-Lawama and Basha 2010) and feet
    5. Syndactyly
    6. Rocker-bottom feet
5. Other features
    1. Short broad neck
    2. Cystic hygroma
    3. Subcutaneous edema
    4. Small thorax
    5. Hypoplastic or atelectatic lungs
    6. Transposition of great vessels
    7. Small abdomen
    8. Hypoplastic genitalia
    9. Short umbilical cord
    10. Absence of hair
    11. Muscle atrophy

4. Classification proposed by Curry (1982): may represent heterogeneity of the condition or different grades of severity, representing the wide spectrum of varying expressivity of the heterogeneous condition (Coto-Puckett et al. 2010)
    1. Group I
        1. Joint contractures
        2. Partial syndactyly
        3. Thin scaly skin
        4. Mild ichthyosis
        5. Poor mineralization of bones
    2. Group II
        1. Massive swelling of hands and feet
        2. More severe ichthyosis
        3. Undermineralized bones leading to intrauterine fractures
    3. Group III
        1. Hypoplastic digits
        2. Most severe ichthyosis (harlequin-like fetus)
        3. Short limbs
        4. Stick-like long bones
5. Prognosis
    1. Stillborn
    2. Die shortly after birth
6. Differential diagnosis (Tarim and Bolat 2010)
    1. Harlequin fetus/ichthyosis (please see the chapter of "▶ Harlequin Ichthyosis")
    2. Restrictive dermatopathy (dermopathy) (Kulkarni et al. 2006; Khanna et al. 2008)
        1. A rare autosomal recessive disorder characterized by extreme tautness of the skin causing restricted intrauterine movement and a fetal akinesia deformation sequence
        2. Uniformly mostly neonatally fatal
        3. Diagnostic findings
            1. Skin tautness with near absence of the dermal elastic fibers, usually with no or only minor anomalies of the internal organs
            2. Abnormal face
            3. Absence of skin cracking (tight skin)
            4. Absence of skin edema
            5. Arthrogryposis multiplex
        4. Secondary skeletal changes with variable radiographic findings which when present is pathognomonic of restrictive dermatopathy
            1. Poorly mineralized skull with large fontanelle
            2. Micrognathia
            3. Thin dysplastic clavicles
            4. Ribbonlike ribs
            5. Overtubulated humerus and forearm bones
    3. Lethal arthrogryposis with ichthyosis (Thakur et al. 2004)
        1. A lethal condition with joint contractures
        2. Subcutaneous edema, ectropion
        3. A severely flattened nose
        4. "O"-shaped open mouth
        5. Extensive peeling of the skin (skin changes of ichthyosis)

4. Cerebro-ocular-facial-skeletal (COFS) syndrome (Gershoni-Baruch et al. 1991)
    1. Microcephaly with brain hypoplasia
    2. Flexion contractures
    3. Micrognathia
    4. Typical, deep set eyes with blepharophimosis and prominent root of the nose: different from the protruding eyes and flattened nose seen in NLS
5. Cerebro-arthro-digital syndrome (Spranger et al. 1980)
    1. Arthromyodysplasia
    2. Dyscephaly
    3. Sacral dysgenesis
    4. Brain malformation
    5. Hypoplastic digits
    6. Suspected environmental causes (ergotamine exposure in one case and diazoxide intake in another)
6. Lethal multiple pterygium syndrome (please see the chapter of "► Lethal Multiple Pterygium Syndrome")
7. Fetal akinesia/hypokinesia sequence (please see the chapter of "► Fetal Akinesia Deformation Sequence")
8. Smith-Lemli-Opitz syndrome (please see the chapter of "► Smith–Lemli–Opitz Syndrome")
9. Miller-Dieker syndrome (please see the chapter of "► Miller-Dieker Syndrome")

Diagnostic Investigations

1. Radiography
    1. Multiple contractures
    2. Hemivertebrae
    3. Kyphoscoliosis
    4. Abnormal occipital bone and biphalangeal fingers (Al-Lawama and Basha 2010)
2. Histopathology of the skin
    1. Hyperkeratosis
        1. With or without parakeratosis
        2. Associated with abundant subcutaneous tissue and excess of fat
    2. Myxomatous connective tissue associated with excess subcutaneous adipose tissue
    3. Epidermal and dermal atrophy
3. Ultrasound of the brain for CNS anomalies
4. Brain CT scan (AL-Lawama and Basha 2010)
    1. Microcephaly
    2. Lissencephaly
    3. Intraventricular hemorrhage
    4. Intracerebral hemorrhage
5. Normal chromosomes

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25%
    2. Patient's offspring: a lethal entity not surviving to reproductive age
2. Prenatal ultrasonography including 3-D U/S (Shapiro et al. 1992; Gülmezoğlu and Ekici 1994; Durr-e-Sabih et al. 2001; Rode et al. 2001; Aslan et al. 2002; Driggers et al. 2002; Shivarajan et al. 2003; Manning et al. 2004; Mattos et al. 2015)
    1. Severe growth retardation: a major feature
    2. Polyhydramnios
    3. Microcephaly/deficient calvarial ossification
    4. CNS abnormalities (banana-shaped cerebellum, hypoplastic cerebellar vermis, enlarged cisterna magna, Dandy-Walker anomaly, choroid plexus cysts)
    5. Abnormal facies including receding forehead
    6. Exophthalmos
    7. Cataract
    8. Flattened nasal bridge
    9. Prominent lips
    10. Micrognathia
    11. Cystic hygromas/hydrops
    12. Pulmonary hypoplasia
    13. Flexion contractures/arthrogryposis
    14. Shortened limbs
    15. Excessive edema of the hands and feet
    16. Syndactyly
    17. Clubbing of the feet (talipes equinovarus)
    18. Absence of breathing movements, sucking, swallowing, or normal isolated arm and leg movements
    19. Restricted fetal movement (Kainer et al. 1996)

3. Prenatal MRI (Mattos et al. 2015)
   1. Proportional growth restriction
   2. Arthrogryposis with contracted upper limbs and club feet
   3. Microcephaly
   4. Hypoplastic cerebellum and micrognathia
   5. Absence of the corpus callosum
   6. Lissencephaly
   7. Micrognathia
   8. A hypersignal with thickening of the cranial subcutaneous tissues
4. Prenatal molecular genetic testing (Mattos et al. 2015)
   1. DNA was extracted from fetal and parental peripheral blood; all coding exons of *PHGDH* were PCR-amplified and subjected to Sanger sequencing.
   2. Sequencing of PHGDH identified a homozygous premature stop codon mutation (c.1297C>T; p.Gln433*) in fetal DNA, both parents (first cousins) being heterozygotes.
5. Management
   1. No specific treatment for the uniformly lethal disorder
   2. Mainly supportive with initial management of ventilatory, thermal, and nutritional support

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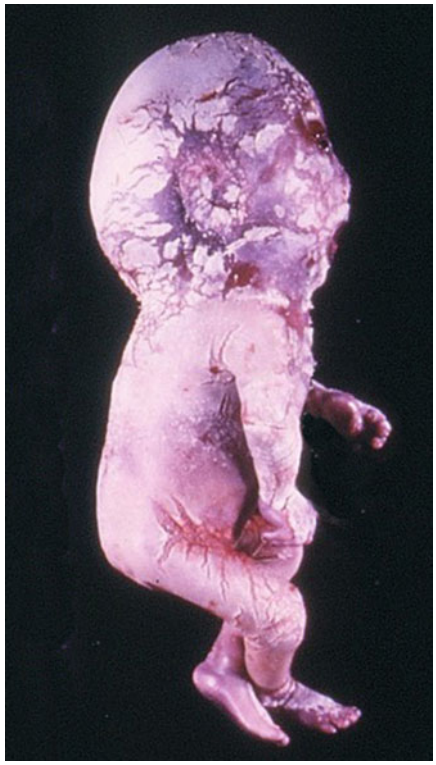

Fig. 1 An infant with Neu-Laxova syndrome showing severe ichthyosis (*thick*, *cracked* skin lesions forming deep fissures), characteristic facial features (absent eyelids, flattened nose, round gaping mouth, low-set ears with poorly developed pinnae), short broad neck, flexion contractures of the limbs, and short, small-caliber umbilical cord. Photomicrographs of skin (*not shown*) demonstrated a prominent hyperkeratosis of the epidermis and a thick layer of subcutaneous adipose tissue due to edema

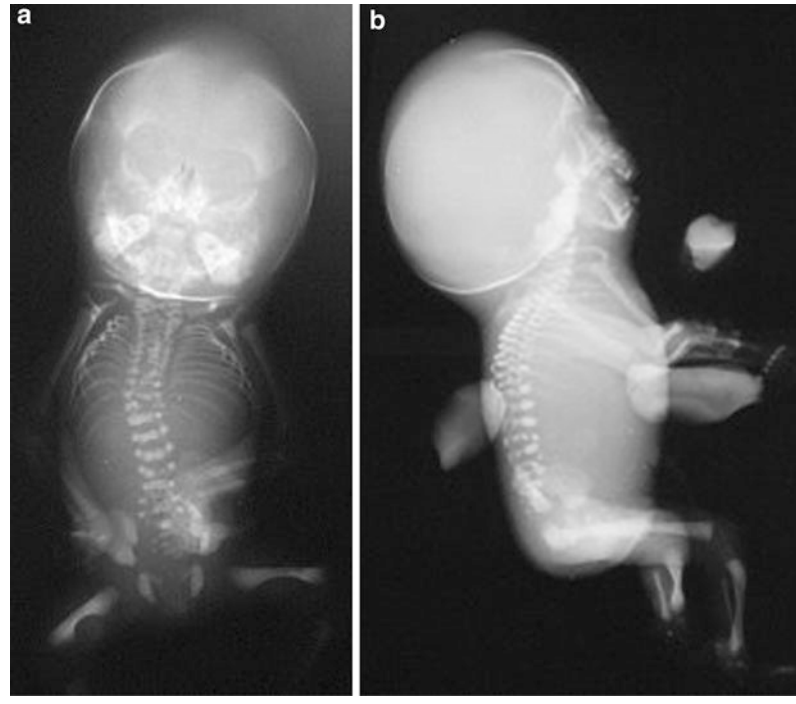

Fig. 2 (**a**, **b**) Radiographs showing hemivertebrae, kyphoscoliosis, and 11 pairs of ribs

Neural Tube Defects

Contents

Neural tube defects (NTDs) are among the most common severe congenital malformations of the central nervous system. Approximately 1 in 500 to 1 in 1,000 pregnancies results in NTDs. About 4,000 fetuses are affected each year in the USA. The incidence varies with geographic areas and ethnic groups. The incidence, however, appears to be decreasing recently.

Synonyms and Related Disorders

Anencephaly; Cephalocele; Cranial meningocele; Cranio-/spinal rachischisis; Cranium bifidum occultum; Encephalocele; Iniencephaly; Meningomyelocele; Spina bifida

Genetics/Basic Defects

1. Caused by a defect in closure of the neural tube, which is normally closed by 28 days.
2. Etiology: complex, involving environmental and genetic factors that interact to modulate the incidence and severity of the developing phenotype.
3. Specific causes are identified in less than 10% of affected infants.
    1. Chromosomal abnormalities
    2. Single-gene mutations
    3. Teratogens
4. Defects in the neural tube closure linked to 5,10-methylenetetrahydrofolate reductase deficiency and defects in the metabolism of folic acid.
5. Low erythrocyte folate in the first trimester of pregnancy: associated with an increased risk of neural tube defects.
6. Mildly elevated homocysteine in some pregnant women who subsequently give birth to infants with NTDs (Akar et al. 2000).
7. Genetic factor (van der Put et al. 1995): *MTHFR C677T* polymorphism: a specific mutation known as *C677T* polymorphism
    1. More common in parents of children affected with NTDs.
    2. This polymorphism affects the enzyme methylenetetrahydrofolate reductase (MTHFR), causing it to require more folic acid to work properly.
8. Major epidemiologic finding in NTDs: the protective effect of perinatal folic acid supplementation that reduces risk by 60–70% (Hall and Soelhdin 1998).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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9. Genetic studies in NTDs
    1. Have focused mainly on folate-related genes and identified a few significant associations between variants in these genes and an increased risk for NTDs.
    2. However, we are witnessing a rapid and impressive progress in understanding the genetic basis of NTDs, based mainly on the development of whole genome innovative technologies and the powerful tool of animal models (Bassuk and Kibar 2009).
    3. NTDs are not vitamin-deficiency disorders in the way that rickets results from early vitamin D deficiency. Rather, folate one-carbon metabolism is a key mechanism in the development of NTDs that is affected by, and interacts with, both genetic and environmental factors. The application of new genomic technologies to NTDs should herald the identification of many further risk factors, enabling understanding of the entire range of causative factors that affect the mother and her neurulation stage embryo (Copp et al. 2013).

Clinical Features

There are several morphologic types of NTDs: open NTDs (anencephaly, cranial or spinal rachischisis, iniencephaly, meningomyelocele, cranioectomesodermal hypoplasia), closed NTDs (cranial meningocele, cranial encephalocele, spinal meningocele alone or with spinal cord abnormality), and myelocystocele.

1. Anencephaly (Lemire et al. 1978)
    1. Refers to an absence of the brain and the calvarium covering the brain
    2. The most severe form of NTDs
    3. Incidence: about 1/1,000 live births
    4. Responsible for about 50% of all NTDs
    5. Infants with anencephaly
        1. Stillborn
        2. Die shortly after birth
    6. Anterior pituitary, eyes, and brainstem usually spared
    7. Remaining tissue covering the basal cranium: a highly vascular and friable membrane referred to as area cerebrovasculosa
    8. Striking craniofacial appearance
        1. Absent cranial vault
        2. An angiomatous membranous mass lying on the floor of the cranium
        3. An absent or backward sloping of the forehead
        4. Frog-like eyes (ocular proptosis)
        5. Puffy eyelids
        6. A flattened nose
        7. Large folded-down ears
        8. Often an open mouth
        9. A short neck
    9. Syndromes associated with anencephaly
        1. Chromosomal disorders [e.g., r(13), trisomy 18, del(13q)]
        2. Monogenic disorder (e.g., Meckel syndrome)
        3. Disruptive sequences (e.g., amniotic bands, maternal hyperthermia)
        4. Associations (e.g., spina bifida, holoprosencephalic face syndrome, craniofacial duplication)
2. Craniorachischisis or spinal rachischisis.
    1. Rachischisis: refers to anencephaly with a contiguous spinal defect involving at least the cervical spine region and extending for varying degrees down the spinal column.
    2. The area cerebrovasculosa and the area medullovasculosa fill the skeletal defects of the cranium and of the spinal column.
    3. Short neck.
    4. Upward-turned face.
    5. Ears touching the shoulders.
    6. Frequent polyhydramnios.
    7. Frequently stillborn.
    8. Neurologic involvement
        1. Primarily limited to brainstem and spinal reflexes
        2. Occasional seizures resembling infantile spasms
3. Iniencephaly (Doğan et al. 1996; Balci et al. 2001).
    1. The name iniencephaly is derived from an abnormality of the neck (inion) and the brain (cephaly) (Kulaylat and Narchi 2000).

2. Triad (Erdincler et al. 1998; Sahid et al. 2000).
    1. Deficient cranial bone
    2. Cervical dysraphism (rachischisis)
    3. Fixed retroflexion of the fetal head and severe lordosis of the cervicothoracic spine
3. Closed or open lesions
    1. A closed lesion when the occipital bone is not malformed
    2. An open lesion when the occipital bone is hypoplastic
4. Site of the neural tube lesion: at the level of the cervical spine
5. Severity of lesion
    1. Spina bifida with intact skin
    2. Meningomyeloencephalocele
    3. Open rachischisis
6. Associated CNS malformations
    1. Anencephaly
    2. Encephalocele
    3. Microcephaly
    4. Hydrocephaly
    5. Holoprosencephaly
    6. Posterior fossa defects
    7. Spinal defects such as cervical dysraphism
    8. Fixed cervical hyperlordosis
7. Other associated malformations
    1. Diaphragmatic hernia
    2. Omphalocele
    3. Thoracic cage deformities
    4. Hypoplastic lungs
    5. Genitourinary malformations
    6. Cyclopia
    7. Cleft lip and palate
    8. Imperforate anus
    9. Clubfoot
    10. Single umbilical artery
8. Die within a few hours in most newborns

4. Cranium bifidum occultum.
    1. The most benign type.
    2. Generally asymptomatic.
    3. Skull defects often close over time.
    4. Persistent parietal foramina (sometimes called "Catlin marks" after the family for which it was described; transmitted as an autosomal dominant trait via a gene located on 11p)
    5. Persistent wide fontanelle
5. Cranial meningocele.
    1. Associated with a defect in the skull
    2. Associated with protrusion of the leptomeninges
6. Encephalocele (Cohen and Lemire 1982; Hall and Soelhdin 1998).
    1. A type of cephalocele (a herniation of cranial contents though a skull defect) that contains the brain
    2. Incidence: 1/10,000 live births
    3. Occurring most frequently in the occipital region (80–90%) and commonly associated with a variety of syndromes, notably Meckel-Gruber syndrome and Walker-Warburg syndrome
    4. Anterior encephaloceles: found more commonly in Roberts syndrome
    5. An isolated malformation of frontal encephalocele: more commonly seen in southeast Asia
    6. Outcome depending on the position of the defect and on the associated anomalies
    7. Chromosome syndromes associated with encephalocele (Hall and Soelhdin 1998)
        1. Trisomy 13
        2. Trisomy 18
        3. Del(13q)
        4. Del(2)(q21 → q24)
        5. Dup(1q)
        6. Dup(6) (q21 → qter)
        7. Dup(7)(qter → p11)
        8. Dup(8)(q23 → qter)
        9. Turner syndrome
    8. Monogenic disorders associated with encephalocele
        1. Meckel syndrome
        2. Cryptophthalmos syndrome
        3. Silverman-Handmaker type and Rolland-Desbuquois type of dyssegmental dysplasias
        4. Knobloch syndrome
        5. Chemke syndrome
        6. Roberts syndrome
        7. Walker-Warburg syndrome
        8. van Voss-Cherstovy syndrome
    9. Disruptive sequences associated with encephalocele

1. Maternal hyperthermia
2. Warfarin embryopathy
3. Amniotic bands

10. "Associations" associated with encephalocele
    1. Absent corpus callosum
    2. Dandy-Walker malformations
    3. Arnold-Chiari malformation
    4. Holoprosencephaly
    5. Craniosynostosis
    6. Ectrodactyly
    7. Frontonasal dysplasia
    8. Hypothalamic-pituitary dysfunction
    9. Klippel-Feil anomaly
    10. Iniencephaly
    11. Myelomeningocele
    12. Oculoauriculovertebral spectrum

7. Spina bifida cystica (the most common lesion).
    1. Myelomeningoceles (meningomyeloceles)
        1. A herniation of the spinal cord and/or nerves through a bony defect of the spine.
        2. Usually open defects in which meninges and/or neural tissue is exposed to the environment associated with leaking CSF.
        3. The most common type of spina bifida cystica (about 90%).
        4. Approximately 20% of affected infants have additional congenital anomalies, such as gastrointestinal, cardiac, and urogenital malformations.
        5. Surviving infants with spina bifida likely have severe, lifelong disabilities and psychosocial maladjustment.
        6. Medical problems
            1. Paralysis
            2. Hydrocephalus
            3. Arnold-Chiari type II malformation (herniation of the cerebellar vermis and brainstem below the foramen magnum)
            4. Endocrine abnormalities
            5. Tethered cord
            6. Syringomyelia (cavitation of the spinal cord whose walls are composed of glial tissue)
            7. Syringobulbia
            8. Deformed limbs and spine
            9. Bladder/bowel/sexual dysfunction
            10. Learning disabilities
        7. Neonates with Arnold-Chiari malformation presenting with
            1. Stridor secondary to vocal cord paralysis
            2. Central apnea
            3. Aspiration
            4. Dysphagia
            5. Hypotonia
            6. Progressive brainstem dysfunction
            7. Myelopathy
            8. Quadriparesis
            9. Nystagmus
            10. Strabismus
            11. Poor sucking
            12. Swallowing difficulties
    2. Meningoceles
        1. A saccular herniation of meninges and CSF through a bony defect of spine and usually covered by normal skin
        2. No herniation of the spinal cord or nerve roots into the dorsal dural sac
        3. A cystic mass full of cerebrospinal fluid
        4. Without associated neurologic problems such as hydrocephalus and Chiari II malformation
    3. Lipomeningocele or lipomyelomeningocele
        1. A lipomatous mass herniating through the bony defect and attaching to the spinal cord, tethering the cord and often its nerve roots
        2. Presentation with a skin-covered mass above the buttocks and eventual neurologic deficits
        3. Absent associated hydrocephalus
    4. Myelocystocele
        1. A large terminal cystic dilatation of the spinal cord secondary to hydromyelia giving rise to a large terminal skin-covered sac.
        2. Constituting 4–6.5% of the skin-covered masses overlying the lower spine.
        3. The majority of cases are dorsally located; only rarely (about 0.5%) are ventral in location.

4. The ventral type is an anterior sacral meningocele, most often presenting as a pelvic mass in females.
5. Cervical myelocystocele.
6. Lumbar myelocystocele.
7. Terminal myelocystoceles accompanying midline abdominal and pelvic defects such as part of the OEIS (*o*mphalocele-*e*xstrophy of the bladder-*i*mperforate anus-*s*pinal defects) complex.
8. Chiari malformation less frequent since the lesion is covered by dura with regular hydrodynamics of the cerebrospinal fluid.
9. Other associated malformations
    1. Genitourinary tract anomalies
    2. Intestinal malrotation
    3. Club feet
10. Differential diagnoses
    1. Meningomyelocele
    2. Lumbosacral and sacrococcygeal teratomas
    3. Lipomas
    4. Lipomyelomeningoceles
    5. Hamartomas

5. Lifelong disability risks in infants with spina bifida
    1. At risk for psychosocial maladjustment
    2. Medical problems resulting from the neurologic defects or from its repair
        1. Paralysis
        2. Hydrocephalus
        3. Arnold-Chiari malformation
        4. Endocrine abnormalities
        5. Tethered cord
        6. Syringomyelia
        7. Syringobulbia
    3. Medical problems as sequelae of the neurologic deficits
        1. Deformations of the limbs and spine
        2. Bowel, bladder, and sexual dysfunction
        3. Learning disabilities

8. Spina bifida occulta.
    1. A bony defect of the spine occurs most often at S1 and/or S2 and is covered by normal skin (a closed lesion)
    2. No herniation of the meninges through the bony defect
    3. Without associated hydrocephalus or Chiari II malformations
    4. Paraspinal cutaneous lesions with high index of suspicion pointing toward the underlying spina bifida (Drolet 2000)
        1. Hypertrichosis or hairy patches.
        2. Lumbosacrococcygeal dimples and sinuses.
        3. Acrochordons (skin tags): a small, flesh-colored to dark brown, sessile or pedunculated lesion consisting of a hyperplastic epidermis enclosing a dermal stalk of connective tissue.
        4. True tails: a caudal midline appendage capable of spontaneous or reflex motion consisting of skin covering muscle, adipose, connective tissue, blood vessels, and nerves but lack vertebrae and abnormal tissue.
        5. Pseudotails: a caudal protrusion composed of adipose (lipoma), teratomatous elements, or cartilage.
        6. Lipomas.
        7. Hemangiomas: indicator for tethered cord syndrome.
        8. Aplasia cutis congenita (congenital absence of skin) or scar.
        9. Dermoid cyst or sinus: 12–35% of children with spina bifida occulta have sacrococcygeal dermoid cysts or sinuses, which rarely connect with the intraspinal canal. Lesions above these levels along the spine are more likely to connect with the intraspinal canal and increasingly associated with spina bifida occulta.
    5. Paraspinal cutaneous lesions with low index of suspicion (Drolet 2000)
        1. Telangiectasia
        2. Capillary malformation (port-wine stain)
        3. Hyperpigmentation (lentigines or café-au-lait-like lesions)
        4. Melanocytic nevi
        5. Teratomas: most common in the sacrococcygeal region in infancy
    6. Neurologic deficits (Jallo 2013)
        1. Weakness of leg or legs

2. Leg atrophy or asymmetry
3. Loss of sensation
4. Painless sores
5. Hyperreflexia
6. Unusual back pain
7. Abnormal gait
8. Radiculopathy
9. Neurogenic bladder
10. Incontinence

9. Multiple NTDs at different sites (Ahmad et al. 2008): The presence of meningomyelocele and/or encephaloceles at multiple (two or more) sites along the vertebral axis is a very rare event occurring in 1% of cases.
   1. Double NTDs
   2. Triple NTDs

Diagnostic Investigations

1. Neurological examination of neonates
   1. Size, site, and level of the lesion
   2. Motor and sensory level
   3. Presence of associated hydrocephalus
   4. Presence of associated symptomatic hindbrain herniation such as Chiari II malformation
   5. Presence of associated orthopedic deformity
2. Neonatal cranial ultrasonography to demonstrate hydrocephalus
3. Radiography
   1. Occult spinal disorders in children (Jallo 2013)
      1. Lamina defects
      2. Hemivertebrae
      3. Scoliosis
      4. Widening of interpedicular distance
      5. Butterfly vertebrae
   2. Generally to detect bony defects
4. CT
   1. Cranial defects
   2. Spinal defects
5. MRI: provides exquisite detail of both the cranial defect and the herniated contents
   1. Cranial defects
   2. Cerebral defects
      1. Hydrocephalus
      2. Gray matter heterotopia
      3. Schizencephaly
      4. Gyral abnormalities
      5. Agenesis and thinning of the corpus callosum
      6. Abnormal thalami
      7. Abnormal white matter
   3. Herniated contents in Chiari malformations
   4. Associated lesions
      1. Diastematomyelia
      2. Syringomyelia
      3. Hydromyelia
      4. Tethered cord

Genetic Counseling

1. Recurrence risk
   1. Affected first-degree relatives
      1. One sib affected (5%)
      2. Two sibs affected (10%)
      3. Three sibs affected (21%)
      4. One parent affected (3–4.5%)
      5. One parent and one sib affected (13%)
   2. Affected second-degree relative: uncle/aunt, half sib (2%)
   3. Third-degree relative: first cousin (1% or less)
2. Prenatal diagnosis (Cameron and Moran 2009)
   1. Risk assessment prior to biochemical and/or ultrasonic screening
      1. The most significant risk factor: a history of having a previous child affected with neural tube defect
      2. Other independent (nongenetic) risk factors (Cameron and Moran 2009; Copp and Greene 2010)
         1. Valproic acid
         2. Folic acid antagonists (methotrexate, aminopterin, carbamazepine, fumonisin, trimethoprim)
         3. Vitamin A
         4. Maternal diabetes
         5. Maternal obesity
         6. Hyperthermia
         7. Micronutrient deficiencies (folate, inositol, vitamin B12, zinc)

2. Two approaches used for NTD screening in low-risk population
    1. Biochemical testing of maternal blood for alpha-fetoprotein (AFP)
        1. Measurement of maternal serum alpha-fetoprotein (MSAFP): a useful tool for mass screening of pregnant women for NTDs.
        2. All cases of anencephaly and about 65% of cases of spina bifida are identified by measurement of MSAFP and ultrasonography.
        3. Not effective in closed NTDs (10% of lesions) which do not increase AFP.
        4. AFP needs to be expressed as multiples of the median (MoM), since the maternal serum level of AFP varies with gestation.
        5. Using 2.5 MoM as screen positive in singleton pregnancies, the detection rate for anencephaly is expected to be >95% and for open NTD between 65% and 80%.
        6. False-positive rates should lie between 1% and 3% (Bradley et al. 2005). A raised serum AFP is not diagnostic for open NTD as it can be associated with other abnormalities including gastroschisis, omphalocele, congenital nephrosis, and fetal demise.
    2. Use of 2D/3D ultrasonography (Budorick et al. 1995)
        1. Used both as a screening test and as a follow-up test after positive results on MSAFP screening (Robinson et al. 1980; Lindfors et al. 1987).
        2. First-trimester detection rates for anencephaly and encephalocele: typically quoted as >90% for anencephaly and encephalocele and lower rates for spina bifida (44%).
        3. Second-trimester scanning improves the detection of spina bifida, typically to 92–95%.
        4. Direct demonstration of the spinal defect.
        5. Indirect signs: lemon sign (referring to a symmetrical bifrontal narrowing of the skull) and banana sign (cerebellar abnormality) (Nicolaides et al. 1986; Campbell et al. 1987; Van den Hof et al. 1990).
        6. Carefully evaluate the whole fetus because of associated malformations in around 20% (Stoll et al. 2007).
    3. Fetal MRI (Saleem et al. 2009)
        1. An important adjunct to the USA in assessing NTD (Kölble et al. 2001)
        2. Can identify topography and contents of sacs and add CNS and non-CNS findings
        3. Influence management decision
    3. Prenatal diagnosis of iniencephaly by careful sonography
        1. Marked fixed retroflexion of the head and neck
        2. Rachischisis
        3. Extreme lordosis of the fetus
    4. Prenatal diagnosis of cephalocele in the first trimester: associated with a high rate of termination of pregnancy and early intrauterine fetal demise (Sepulveda et al. 2015)
    5. Amniotic fluid alpha-fetoprotein (AFAFP) and amniotic fluid acetylcholinesterase (AFAChE): confirmatory tests for spina bifida
3. Management: complex and challenging
    1. Prevention (Smithells et al. 1983; Milunsky et al. 1989; American Academy of Pediatrics & Committee on Genetics 1999; Toriello 2005; Green and Copp 2014; Salib et al. 2014)
        1. Folic acid supplementation of 0.4 mg/day to all women capable of becoming pregnant: decrease the first occurrence of NTDs by at least 40%
        2. Folic acid supplementation of 4 mg/day in families with previous children born with NTDs: decrease risk of recurrence by 70%
        3. Periconceptional use of folic acid supplementation will prevent 50–70% of NTDs (Czeizel and Dudas 1992; Molloy et al. 1999; Botto et al. 1999; Iqbal 2000)

2. Medical management
    1. Antibiotic prophylaxis to prevent meningitis and ventriculitis
    2. Urological management
    3. Management of rectal incontinence
    4. Preventable conditions
        1. Urinary tract infections
        2. Calculi
        3. Skin ulcerations
        4. Latex allergy and sensitization
3. Surgical treatment
    1. Closing all but the prognostically worst cases
    2. Concurrent shunting of coexisting hydrocephalus often necessary
    3. Decompression of the posterior fossa and/or cervical cord in Chiari II malformations
    4. Spina bifida occulta: prophylactic surgical repair more effective than waiting for patients to experience a significant neurologic deficit such as a neurogenic bladder or leg weakness from these occult spinal lesions
    5. Orthopedic management of scoliosis
4. Fetal spina bifida repair (Fichter et al. 2008)
    1. Position statement on fetal myelomeningocele (MMC) repair by MMC Maternal-Fetal Management Task Force (Cohen et al. 2014).
    2. Several reports of intrauterine repair of meningomyelocele with benefits to motor function and a decreased incidence of shunt-dependent hydrocephalus and a reversal of hindbrain herniations (Bruner et al. 1999; Talipan et al. 1999; Rintoul et al. 2002).
    3. Especially fetuses treated before 26 weeks of gestational age, with small ventricles (<14 mm) at the time of surgery, and lesion levels below L2 seem to profit from fetal surgery.
    4. However, the clinical relevance of the observed regression of Chiari II malformation is still in dispute, and a positive effect on sensorimotor function could only be observed for patients with higher lumbar and thoracic spinal defects in the early postnatal period.
    5. Rehabilitation programs
        1. Physical therapy
        2. Occupational therapy
        3. Speech therapy
        4. Recreational therapy

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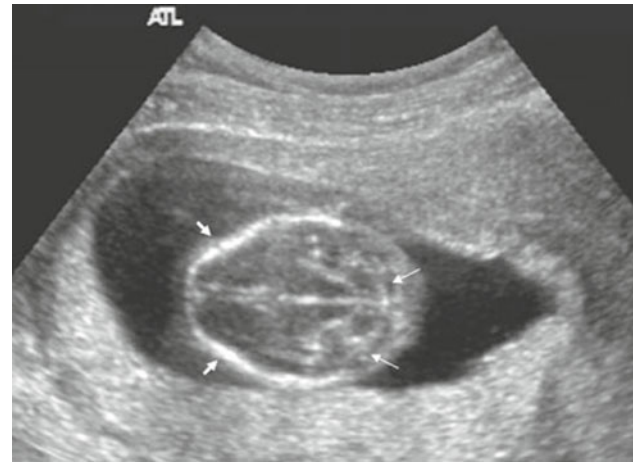

Fig. 1 Inward scalloping of the frontal bones, known as "lemon sign" (*short arrows*) and "banana sign" configuration of the cerebellum (*long arrows*), in a fetus with open spina bifida

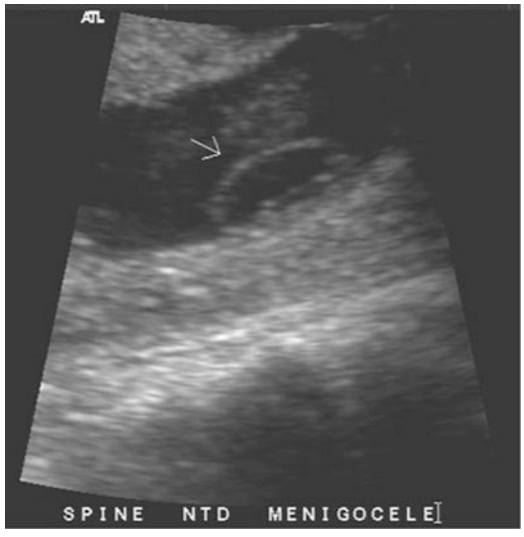

Fig. 2 A paraspinal unilocular cyst (*arrow*) in a fetus with lumbosacral meningocele

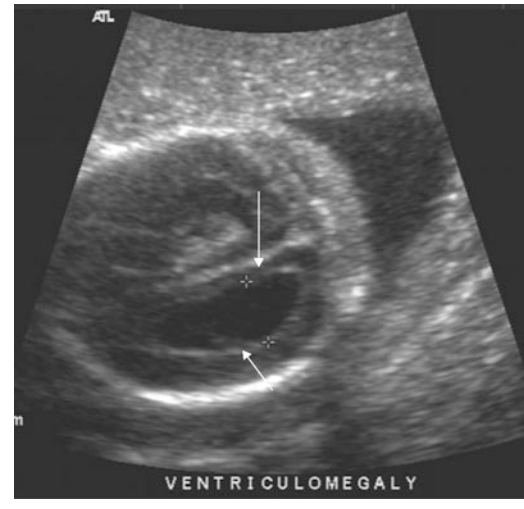

Fig. 3 Ventriculomegaly (*arrows*) observed in a fetus with lumbar meningomyelocele

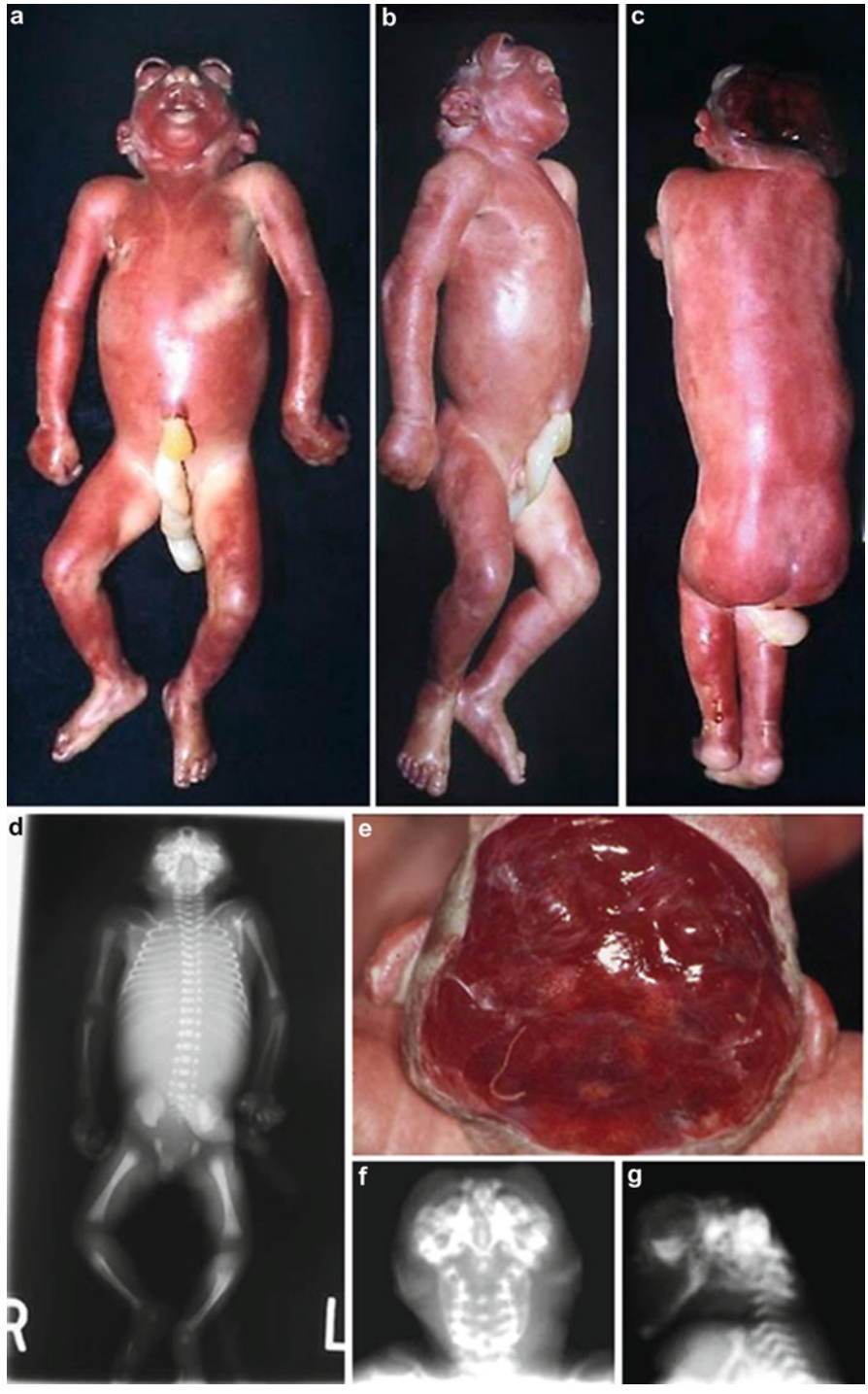

Fig. 4 (**a**–**g**) A stillbirth (**a**–**c**, **e**) with classic anencephaly showing absent cranial vault, an angiomatous mass on the skull base, an absent forehead, protuberant, puffy "frog-like" eyes, an open mouth, large folded-down ears, and a short neck. Radiographs (**d**, **f**, **g**) showed the absent calvarium

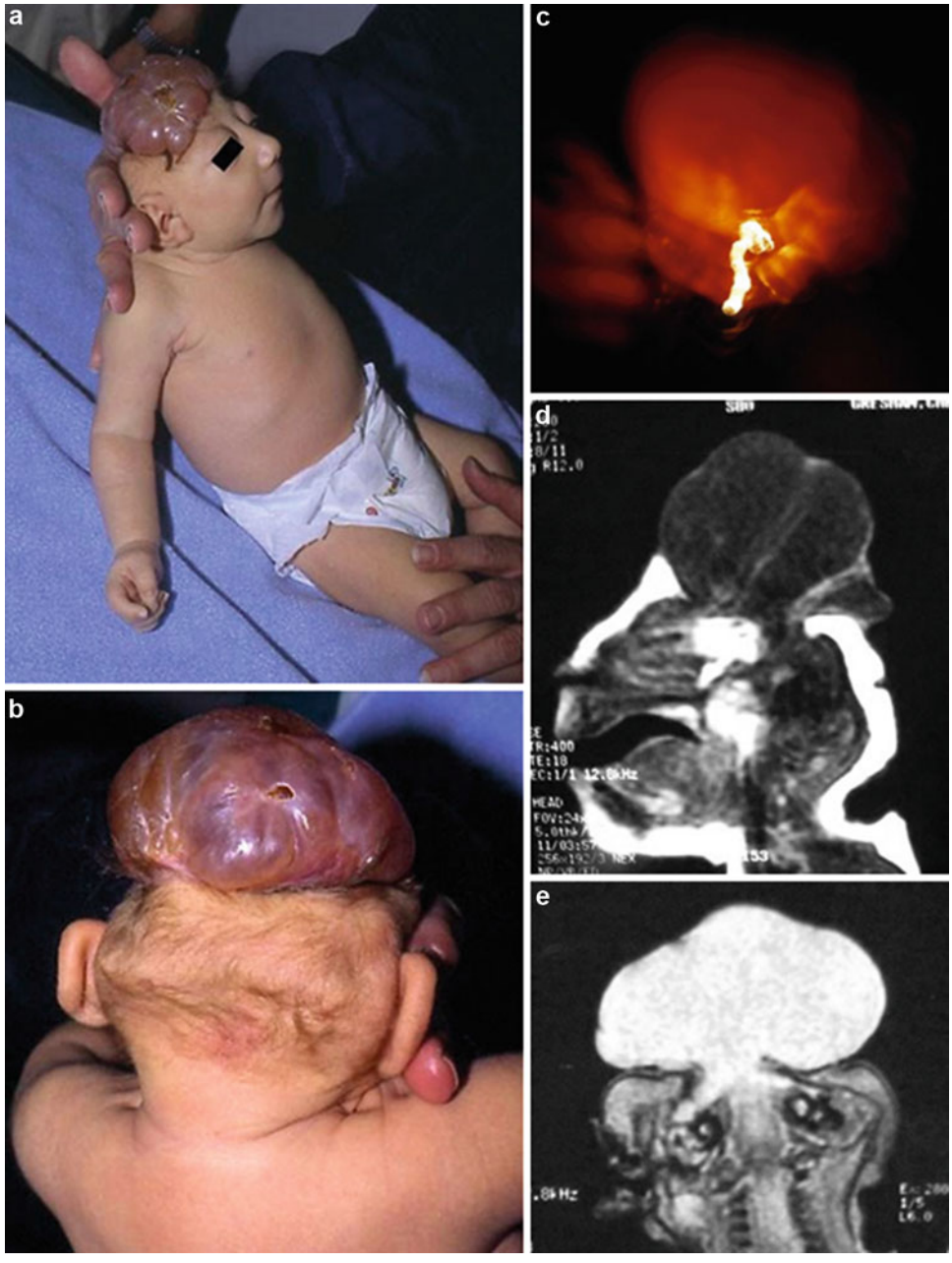

Fig. 5 (**a**–**e**) A newborn with anencephaly/meningocele (**a**) showing the presence of a meningeal sac above the base of the skull (**b**) without containing the brain tissue, illustrated by transillumination (**c**) and MRI of the brain with (**e**) or without contrast (**d**)

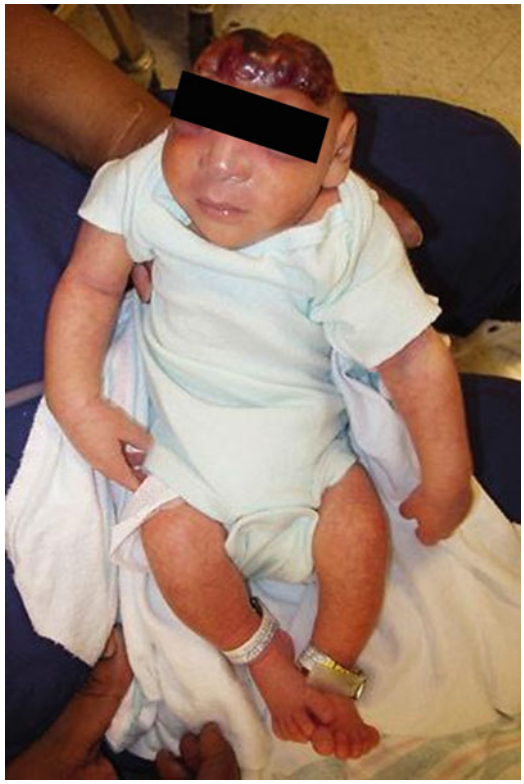

Fig. 6 Another neonate with anencephaly/meningocele showing similar craniofacial anomalies

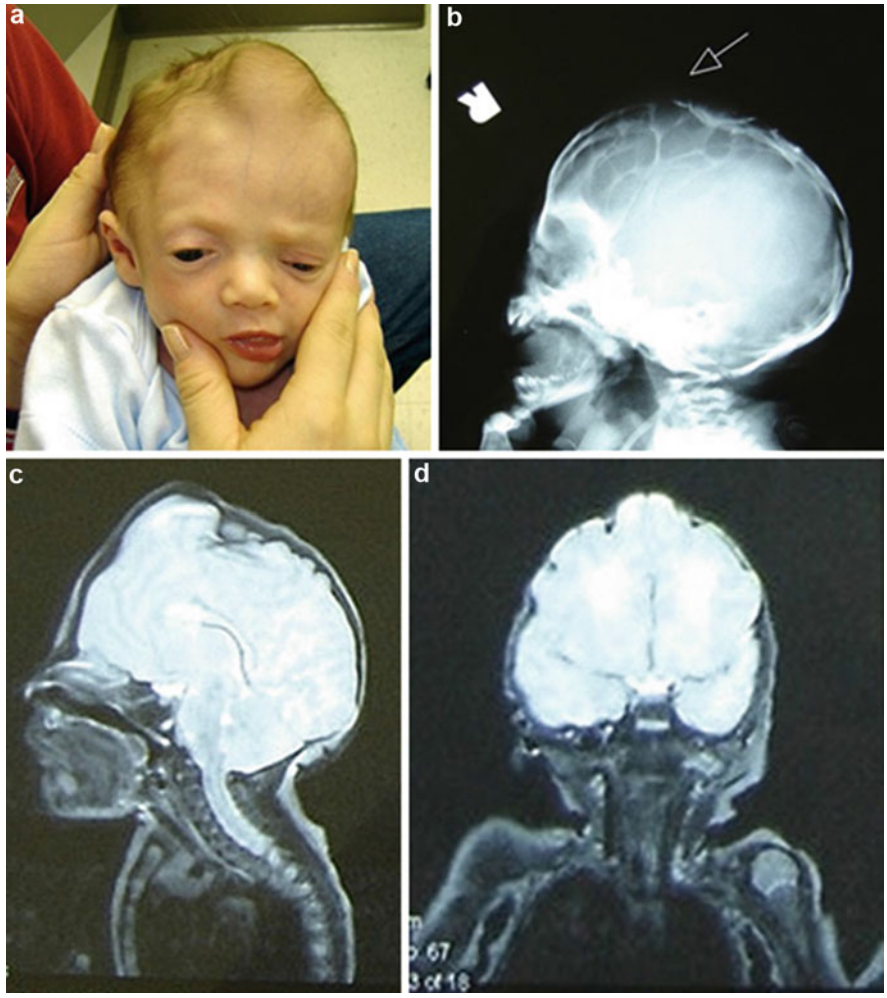

Fig. 7 (**a**–**d**) A 2-week-old infant with frontal encephalocele (**a**), illustrated by lateral skull radiograph (**b**) and MRI of the brain (**c**, **d**)

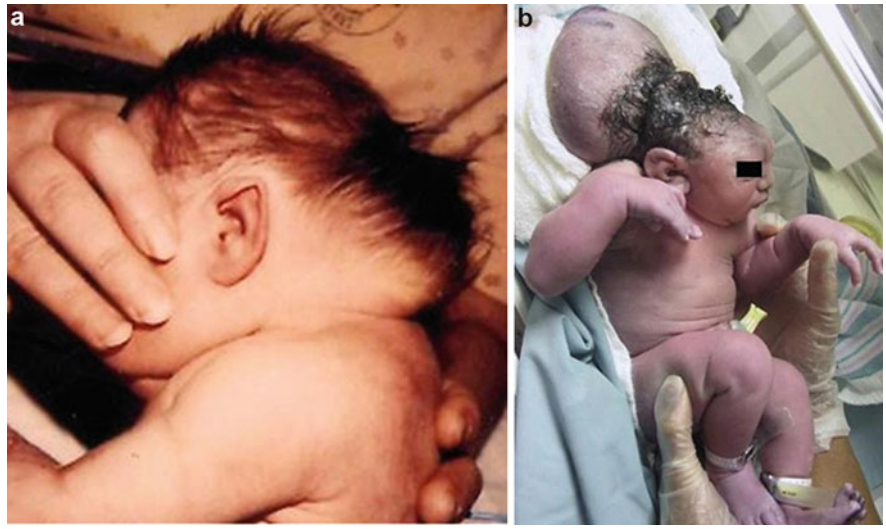

Fig. 8 (**a**, **b**) Newborns with an occipital encephalocele

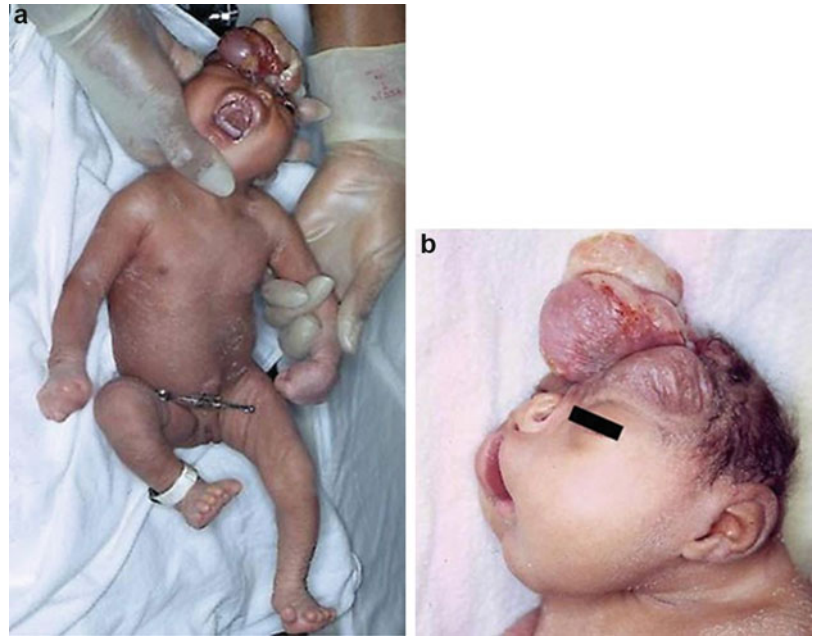

Fig. 9 (**a**, **b**) Encephalocele associated with amniotic band syndrome

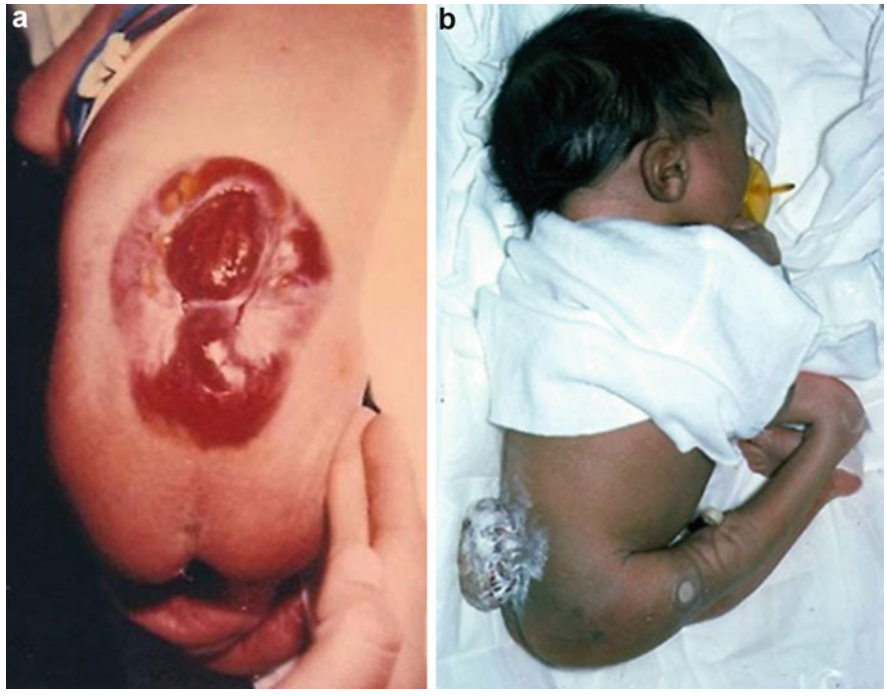

Fig. 10 (**a**, **b**) Newborns (**a**, **b**) with a lumbosacral myelomeningocele

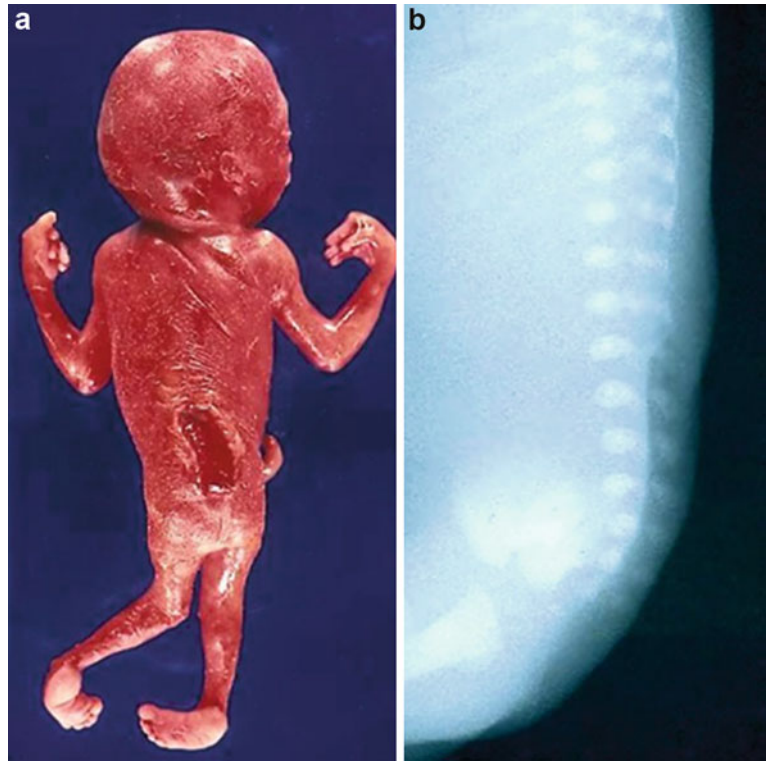

Fig. 11 (**a**, **b**) A fetus with trisomy 18 and open lumbosacral spina bifida (**a**), illustrated by lateral radiograph (**b**)

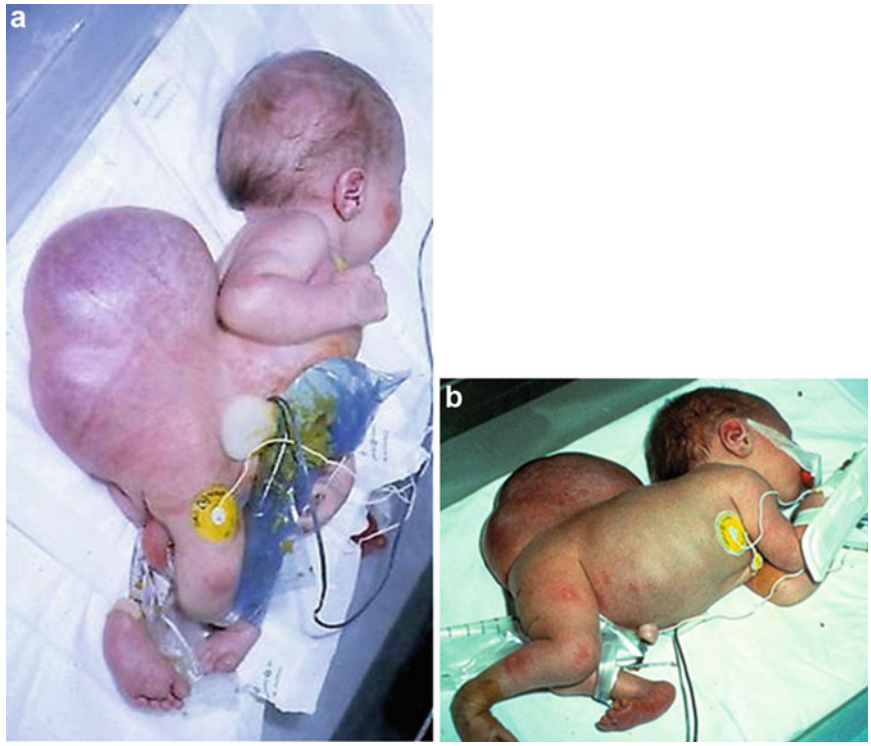

Fig. 12 (**a**, **b**) Two infants (**a**, **b**) with a large lumbosacral myelocystocele covered with skin

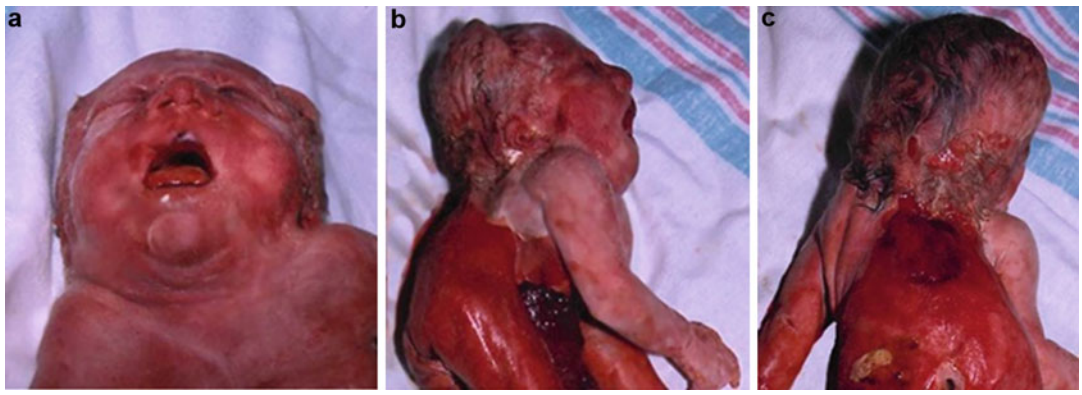

Fig. 13 (**a**–**c**) A stillborn with iniencephaly showing deficient cranium, short neck, cervical rachischisis, fixed retroflexion of the head, and severe lordosis of the cervicothoracic spine (**a**–**c**)

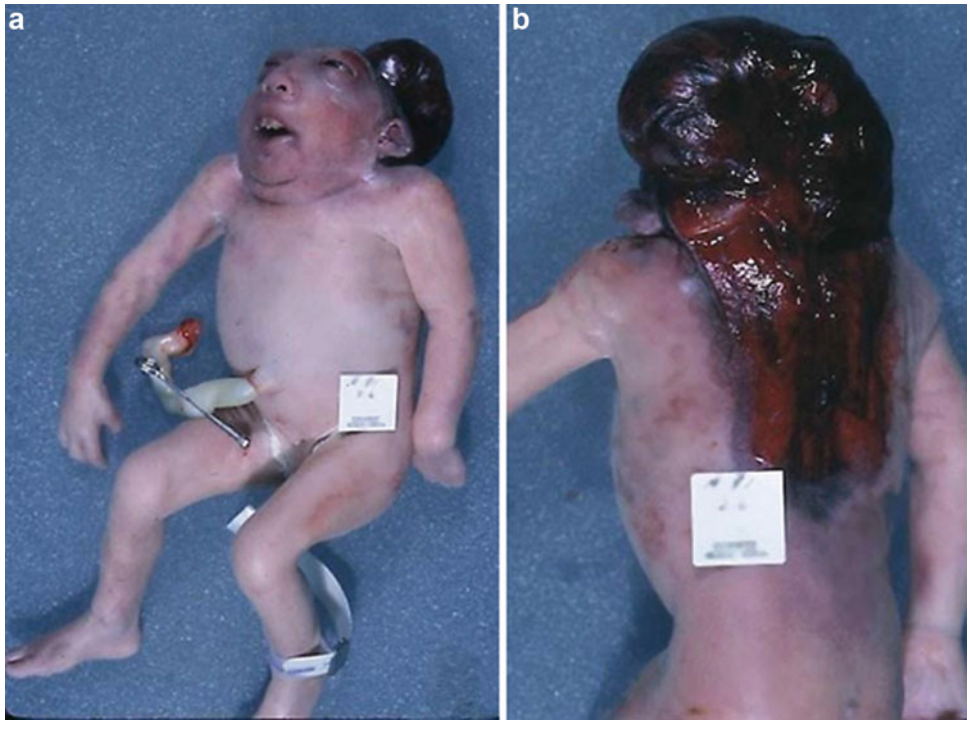

Fig. 14 (**a**, **b**) A stillborn with craniorachischisis showing anencephaly with a contiguous spinal defect involving cervical spine region and extending down the spinal column, short neck, upward-turned face, and ears touching the shoulders (**a**–**b**)

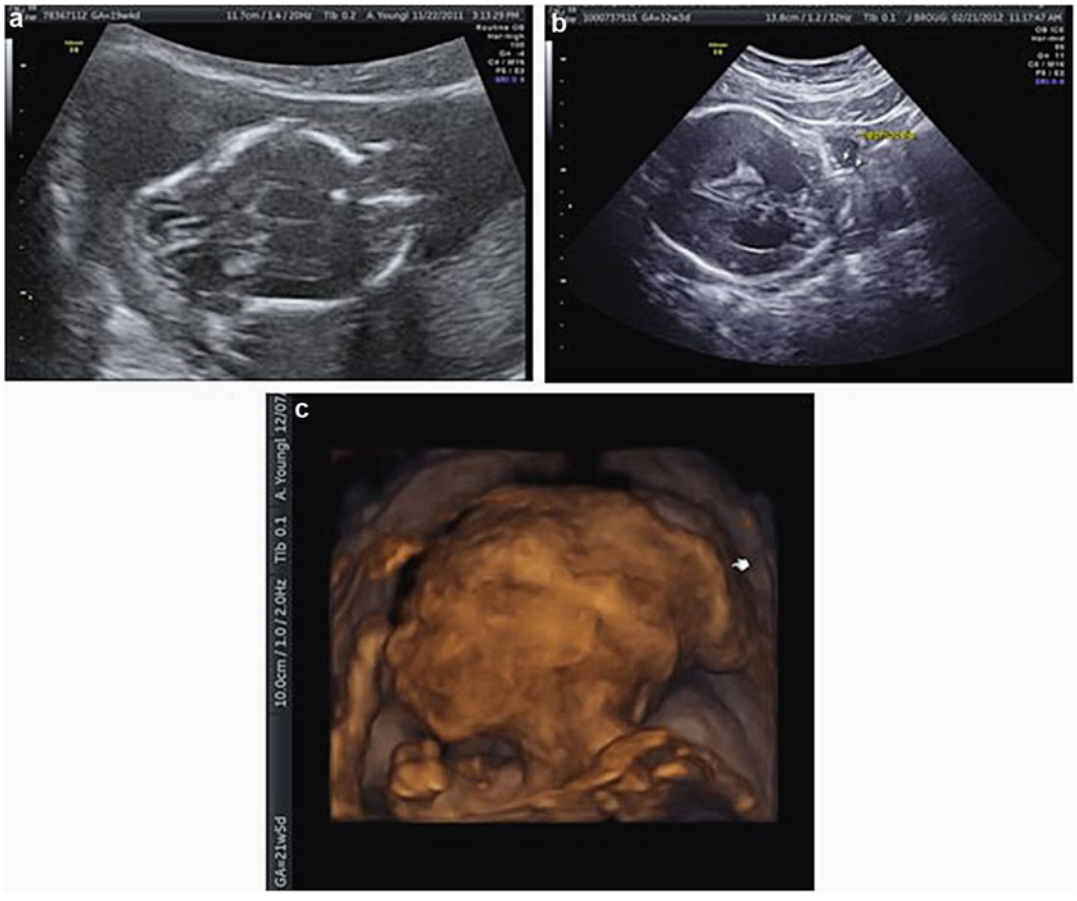

Fig. 15 (**a**–**c**) Ultrasound at 19w4d (**a**) showed occipital cephalocele. Ultrasound at 32w3d (**b**) showed lateral ventriculomegaly and occipital cephalocele. 4D real-time ultrasound (**c**) showed lateral view of the fetal craniofacial structures with occipital cephalocele (*arrow*) (Courtesy of Dr. Rose Brouillette)

Neurofibromatosis 1

Contents

Neurofibromatosis 1 (NF1) was described in 1882 by von Recklinghausen (1882) who gave the disease its first full description, including recognition that the tumors arose from the fibrous tissue surrounding small nerves, leading to his designation of these tumors as "neurofibromas." Thus, it is also called von Recklinghausen disease. It is one of the most common dominantly inherited genetic disorders affecting about 1 in 3000 newborns (Friedman 1999) and 1,000,000 people worldwide.

Synonyms and Related Disorders

Neurofibromatosis-Noonan syndrome; Peripheral-type neurofibromatosis; von Recklinghausen disease

Genetics/Basic Defects

1. Inheritance
   1. Autosomal dominant
   2. High spontaneous mutation rate
      1. One of the highest in humans (1×10^{-4} per gamete per generation).
      2. 50% of the cases are due to new mutations (Friedman 1999).
      3. Most patients are expected to have different mutations due to the high mutation rate at the *NF1* locus.
   3. Full penetrance (Carey et al. 1979; Riccardi and Lewis 1988): essentially 100% in adults after careful examination by a slit-lamp examination
   4. Widely variable expressivity even among family members with the same mutation (Carey et al. 1979, 1986; Riccardi and Lewis 1988; Rasmussen and Friedman 2000; Korf and Rubenstein 2005)
   5. Highly pleiotropic
2. The *NF1* gene
   1. Mapped to pericentromeric region of 17q11.2 (Barker et al. 1987).
   2. Entire sequence of the expressed *NF1* gene has been identified by a positional cloning strategy.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_178

3. A large size of the gene spanning over 350 kb of genomic DNA.
4. Consisting of at least 60 exons.
5. Translated into a 240-kDa protein, neurofibromin.

3. Mutations of the *NF1* gene
   1. Most described mutations are unique to a particular family.
   2. Type of mutations (over 250 different mutations described)
      1. Stop codon
      2. Substitutions
      3. Deletions of only one or a few base pairs, multiple exons, or the entire gene
      4. Insertions
      5. Intronic changes affecting splicing
      6. Alterations of the 3′ untranslated region of the gene
      7. Gross chromosomal rearrangements
   3. Severe truncation of the gene product in about 70% of the germ-line mutations
   4. *NF1* gene usually classified as a tumor suppressor gene (Shen et al. 1996) since mutations in both *NF1* alleles are detectable in malignant tumors associated with NF1 and in benign tumors, such as neurofibromas
4. *NF1* microdeletion syndrome (Moles et al. 2012)
   1. Approximately 5% of individuals with NF1 have a 1.4-Mb heterozygous 17q11.2 deletion encompassing *NF1*, formed through nonallelic homologous recombination (NAHR) between the low-copy repeats that flank this region
   2. NF1 microdeletion syndrome is more severe than NF1 caused by gene mutations, with individuals exhibiting:
      1. Facial dysmorphisms
      2. Developmental delay
      3. Intellectual disability
      4. Excessive neurofibromas
5. *NF1* microduplication syndrome (Moles et al. 2012)
   1. Clinical features seen in more than one individual with this microduplication include:
      1. Developmental delay
      2. Facial dysmorphisms
      3. Variable intellectual disability
      4. Seizures
   2. Other major features seen in single cases include:
      1. Microcephaly
      2. Macrocephaly
      3. Autism
      4. Cleft lip and palate
      5. Polymicrogyria
      6. Iris coloboma
   3. Neurofibromas were not noted in any of these individuals.
6. Knudson two-hit hypothesis is also applicable to explain the mechanism by which the manifestations of *NF1* occur (Dupuis and Nezarati 2001):
   1. A mutated tumor suppressor gene (the first hit)
      1. Inherited from a parent
      2. Presents in every cell of the body
   2. A second mutation (hit) in some somatic cells of the individual
      1. Knocks out the other copy of the gene
      2. Resulting in complete loss of the gene product and unregulated cell growth/division
      3. Resulting in a predisposition to cancer in the cells
7. Pathogenesis of NF1 (Boyd et al. 2009)
   1. Neurofibromin
      1. The *NF1* gene protein product.
      2. A tumor suppressor expressed in many cells, primarily in neurons, glial, and Schwann cells, and early in melanocyte development (Stocker et al. 1995; Zhu and Parada 2001).
      3. A regulator of ras guanosine triphosphatase activity (GTPase-activating protein, GAP), and as such, serves as a regulator of signals for cell proliferation and differentiation (Korf and Rubenstein 2005).
      4. Neurofibromin interacts with the proto-oncogene RAS to suppress tumor formation (Karajannis and Ferner 2015). Loss of function of neurofibromin may, therefore, remove

this regulation and lead to uncontrolled cell proliferation.
5. Neurofibromin is expressed in blood vessel endothelial and smooth muscle cells, and NF1 vasculopathy may result from an alteration of neurofibromin function in these cells (Hamilton and Friedman 2000).

2. Schwann cells in neurofibromas and melanocytes in café-au-lait macules:
1. Have a mutation in both *NF1* alleles, including a germ-line and an acquired somatic mutation.
2. Considered the primary tumor cell in their respective cutaneous manifestation.
3. Based on these findings, it is likely that NF1 functions as a tumor suppressor gene (Maertens et al. 2007; de Schepper et al. 2008).
4. Both of these cell types are descendants of neural crest.
5. The exact timing of the acquired mutation is unknown but is crucial in the development of the various manifestations:
1. Experiments have shown that *NF1* gene inactivation at the neural crest stage and mature Schwann cell stage do not lead to tumor formation.
2. However, in a progenitor intermediate step between these two stages, tumor formation occurs with *NF1* gene inactivation (Wu et al. 2008).

8. Marked heterogeneity in NF1
1. Whole gene deletion with distinctive phenotype
1. Early onset of cutaneous neurofibromas
2. Facial anomalies
1. Macrocephaly
2. Hypertelorism
3. Ptosis
4. Down-slanting palpebral fissures
5. Short nose
6. Low-set ears
7. Micrognathia
3. Developmental delay
4. Other standard features of NF1
2. Alternate forms of NF1 (conditions with incomplete/atypical features)
1. Mixed neurofibromatosis
2. Localized neurofibromatosis
1. Segmental neurofibromatosis (occasional localized café-au-lait spots, segmental distribution of dermal neurofibromas, no systemic manifestations, uncommon internal manifestations of neurofibromas)
2. Gastrointestinal neurofibromatosis
3. Familial spinal neurofibromatosis (multiple café-au-lait spots and neurofibromas involving spinal cord, lack dermal neurofibromas, and Lisch nodules)
4. Familial café-au-lait spots (autosomal dominant café-au-lait spots in rare multi-generation families, lack of neurofibromas, axillary freckling, and Lisch nodules)
3. Related forms of NF1 (conditions with additional features)
1. Neurofibromatosis/Noonan syndrome (may or may not fit the criteria of NF1 but with features of Noonan syndrome)
2. Watson syndrome
1. Multiple café-au-lait spots
2. Pulmonary stenosis
3. Intertriginous freckling
4. Short stature
5. Low intelligence

9. Several pathways are thought to be involved in the development of tumors associated with NF1 (Brems et al. 2009):
1. Rat sarcoma viral oncogene homologue (RAS)-mitogen-activated protein kinase (MAPK): Neurofibromin is involved in the downregulation of RAS-MAPK pathway, and NF1 belongs to the group of RAS-MAPK disorders that include Noonan, cardiofaciocutaneous, Costello, LEOPARD, and NF1-like syndrome.
2. Mammalian target of rapamycin (mTOR).
3. P21 protein (Cdc42/Rac)-activated kinase 1 (PAK1).

10. Variable expressivity (one of the hallmarks of NF1)

1. Intrafamilial variability (marked phenotypic differences may be observed within the same family)
2. Interfamilial variability (full spectrum of the disease, mild to severe form, may be present in different families in which affected individuals have the same NF1 mutation)

11. Prototype of a pleiotropic congenital multiple dysplasia syndrome involving CNS, vascular and skeletal systems, and a predilection for hamartomas, dysplasia, and malignancies.
12. The terms "mosaic generalized neurofibromatosis 1" and "mosaic localized neurofibromatosis 1" were introduced to reflect the disease pathogenesis and, more specifically, the time of the mutational event (Ruggieri and Huson 2001; Hardin et al. 2014):
    1. Somatic mutations giving rise to limited disease, such as SNF, are manifestations of mosaicism because an individual has a mixture of cells, some that have normal copies of the gene of interest and others that have an abnormal copy of that same gene.
    2. If the mutation occurs before tissue differentiation (early somatic mutation), the clinical phenotype will be generalized disease and clinically indistinguishable from nonmosaic form.
    3. Mutations that occur later in development (late somatic mutation) give rise to disease that is confined to a single region, often described as segmental form.
    4. It is known that early somatic mutations cause generalized disease, whereas mutations late in embryogenesis give rise to an affected single region or organ (localized disease) (Redlick and Shaw 2004).
    5. Individuals with the mosaic form:
        1. Less likely to have severe disease even with a generalized phenotype
        2. Lower offspring recurrence risk than individuals with the nonmosaic form
13. NF1 genotype-phenotype correlations (Pasmant et al. 2012; Shafty et al. 2016)
    1. Difficult to identify because of the complexity of the NF1 phenotype, its strong age dependency, the relatedness of many clinical features, and the huge heterogeneity of pathogenic NF1 mutations.
    2. Some NF1 patients with a given *NF1* mutation may develop very severe disease, while others with the same mutation have only mild symptoms.
    3. This phenotypic variability may be due to both modifier genes and environmental factors.

Clinical Features

1. Extreme interfamilial and intrafamilial clinical variability (Riccardi 1981)
    1. NF1 has a highly variable and unpredictable expression, even among affected individuals with the same mutation and within the same family (Ko et al. 2013).
    2. In neoplasms, the "second hit" theory explains the high variability even within members of the same family (Shafty et al. 2016).
2. Often not diagnosed at birth, especially a new mutation case
3. Cutaneous manifestations
    1. Café-au-lait spots (analogy of the color to coffee with milk).
        1. Present in nearly all patients
        2. Round or oval, discrete, well-circumscribed, uniformly light-brown-pigmented, macular lesions
        3. Usually present at birth but continue to increase in number and size during the first decade
        4. Six or more café-au-lait spots exceeding 0.5 cm in diameter in prepubertal children or exceeding 1.5 cm in broadest diameter in postpubertal individuals: the pathognomonic sign for NF1
    2. Hyperpigmentation patches may be associated with underlying plexiform neurofibromas, which are congenital in origin and

which may lead to extensive localized hypertrophy.
3. Freckles in the axillary, groin, and intertriginous areas (almost 90%): a helpful diagnostic feature.
4. Dermal neurofibromas, usually present in adults with NF1.
5. Xanthogranulomas (2–5%).
6. Hemangiomas (5–10%).

4. Lisch nodules (asymptomatic pigmented iris hamartomas)
   1. An extremely important diagnostic feature
      1. A characteristic sign of NF1 present in 97% of postpubertal patient
      2. Lesions typically not detected before 5 years of age
      3. Often appear before development of neurofibromas
   2. Best observed with slit-lamp examination
   3. Raised, often pigmented nodules of the iris, pathologically representing hamartomas
   4. Never resulting in significant disease
5. Peripheral neurofibromas
   1. Benign histologically
   2. May involve the viscera, such as the bowel, bladder, and liver, causing bleeding and obstruction
   3. May result in functional compromise and cosmetic disfigurement
   4. Increase in size and number during puberty and pregnancy
6. Gross forms of neurofibromas (Woodruff 1999)
   1. Localized cutaneous neurofibromas (nodular or polypoid): the most common form of neurofibromas. Numerous localized cutaneous neurofibromas are the hallmark of NF1.
   2. Localized intraneural neurofibromas (causing fusiform enlargement of the affected nerve).
   3. Plexiform neurofibromas (25%) (Korf 1999):
      1. Diffuse lesion involving nerve, muscle, connective tissue, vascular elements, and overlying skin
      2. Commonly leading to overgrowth of surrounding tissues during childhood
      3. Usually congenital
      4. Almost invariably apparent by 4 or 5 years of age
      5. One of the most common and debilitating complications of NF1
      6. Account for substantial morbidity, including disfigurement, functional impairment, and life-threatening complications
      7. Subject to transformation into malignant peripheral nerve sheath tumor (2–5%)
   4. Diffuse neurofibromas involving skin and subcutaneous tissue
   5. Massive soft-tissue neurofibromas (extreme neurofibromatous growth-producing massive, diffuse infiltration of soft tissue of a body part, often a distal extremity, leading to localized gigantism, cape formation, or, at the extreme end of the spectrum, formation of disfiguring redundant soft-tissue masses)
7. Certain selected clinical features of NF1 in different age groups (Riccardi 1992)
   1. Infancy
      1. Pseudarthrosis
      2. Seizures
      3. Constipation
      4. Congenital glaucoma
      5. Deafness
      6. Optic gliomas
   2. Childhood
      1. Optic gliomas
      2. Other brain tumors
      3. Kyphoscoliosis
      4. Genu valgum
      5. Seizures
      6. Cognitive disorders
         1. Developmental delay
         2. Learning disabilities
         3. Mental retardation
      7. Speech impediments
      8. Short stature
      9. Macrocephaly
      10. Early puberty
      11. Hypertension
      12. Embryonal tumors
      13. Leukemia

3. Preadolescence and adolescence: worsening of previous problems such as:
    1. Scoliosis
    2. Cosmetic disfigurement
    3. Major psychologic burden
    4. Malignancy (neurofibrosarcoma)
4. Early adulthood
    1. Increase in the number and size of cutaneous, subcutaneous, and plexiform neurofibromas
    2. Cosmetic disfigurement
    3. Functional compromise
        1. Pain
        2. Paralysis
        3. Gastrointestinal hemorrhage
        4. Renovascular hypertension
5. Adulthood
    1. An increased risk of developing a specific cancer (2–5% of patients with NF1)
    2. Neurofibrosarcoma and malignant peripheral nerve sheath tumor commonly arise in a plexiform neurofibroma in a young adult with symptoms of pain or rapid growth.

8. Skeletal involvement (50% of cases)
    1. Short stature (30%)
    2. Scoliosis
        1. Observed in approximately 20% of children with NF1
        2. The most common skeletal defect
        3. With or without classic dystrophic features such as vertebral scalloping and rib penciling
    3. Kyphosis
    4. Cervical spine abnormalities
    5. Spondylolisthesis
    6. Congenital pseudarthroses (3%), frequently with bowing of the tibia and fibula (2–5%)
        1. A peculiar and uncommon complication
        2. First noted as bowing, particularly of the tibia and fibula, in young children
        3. May progress to thinning of the cortex, pathologic fracture, and severe difficulties with nonunion of the fragments
        4. May go on to form a pseudarthrosis, or false joint, leaving the limb severely compromised
    7. Macrocephaly (40%)
    8. Skull bony defects
        1. Posterosuperior orbital wall bony defect
        2. Overgrowth of cranial bones
        3. Craniofacial asymmetry
        4. Sphenoid wing dysplasia (5–10%)
    9. Ocular hypertelorism
    10. Hemihyperplasia of a limb or digit
    11. Spina bifida
    12. Absent patella
    13. Elevated scapulas
    14. Congenital dislocation (hip, radius, ulna)
    15. Clubfoot
    16. Syndactyly
    17. Complete or partial absence of the limb bones
9. Endocrine abnormalities
    1. Sexual precocity (2–5%, the most common endocrine abnormality)
    2. Hypopituitarism
    3. Hypogonadism
    4. Gigantism
    5. Acromegaly
    6. Delayed sexual development
    7. Obesity
    8. Hypoglycemia
    9. Diabetes insipidus
    10. Goiter
    11. Myxedema
    12. Hyperparathyroidism
10. Cardiovascular diseases
    1. Vasculopathy
        1. Asymptomatic throughout life in many patients
        2. Symptomatic vasculopathy: uncommon
        3. Affect vessels, from the aorta to small arterioles, and result in vascular stenosis, occlusion, aneurysm, pseudoaneurysm, rupture, or fistula formation
        4. Renal arteries: the most frequently involved site
        5. NF1-associated cerebrovascular disease in children: presents with weakness, involuntary movements,

headaches, or seizures as a result of cerebral ischemia
6. NF1-related cerebrovascular disease in adults: similar symptoms and signs as a result of intracranial hemorrhage

2. Hypertension
1. Extremely common in adult patients with NF1 (33%)
2. Causes
1. Essential hypertension
2. Renal artery stenosis
3. Pheochromocytomas

3. Congenital heart disease (0.4–6.4%)
1. Pulmonary stenosis (recognized feature of Watson syndrome, NF1-Noonan syndrome, and individuals with large deletions of the NF1 gene)
2. Left heart obstruction (aortic stenosis or coarctation)
3. Other CHD

11. Neuropsychological impairment (Gutmann 1998; Ozonoff 1999; Kayl and Moore 2000; North 2000)
1. Cognitive impairments (30–65%)
2. Learning disabilities including attention deficit hyperactivity disorder and deficits in visuospatial processing (40–60%)
1. Easy distractibility
2. Impulsiveness
3. Deficient visual-motor coordination
4. Language and vocabulary deficits

3. Behavioral difficulties
4. Emotional and psychosocial difficulties
5. Mental retardation (4–8%)
6. Hydrocephalus (5%)
7. Neurosensory hearing loss (5%)

12. Tumor types associated with NF1 (Brems et al. 2009)
1. Non-nervous system tumors
1. Adulthood
1. Gastrointestinal stromal tumor
2. Somatostatinoma
3. Pheochromocytoma
4. Breast cancer

2. Childhood: rhabdomyosarcoma

2. Nervous system tumors
1. Adulthood and childhood
1. Astrocytoma
2. Malignant peripheral nerve sheath tumor

2. Childhood: neuroblastoma

13. Lifetime risk of different tumors in children and adults with neurofibromatosis 1 (Korf 2000; Lakkis and Tennekoon 2000; Hirbe and Gutmann 2014)
1. Glioma of the optic pathway (15–20%)
2. Other brain tumors (more than fivefold increase)
3. Malignant peripheral nerve sheath tumors (8–13%)
4. Gastrointestinal stromal tumor (4–25%)
5. Duodenal carcinoid tumor (1%)
6. Leukemia (about sevenfold increase)
7. Breast cancer (about fivefold increase)
8. Rhabdomyosarcoma (1.4-6%)
9. Pheochromocytoma (0.1–5.7%)

14. Major complications (Liebermann and Korf 1999)
1. Central nervous system
1. Optic glioma
2. Astrocytoma
3. Learning disability
4. Cord compression

2. Peripheral nervous system: nerve compression
3. Cutaneous
1. Cosmetic impairment due to neurofibromas
2. Pruritus: generalized itching or itching localized to newly developing neurofibromas experienced by many individuals

4. Orthopedic
1. Limb overgrowth
2. Scoliosis; long bone dysplasia

5. Vascular stroke
1. Hypertension
2. Aneurysm

6. Endocrine: precocious puberty
7. Gastrointestinal
1. Constipation: observed especially in patients with plexiform neurofibromas in the pelvic area which interfere with autonomic innervation of the colon and

produce both bowel and bladder problems
2. Obstruction
8. Ophthalmologic
1. Optic glioma
2. Glaucoma
9. Headache (10–20%)
1. Bothersome but usually not a disabling complaint.
2. Headache possibly indicates the presence of an intracranial tumor but no identifiable etiology in many patients.

15. Pathological manifestations of NF1 (Woodruff 1999)
1. Epidermis (pigmented macule or café-au-lait spot).
2. Iris (Lisch nodule, optic glioma).
3. Skeleton (malformations).
4. Blood vessels (mesodermal vascular dysplasias): Intrinsic lesions of arterial walls (vasculopathy) are important manifestations of NF1. It appears to contribute to excess mortality of young patients with NF1.
1. Asymmetric
2. Renal artery stenosis with consequent hypertension
3. Occlusion resulting in cerebral or visceral infarcts
4. Aneurysms resulting in hemorrhage
5. Arteriovenous fistulae
5. Brain
1. Glial hamartomas
2. Astrocytomas
6. Adrenal (pheochromocytoma)
7. Intestine
1. Somatostatinoma
2. Gastrointestinal autonomic nerve tumor
8. Peripheral nerve sheath
1. Neurofibromas
2. Malignant peripheral nerve sheath tumors

16. NIH diagnostic criteria (National Institutes of Health 1988)
1. National Institutes of Health consensus development conference identified seven important components of neurofibromatosis. Two or more of these components must be present for a diagnosis of neurofibromatosis:
1. Six or more café-au-lait spots, which are more than 5 mm in diameter in prepubertal patients and more than 15 mm in diameter in postpubertal individuals
2. Two or more neurofibromas of peripheral nerves of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal region
4. Optic glioma (age of presentation at preschool years) (Gutmann 1998)
5. Two or more Lisch nodules (hamartomas of the iris)
6. A distinctive bony lesion such as dysplasia of the sphenoid at the base of the skull or pseudarthrosis or thinning of the long bone cortex, with or without complete interruption of the bone
7. A first-degree relative (parent, sib, or offspring) affected with neurofibromatosis type 1 which was diagnosed according to the preceding criteria
2. These diagnostic criteria have been shown to be both highly specific and sensitive for adults with NF1 (Gutmann et al. 1997).
3. Because some of the criteria may not manifest until later in life, they are not as sensitive in children, especially those under the age of 8.
4. A 2000 retrospective review of nearly 1900 cases of NF1 found that 46% of sporadic cases did not meet criteria by age 1; however, 97% met criteria by age 8, and all fulfilled them by age 20 (DeBella et al. 2000).

17. Syndromes related to NF1 (Ruggieri 1999)
1. Neurofibromatosis type 2 (bilateral vestibular neurofibromatosis)
1. Clinically and genetically distinct from NF1.
2. *NF2* gene is mapped to chromosome 22.
3. Inheritance: autosomal dominant.

4. Often with a small number of café-au-lait spots (rarely more than six).
5. Often with one or two peripheral neurofibromas (usually not more).
6. Occasionally with Lisch nodules.
7. Posterior subcapsular cataracts detected by ophthalmologic examination in a sizable proportion of patients.
8. The hallmark of NF2: development of bilateral eighth cranial nerve tumors, properly called vestibular schwannomas rather than acoustic neuromas (by age 30 years in 95% of patients).
9. Other tumors of cranial and cervical nerve roots common.
10. NF2 much less common than NF1, affecting approximately 1 in 40,000 individuals.

2. Segmental or mosaic NF1
   1. Caused by somatic mutation of the *NF1* gene (Tinschert et al. 2000).
   2. Presence of NF1 features (café-au-lait spots, freckling and peripheral or plexiform neurofibromas, and Lisch nodules) in an individual with a segment of the body affected, which varies from a narrow strip to one quadrant and occasionally to one half of the body (Ruggieri and Huson 2001).
   3. Family history with invariably normal parents who, on rare occasions, can have a child with classic NF1.
   4. Presence of strong circumstantial evidence suggests somatic mutation of the *NF1* gene early in embryogenesis so that derivatives of that mutant line display the features of NF1.
   5. May transmit the disease if the mosaicism involves the germ line.
   6. Germ-line mosaicism for an *NF1* gene mutation has been observed in a clinically unaffected father of a child with new onset NF1.
   7. Somatic mosaicism for an *NF1* gene deletion has been detected in an individual with NF1 (Colman et al. 1996). Somatic mosaicism plays an important role in phenotypic and genetic aspects of NF1 and may even be a relatively common phenomenon.
   8. Possibility of demonstrating similar somatic mosaicism if cases of segmental NF1 are analyzed.
3. Watson syndrome
   1. Pulmonary stenosis with café-au-lait spots
   2. Dull intelligence
   3. Short stature
   4. A small number of neurofibromas
   5. Lisch nodules
   6. Deletions present in the NF1 gene in at least two families: no distinguishing aspect between the deletions causing Watson syndrome and those associated with more classic NF1
4. Neurofibromatosis 1-Noonan syndrome (Opitz and Weaver 1985)
   1. A Noonan syndrome phenotype in patients with NF1 (about 12%).
   2. Clinical features in addition to NF1
      1. Ocular hypertelorism
      2. Down-slanting palpebral fissures
      3. Low-set ears
      4. Webbed neck
      5. Pulmonic stenosis
      6. Pectus excavatum
      7. Mild hypertelorism
      8. Short stature
   3. Relatives affected with NF1 present with or without concomitant features of Noonan syndrome.
   4. Current understanding: The phenotype of NF1 can include features overlapping with those described in Noonan syndrome, but these disorders are probably genetically distinct.
5. Predominance of spinal tumors and relatively few peripheral neurofibromas identified in rare families
   1. Locus heterogeneity
   2. Not representing a distinct subtype of NF

18. Prognosis of NF1
    1. Progression of the disease with time
    2. Pregnancies in women with NF1

1. Normal pregnancies in most patients but serious complications have been noted in some patients.
2. Rapid increase in the number (60%) and size (52%) of neurofibromas during pregnancy (Dugoff and Sujansky 1996).
3. First onset of hypertension or marked exacerbation of preexisting hypertension during pregnancy.
4. Delivery complicated by large pelvic or genital neurofibromas often necessitates cesarean section in pregnant women with NF1.

3. Anesthetic risk
   1. Intraoral lesions compromising the airway (5%)
   2. Coexisting kyphoscoliosis (2%) and fibrosing alveolitis (20%) complicating the perioperative period
   3. Careful regional anesthesia to monitor the existence of neurofibromas affecting peripheral nerves and nerve roots
   4. Possible long-term muscular blockade following the use of suxamethonium and non-depolarizing muscle relaxants
4. Average life expectancy overall reduced by at least 15 years
   1. Malignancy and hypertension contributing to increased morbidity and mortality in adults with NF1 (Zöller et al. 1995)
   2. Risk for neurofibromatosis-related malignancy (8%)
   3. Most common malignancy: malignant peripheral nerve sheath tumors (Poyhonen et al. 1997)
   4. Better prognosis in patients with only mild and cosmetic symptoms of the disease

Diagnostic Investigations

1. Diagnosis of neurofibromatosis 1 based largely on clinical criteria despite progress in defining the molecular genetics of the disorder
2. Slit-lamp examination of the eyes to detect Lisch iris nodules
3. Radiography to detect bony abnormalities
   1. Skull
      1. Macrocephaly
      2. Absence of the greater and lesser wings of the sphenoid
      3. Absence of the orbital floor
      4. Hypoplasia of the lesser wings of the sphenoid
      5. Enlarged orbits
      6. Enlargement of cranial foramina
      7. Enlargement of orbital margins
      8. Sclerosis in the vicinity of the optic foramen (optic nerve sheath meningioma)
      9. Facial asymmetry
      10. Hypoplasia of the paranasal sinuses
      11. Mandibular abnormalities
      12. Mandibular hypoplasia with flattening of the external contour
      13. Thinning of the ramus
      14. Coronoid hyperplasia
      15. Widening of the lateral and medial coronoid spaces
      16. Calvarial defects adjacent the left lambdoid suture
      17. Osseous defects associated with multiple frontonasal osseomeningeal defects causing cerebrospinal fluid (CSF) rhinorrhea
   2. Chest
      1. Inferior rib notching
      2. Twisted ribbonlike ribs in the upper thoracic cage
      3. Posterior mediastinal masses secondary to intrathoracic meningoceles
      4. Mediastinal and lung masses secondary to neurofibromas
      5. Dumbbell neurofibromas
      6. Progressive pulmonary interstitial fibrosis leads to formation of bullae and honeycomb lung.
      7. Increased incidence of spontaneous pneumothorax and hemothorax
      8. Dilatation/enlargement of the central pulmonary arteries and peripheral pruning of vessels secondary to changes of

interstitial lung disease and pulmonary hypertension

3. Spine
    1. A sharply angled kyphoscoliosis centered at the thoracolumbar junction in 50% of patients
    2. Enlargement of the intervertebral foramina
    3. Scalloping of the vertebral bodies (anterior, posterior, lateral)
    4. Hypoplasia of the vertebral pedicles
    5. Wedged-shaped vertebrae
    6. Spondylolisthesis
    7. Spinal clefts
    8. Osteolysis
    9. Spindling of the transverse processes
4. Appendicular skeleton
    1. Bowing of long bones
    2. Hyperplasia or hypoplasia of long and short bones
    3. Pseudarthrosis
    4. Erosions
    5. Periosteal dysplasia
    6. Intramedullary longitudinal osteosclerotic streaks
    7. Single or multiple cystic bone lesions
    8. Focal gigantism
    9. Protrusio acetabuli
    10. Dislocation of the hip
    11. Dislocation of the radius and ulna
    12. Absence of a patella
    13. Neuropathic arthropathy of the knee
5. Gastrointestinal
    1. Neurofibromas within the stomach, small and large bowels, and rectum
    2. Intussusception of the bowel presenting with intestinal obstruction
    3. Bowel obstruction simulating Hirschsprung disease secondary to plexiform neurofibroma of the colon
    4. Pseudoobstruction
    5. Biliary strictures and bile duct intraluminal neurofibromas rarely reported
6. Urinary tract
    1. Renal collecting system and bladder intrinsically involved or extrinsically compressed or displaced by neurofibromas
    2. Intravenous urogram providing useful information regarding the nature and site of obstruction and function
4. Echocardiography for pulmonic stenosis, aortic coarctation, or other CHD
5. CT imaging
    1. Solid fusiform masses
        1. Present in the distribution of nerves, with central areas of low attenuation and calcification
        2. May present in the paravertebral, laryngeal, mediastinal, abdominal, and pelvic/ischiorectal fossae
    2. Plexiform neurofibromas seen as widespread sheets of nodular tissue.
    3. Paraspinal neurofibromas, seen at every level, vary in size, may be dumbbell shaped, or may comprise fusiform/spherical soft-tissue masses.
    4. Mesenteric plexiform neurofibromas trap mesenteric fat within an entangled network.
    5. Nonneoplastic cerebral and cerebellar calcification and choroid plexus calcification on cranial CT scans.
    6. Hydrocephalus in NF1 results from benign aqueduct stenosis or a glioma of the tectum/tegmentum of the mesencephalon.
    7. Intracranial nerve sheath tumors with associated bone erosions.
    8. Meningiomas with associated changes in the calvarium/skull.
    9. Extrinsic bladder involvement, intrinsic infiltrative processes, or extrinsic compression of the renal collecting system by a neurofibroma.
    10. A role in the investigation of thoracic, abdominal, and pelvic complications of NF1.
6. MRI imaging (Vézina 2015)
    1. Brain (Van Es et al. 1996)
        1. T2 hyperintensities (64%).
        2. T1 hyperintensities (32%).
        3. Optic nerve glioma (22%).

4. An intracranial tumor (ependymoma) and sphenoid wing dysplasia were evident in individual patients.
2. Internal lesions
1. Mediastinal masses
2. Spinal cord tumors
3. Deep plexiform neurofibromas
4. Neurofibromas of the brachial or sacral plexus
5. Neurofibromatosis-related vasculopathy

7. Histopathology
1. Confirmation of neurofibromas
1. Arisen from cells in the peripheral nerve sheath
2. Consist of a mixture of cell types, including Schwann cells, fibroblasts, mast cells, and vascular elements
3. Low-power view of neurofibroma: the myelinated and nonmyelinated fibers and s Schwann cell with abundance of collagen (Brasfield and DasGupta 1972)
2. Verification of malignant transformation to neurofibrosarcoma

8. Linkage analyses using polymorphic markers that segregate with the disease in familial cases.
9. Either FISH, loss of heterozygosity, or Southern blotting analyses reveal 5% of patients with large deletions of *NF1* gene encompassing part or the whole *NF1* gene (Kluwe et al. 2004).
10. Mutation analysis in sporadic and familial cases (Friedman 2014):
1. Protein truncation test based on the detection of truncated proteins via in vitro transcription and translation from RT-PCR fragments spanning the entire *NF1* cDNA
1. *NF1* mutations detected
1. Nonsense mutations
2. Frameshift mutations
3. Splicing mutations
2. Method of exploring the RNA for changes that are compatible with mutations in the gene
3. Positive in 80% of the cases
2. Gene sequencing: specific search of exon by exon for the mutation

11. Multistep detection protocol: preferred because of the large size of the NF1 gene and the lack of mutation hotspots:
1. Testing methods
1. Protein truncation assay yielding identification of mutations in 73% of patients (Park and Pivnick 1998)
2. Sequence analysis
3. FISH: provides a simple and rapid means of identification of NF1 gene deletions (Wu et al. 1995, 1997)
4. Long-range RT-PCR
5. Southern blot analysis
6. Cytogenetic analysis
2. NF1 mutations detected
1. Nonsense mutations
2. Frameshift mutations
3. Splicing mutations
4. Missense mutations
5. Deletions
6. Other rearrangements
3. Mutation detection rate in patients with a clinical diagnosis of NF1: >95%

12. Presymptomatic/preconceptional genetic testing: molecular characterization in familial and in sporadic cases
13. Limitation of genetic testing
1. Lack of genotype-phenotype correlations: A positive test will not predict disease severity or outcome.
2. Two exceptions
1. Complete loss of the *NF1* gene along with multiple contiguous genes
1. Occurs in 4–5% of patients with NF1 (Kluwe et al. 2004).
2. Patients with whole gene deletion present with a very large neurofibroma burden, more severe cognitive impairment, large hands and feet, and dysmorphic facial features and have a higher lifetime risk of developing malignant peripheral nerve sheath tumors (MPNST) (Leppig et al. 1997; De Raedt et al. 2003).

2. A 3-base pair in-frame deletion in exon 17 of the *NF1* gene: Patients with this genetic mutation have an absence of cutaneous neurofibromas and appear to have a lower incidence of serious complications.

Genetic Counseling

1. Recurrence risk
    1. Patient's sibling
        1. Risk not increased unless a parent is affected or has gonadal mosaicism.
        2. If a parent is affected, the risk to the sibs is 50%.
        3. Possibility of germ-line mosaicism in a clinically normal parent: recurrence risk based on the percentage of the germ-line mosaicism.
    2. Patient's offspring
        1. Risk: 50% of inheriting the disease with extremely variable disease manifestations.
        2. Risk of having a child with NF1 in a patient affected with segmental NF1
            1. A small but greater than the general population risk.
            2. A lower offspring recurrence risk than individuals with the nonmosaic form (Ruggieri and Huson 2001).
            3. A low probability of transmitting the disease in segmental NF1 (Sloan et al. 1990).
            4. Some cases of segmental NF1 apparently being "transmitted" to offspring; the mechanism (if one exists) behind this is unclear (Boyd et al. 2009).
            5. Segmental neurofibromatosis is believed to be due to somatic mosaicism for a mutation in the NF gene. The mutation occurred postconceptionally and present in the limited population of cells. Gonadal cells may or may not have a mutation (Dupuis and Nezarati 2001).
            6. Postzygotic mutation may occur in both somatic and gonadal cell lines (Messiaen et al. 2011). Gonadal mosaicism is responsible for instances of individuals with mosaic neurofibromatosis having children with generalized neurofibromatosis (Gabhane et al. 2010). As a result, patients diagnosed as mosaic NF1 who are considering having children should be made aware of the small risk of having a child with classic NF1, with the exact risk of this occurring still unknown (Hardin et al. 2014).
2. Prenatal diagnosis
    1. Influence of knowledge of the disease in the reproductive decisions of affected individuals (Ars et al. 1999)
        1. Interest in prenatal test by 41% of the subjects considering becoming pregnant
        2. Only 10% considering terminating an affected pregnancy
    2. Prenatal diagnosis of NF1 difficult to be made in the past due to the following reasons (Vitale et al. 2002):
        1. Large size of the NF1 gene
        2. Lack of any hotspots where the mutations arise
        3. Variable expression even within members of a family with NF1
        4. Lack of a tight genotype-phenotype correlation
        5. High spontaneous mutation rate
    3. Molecular genetic testing. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed (van Minkelen et al 2014).
        1. Direct characterization of the mutation from a parent affected by NF1
        2. Analysis of the genomic DNA mutation from the fetus either by amniocentesis or CVS
        3. Indirect linkage analysis to familial cases using informative polymorphic markers
        4. Protein truncation test
        5. Fluorescence in situ hybridization

4. Molecular diagnosis, unfortunately, cannot predict clinical expression of the disease in the fetus.
5. Preimplantation genetic diagnosis: may be an option for some families in which the NF1 pathogenic variant has been identified (Spits et al. 2005; Chen et al. 2011; Friedman 2014). Advances in biopsy and diagnostic techniques which increase the number of unaffected embryos identified may improve live birth rates for patients with NF1 (Merker et al. 2015).

3. Management
    1. Health supervision for children with neurofibromatosis is available from American Academy of Pediatrics Committee on Genetics (1995).
    2. Developmental assessment in children.
    3. Medical management for itching, pain, depression, and other psychological and social problems.
    4. Treatment of hypertension depending on the etiology.
        1. Pheochromocytomas
        2. Renal artery stenosis
    5. Laser or electrocautery for small discrete cutaneous or subcutaneous neurofibromas.
    6. Surgical resection of tumors.
        1. Resection of neurofibromas pressing on vital structures, obstructing vision, or rapidly growing lesions causing irritation, discomfort, and pain
        2. Plexiform neurofibromas: extremely difficult to approach surgically and often recur after resection because of residual cells resting deeply in the soft tissues
        3. Resection of spinal cord tumors: quite difficult but often is necessary to prevent progressive paraplegia or quadriplegia
    7. Surgical treatment of disfigurement.
        1. Excision of multiple neurofibromas
        2. Reconstructive surgery for plexiform neurofibromas
    8. Children should be watched carefully for signs of malignant transformation and undergo biopsy for neurofibromas that exhibit rapid growth. Management of sarcomas should be aggressive with consideration given to re-excision, placement of brachytherapy catheters, metastasectomy, and limb salvage with adjuvant therapy when possible (Neville et al. 2001).
    9. Orthopedic care indicated for rapidly progressive scoliosis and for some severe bony defects.
    10. Optic pathway gliomas in most children with NF1 (Jett and Friedman 2010).
        1. Usually do not require treatment.
        2. Chemotherapy is the treatment of choice for progressive tumors.
        3. Surgical treatment: reserved for cosmetic palliation in a blind eye.
        4. Radiotherapy usually avoided because of the risk of inducing malignancy or moyamoya in the exposed field.
    11. Treatment of congenital pseudarthrosis of the tibia: challenging (Vitale et al. 2002)
        1. Bracing mainly of early treatment before fracture develops
        2. A knee-ankle-foot orthosis when weight bearing
        3. Intramedullary rod fixation, often in combination with autogenous bone grafting of the pseudarthrosis site
    12. Advise high-risk pregnancy care to pregnant patient with neurofibromatosis (Blickstein et al. 1988)
        1. Maternal hypertension
        2. Aggravating features of neurofibromatosis
    13. A case of neurofibromatosis-Noonan syndrome (NFNS) diagnosed to have growth hormone deficiency (GHD) who received GH treatment until reaching final height (Vuralli et al. 2016). The findings in this patient show that short stature is a feature of NFNS and can be caused by GHD.
    14. A multidisciplinary approach to care, entailing a dedicated team of specialists throughout the lifetime of the patient (Hirbe and Gutmann 2014).
    15. Recent advances have implicated several crucial signaling pathways involved in malignant peripheral nerve sheath tumor

malignant growth and uncovered new potential drug targets. These include the use of chromatin remodelers to restore the epigenetic status of SUZ12 deficiency as well as to identify targets to block angiogenesis and cell migration that are commonly upregulated in malignant peripheral nerve sheath tumors, including the STAT3/HIF and RHO/ROCK signaling pathways (Rad and Tee 2016).

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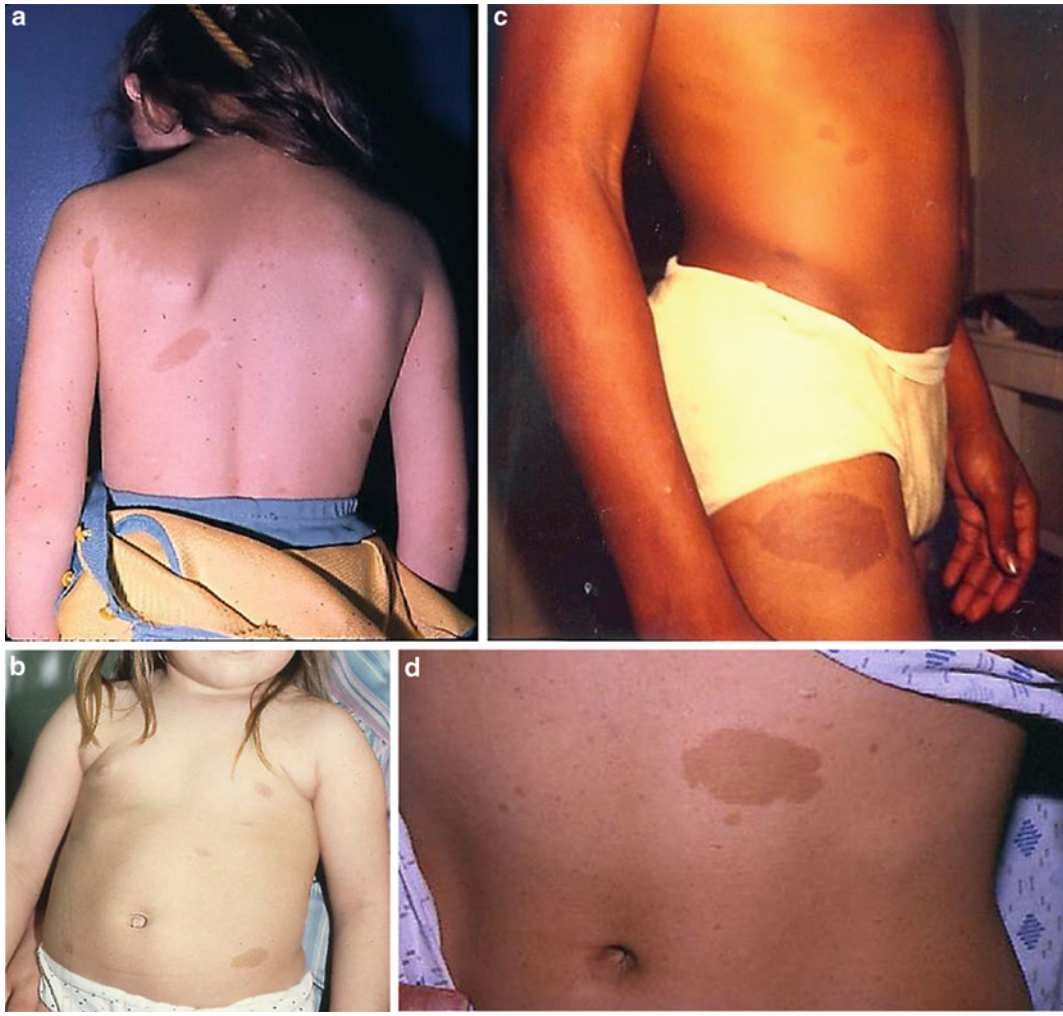

Fig. 1 (**a**-**d**) Typical café-au-lait spots in four different patients (**a**, **b**, **c**, **d**)

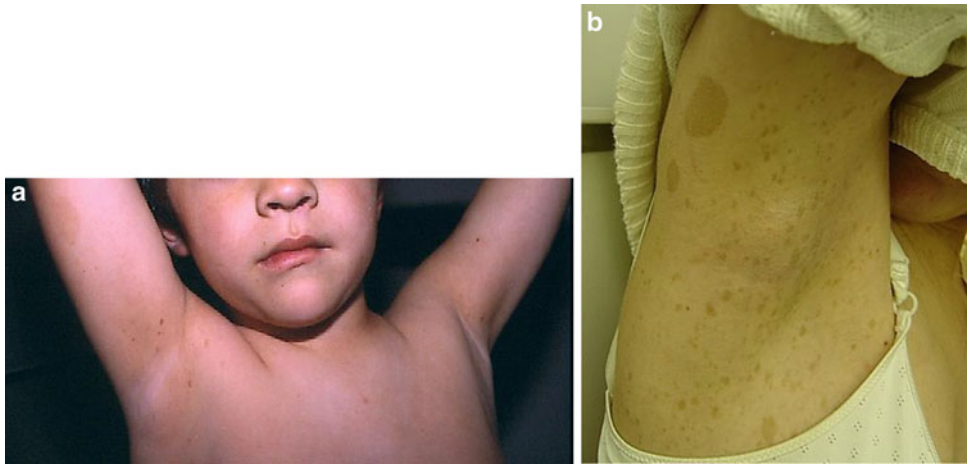

Fig. 2 (**a**, **b**) Axillary freckles in a child (**a**) and an adult (**b**)

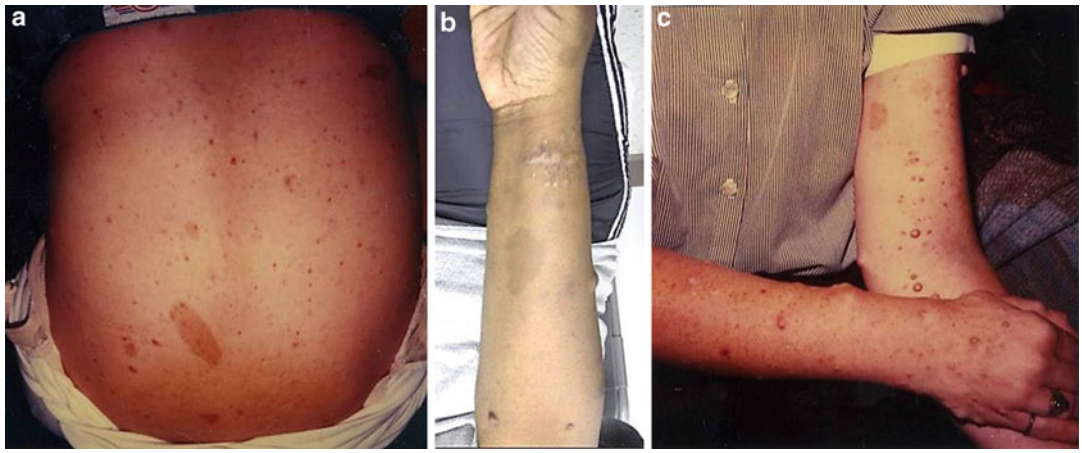

Fig. 3 (**a**–**c**) Café-au-lait spots and numerous localized cutaneous neurofibromas in three different patients (**a**, **b**, **c**)

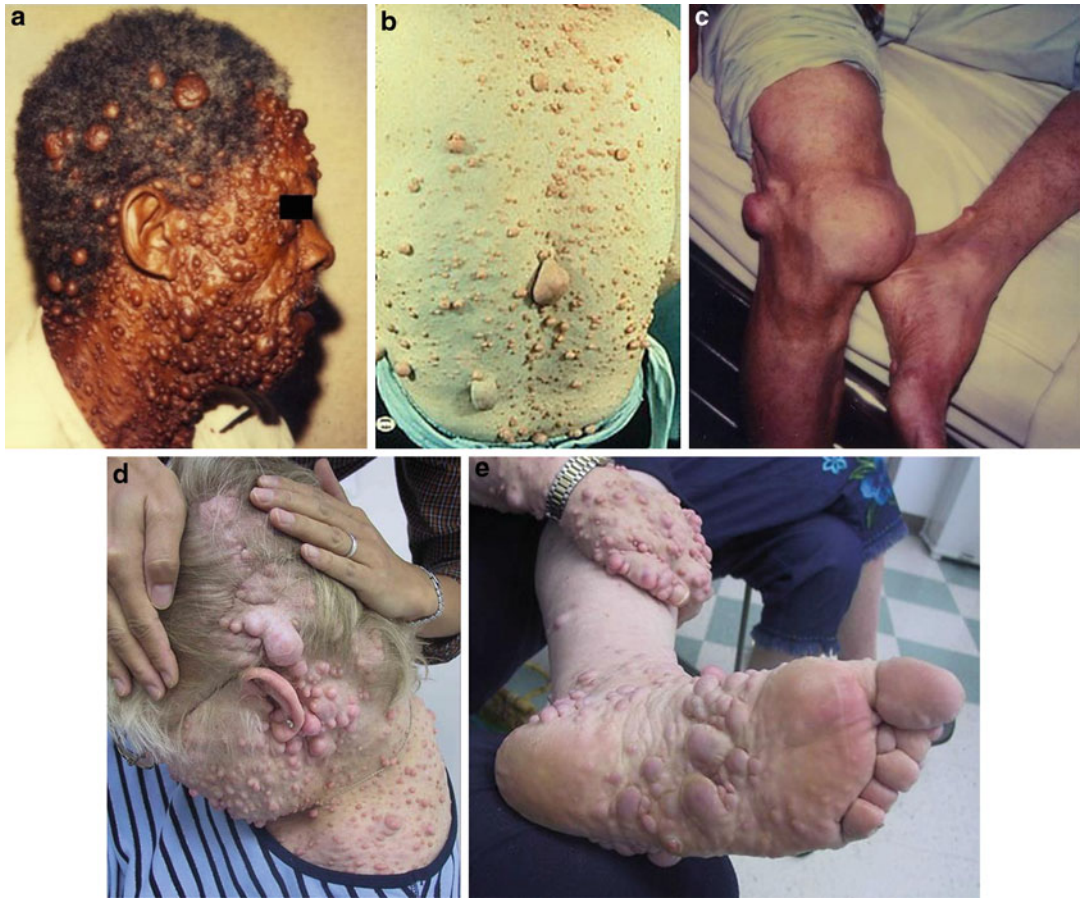

Fig. 4 (**a**–**e**) Diffuse cutaneous neurofibromas (nodular and polypoid shapes) in four patients (**a**, **b**, **c**, **d**, **e**) affecting skin and subcutaneous tissue resulting in marked cosmetic disfigurements and functional disturbances

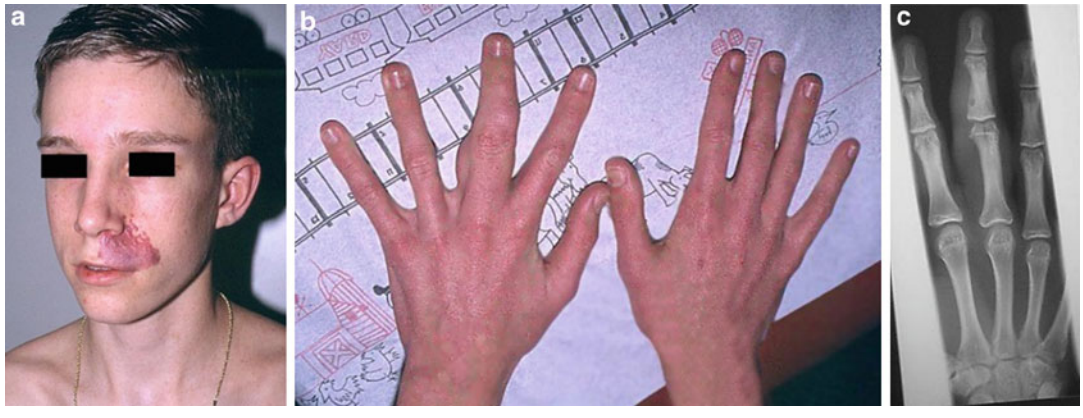

Fig. 5 (**a**–**c**) Neurofibromas involving vessels of the face (**a**) and subcutaneous tissue of the fingers (**b**, **c**)

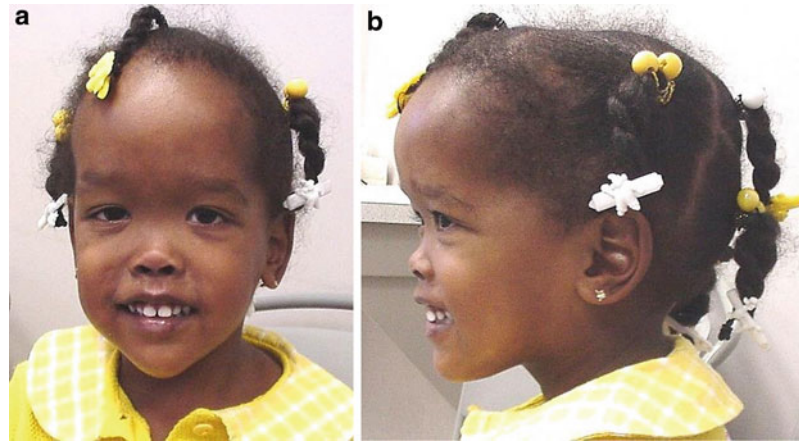

Fig. 6 (**a**, **b**) Macrocephaly with prominent forehead and depressed nasal bridge

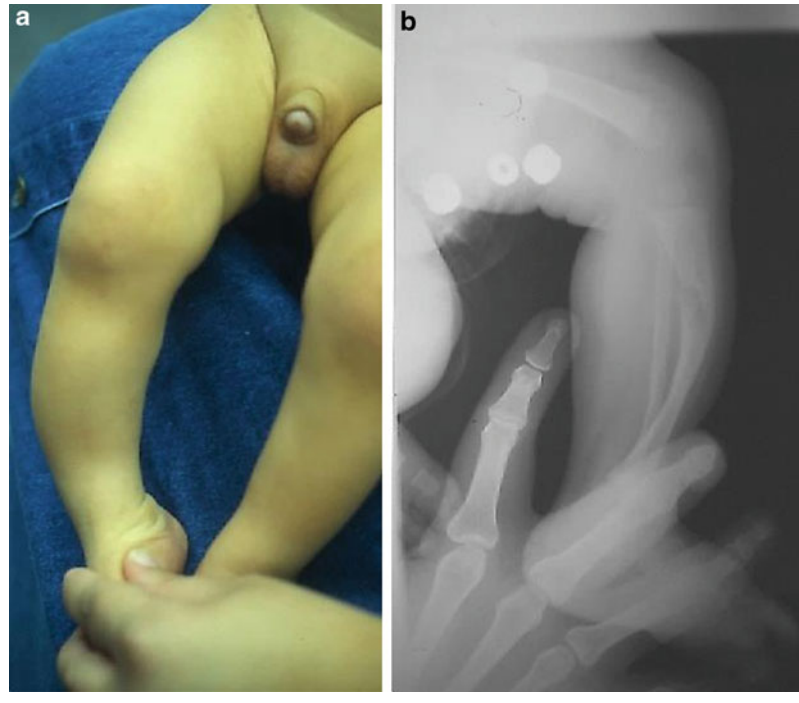

Fig. 7 (**a**, **b**) Pseudarthrosis of right tibia manifesting as bowed leg

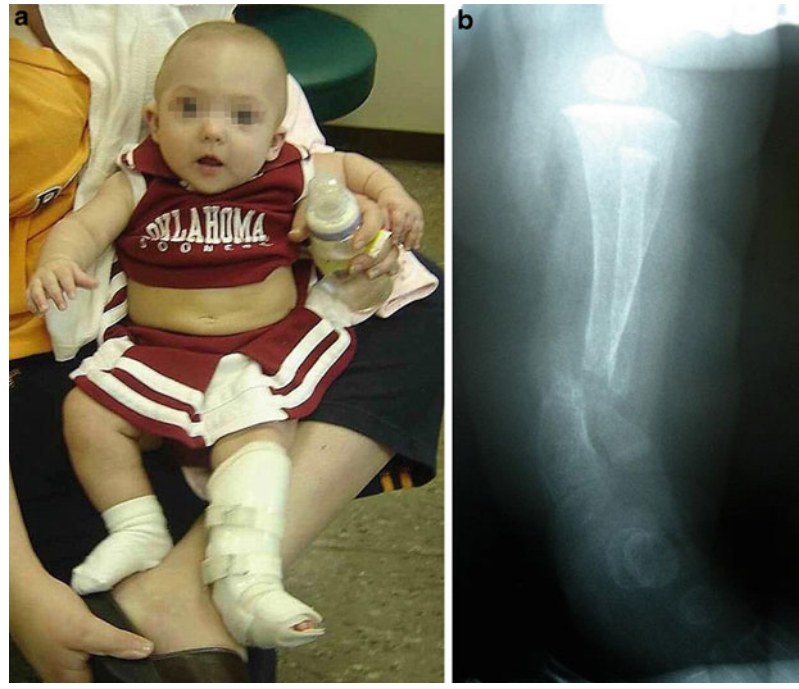

Fig. 8 (**a**, **b**) A child with NF1 (**a**) having pseudarthrosis of the left tibia and fibula resulting in fractures (**b**)

Fig. 9 Localized intraneural neurofibromas of a median nerve, causing fusiform enlargement of the affected nerve

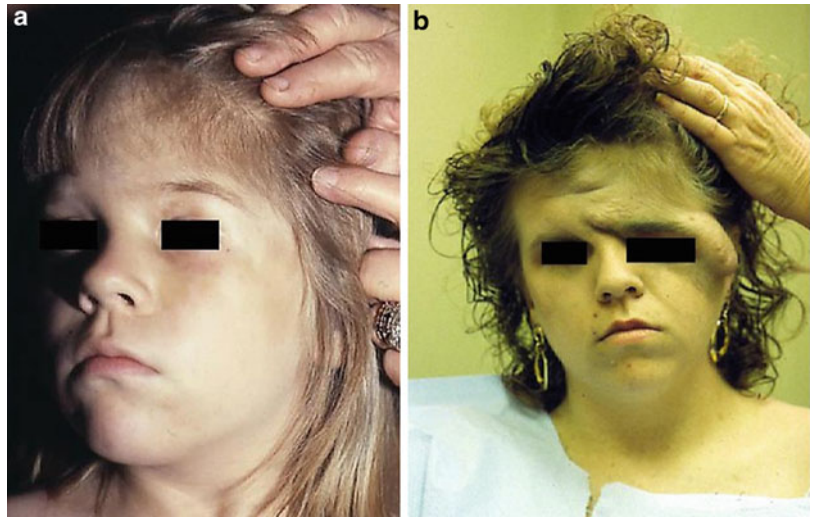

Fig. 10 (**a**, **b**) Plexiform neurofibromas affecting left orbital region in different ages (**a**, **b**)

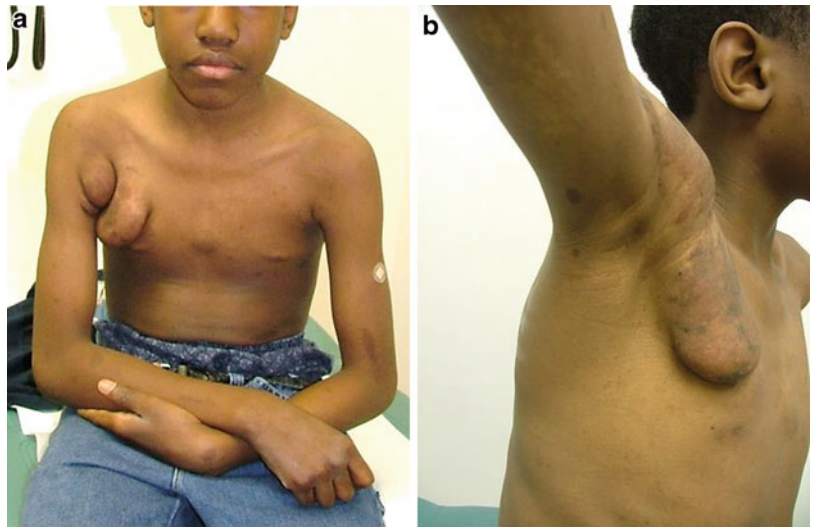

Fig. 11 (**a**, **b**) A 12-year-old boy with NF1 showing a large plexiform neurofibroma on the right upper chest

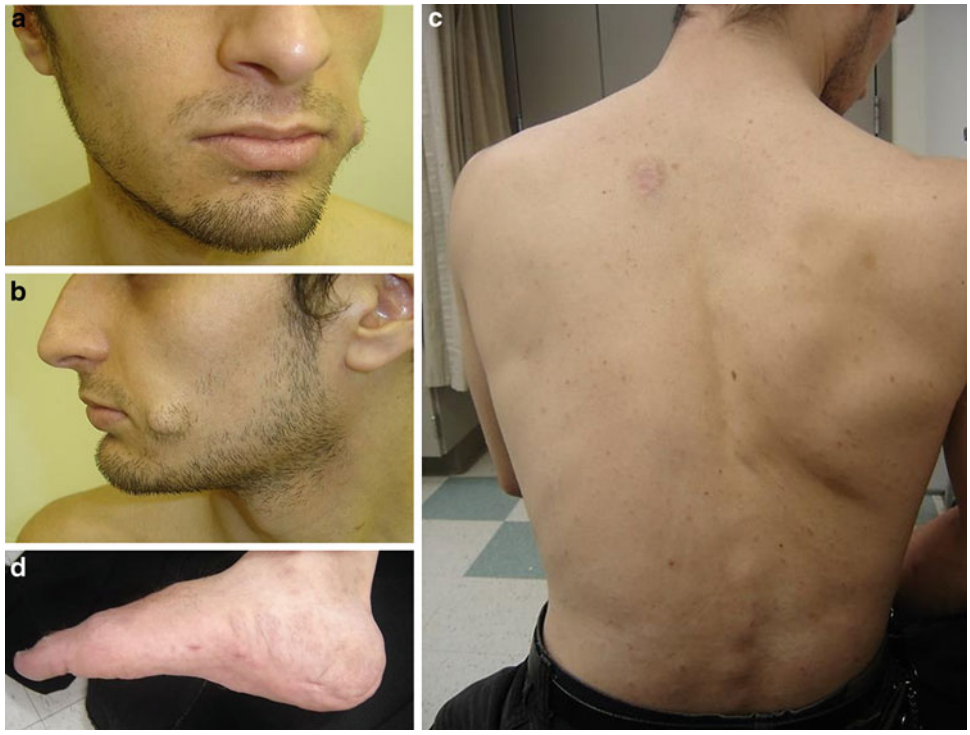

Fig. 12 (**a**–**d**) A man with NF1 showing plexiform neurofibromas on the left cheek (**a**, **b**), right upper back (**c**), and sole of the foot (**d**)

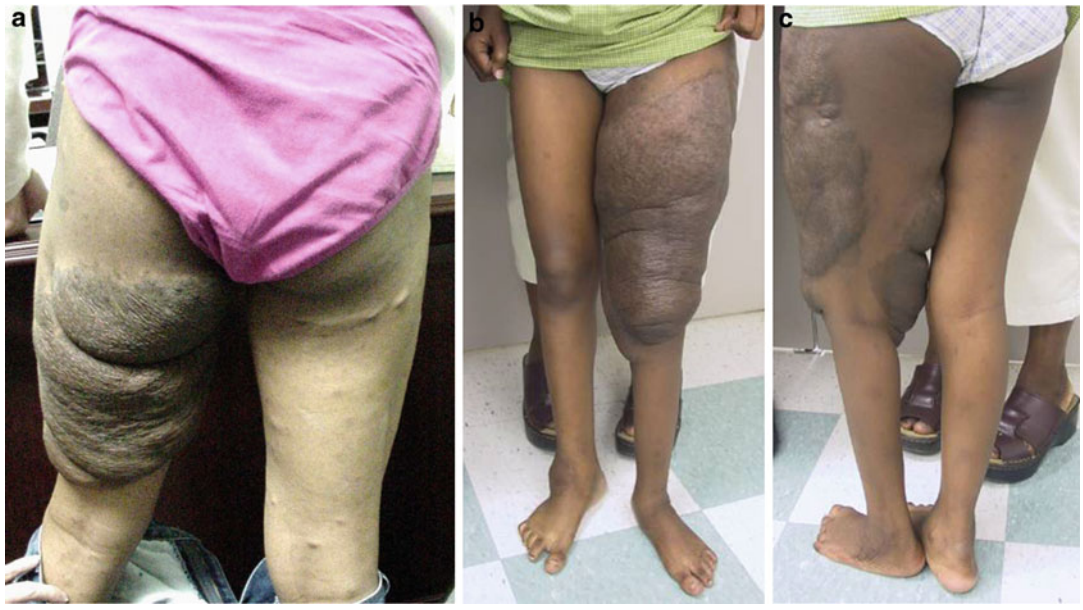

Fig. 13 (**a**–**c**) Massive soft-tissue neurofibromas affecting two patients (**a**, **b**, **c**). Extreme neurofibromatous growth producing massive, diffuse infiltration of soft tissue of the thigh producing disfiguring redundant soft-tissue masses

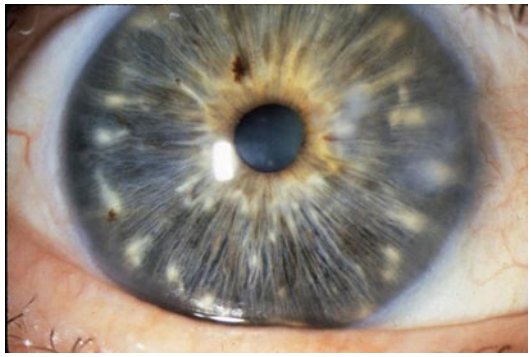

Fig. 14 Tannish-white iris Lisch nodules in a patient with NF1

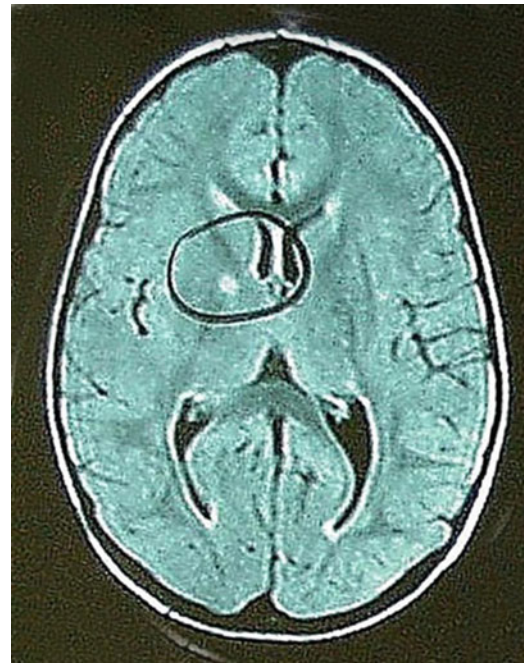

Fig. 15 MRI of the brain showing a hamartomatous lesion of the right globus pallidus. This patient has numerous cutaneous café-au-lait spots of varying size and typical axillary freckles. He was shown to have a truncating mutation in the segment 3 of the neurofibromin (*NF1*) gene

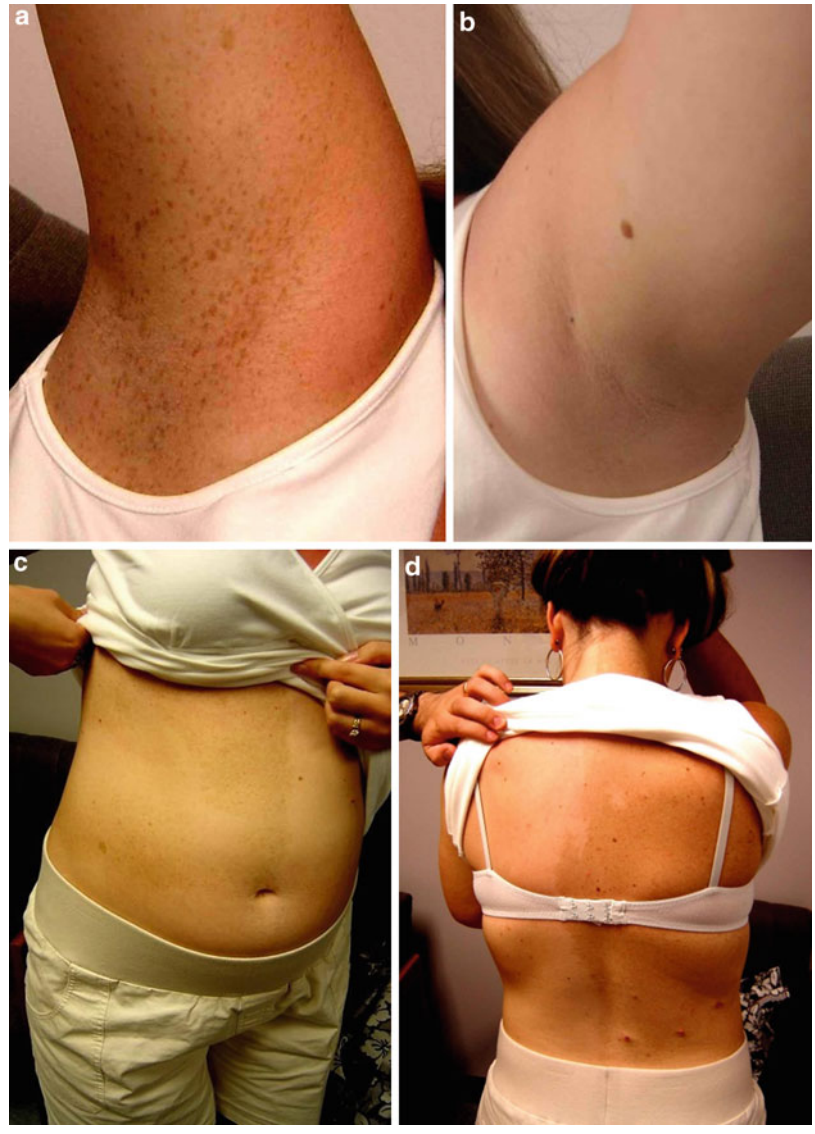

Fig. 16 (**a**–**d**) A 26-year-old female with segmental neurofibromatosis showing axillary freckles (**a**), multiple small neurofibromas, and hyperpigmentation, all involving the right side of the body (**c**, **d**). Left side of the body is spared, including left axilla which showed no freckles (**b**)

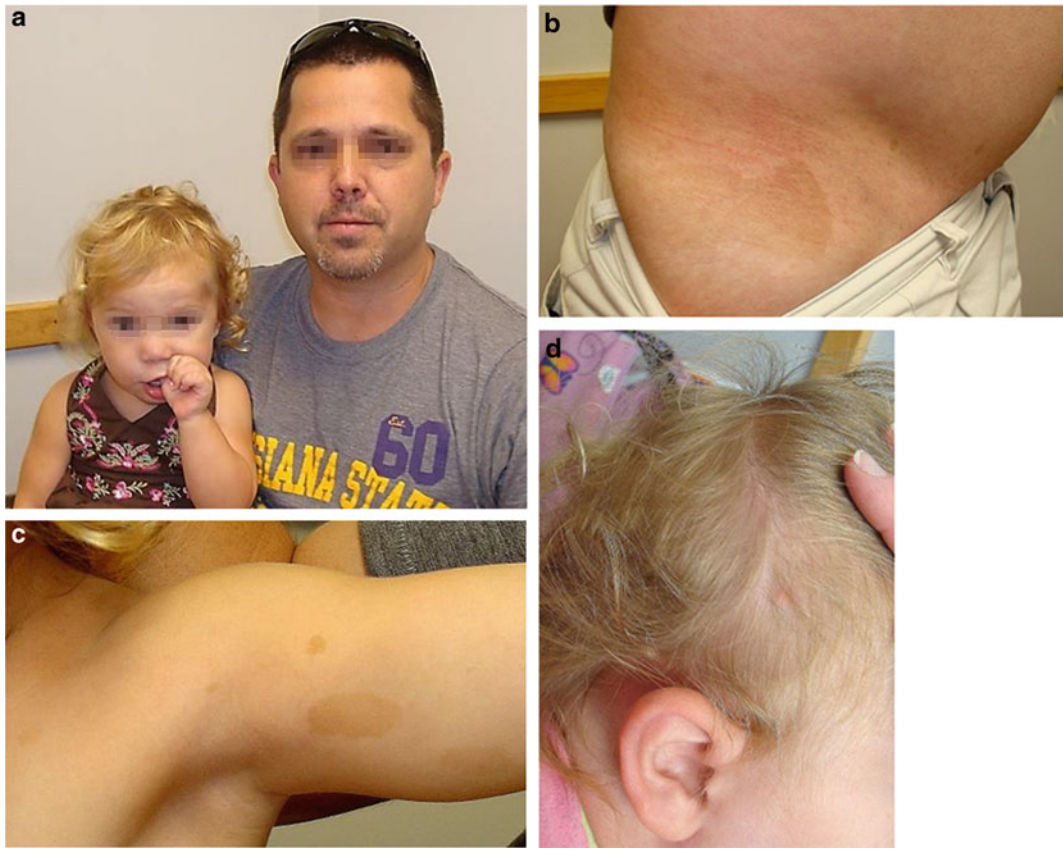

Fig. 17 (**a**–**d**) A 36-year-old father (**a**, **b**) presents with >8 large café-au-lait spots, bilateral axillary freckling, several cutaneous, intradermal, and subcutaneous neurofibromas. A heterozygous missense alteration in exon 13 of the *NF1* gene was identified (c.2072 T > C) (p.Leu691Pro). The 2-year and 3-month-old daughter (**a**) was found to have multiple café-au-lait spots (**c**) with a single neurofibroma on the right scalp (**d**)

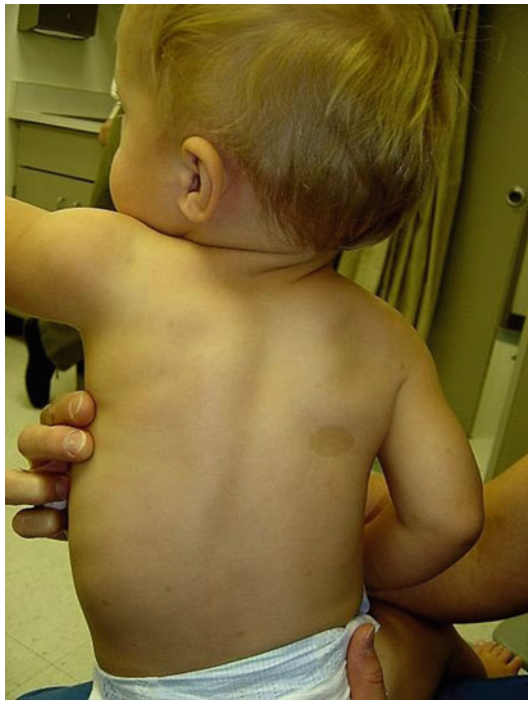

Fig. 18 A 14-month-old infant was seen because of multiple café-au-lait spots without neurofibroma. A splice mutation was identified in the *NF1* gene, 6641 + 1 G > T, leading to skipping of exon 35. This finding confirms the diagnosis of NF1 in this patient

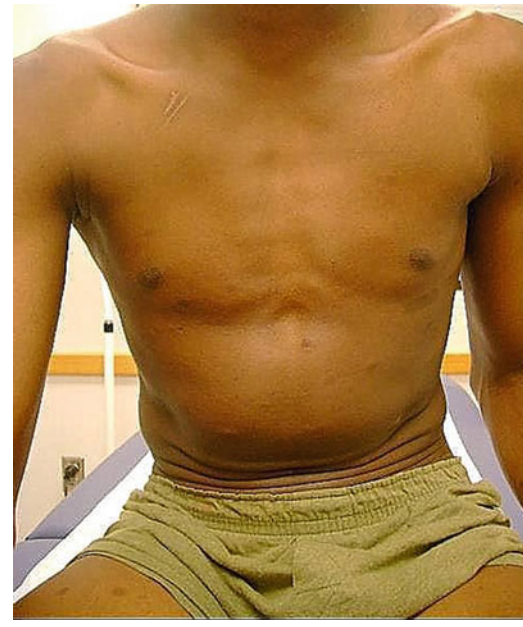

Fig. 19 A 13-year-old boy with multiple café-au-lait spots, axillary freckles, and small neurofibromas throughout the body. The molecular study revealed a recurrent deep intronic splicing mutation in the *NF1* gene (c.5749 + 322 A > G). This mutation leads to missplicing of intron 30. This finding confirms the diagnosis of neurofibromatosis 1

Neurofibromatosis 2

Contents

Historically, neurofibromatosis 2 (NF2) has been previously known as bilateral acoustic neurofibromatosis or central neurofibromatosis. It has frequently been confused with the more common neurofibromatosis 1 (NF1), also known as von Recklinghausen disease or peripheral neurofibromatosis (MacCollin and Mautner 1998). Gardner and Frazier in 1930 were the first to persuasively argue that bilateral vestibular tumors can be clinically and pathologically distinguished from both von Recklinghausen neurofibromatosis and from sporadic tumors from studying a large family with 38 affected members over five generations. The first clear description of NF2 was made by Wishart in 1822 (Wishart 1822). NF2 occurs in about 1 in 25,000 live births.

Synonyms and Related Disorders

Bilateral acoustic neurinoma; Bilateral acoustic neurofibromatosis; Bilateral acoustic schwannomas; Central neurofibromatosis

Genetics/Basic Defects

1. An autosomal dominant disorder: resulting from a mutation in the *NF2* tumor suppressor gene on chromosome 22q12 (Asthagiri et al. 2009):
   1. Truncating mutations (nonsense and frameshifts): most frequent germ line event causing the most severe disease.
   2. Single and multiple exon deletions are also common.
2. *NF2* tumor suppressor gene: consists of 17 exons that encode for a 69-kDa protein product called merlin (moesin-ezrin-radixin-like protein) or schwannomin (Rouleau et al. 1993; Trofatter et al. 1993)
3. Consistent with Knudson's two-hit hypothesis for tumorigenesis (tumor formation initiates when both alleles of this gene are inactivated) (Knudson 1971):

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_179

1. Patients inherit a germ line mutation of one affected allele from a parent or acquire a de novo mutation of an allele at the postzygotic stage of embryogenesis.
2. Subsequent development of tumors in susceptible target organs, such as nervous system, eyes, and skin, from cells that lose function of the wild-type (normal) *NF2* allele.

4. Abnormal or absent merlin function can disrupt tumor suppression in NF2.
5. High frequency of somatic mosaicism in patients with de novo mutations (Kluwe and Mautner 1998; Moyhuddin et al. 2003; Evans et al. 2007):
   1. Mutation takes place after conception in patients with mosaicism, resulting in two separate cell lineages.
   2. Patients with mosaicism tend to have mild generalized or even localized disease (e.g., unilateral vestibular schwannoma with ipsilateral tumors).
   3. Only a portion of the germ cells in a person with *NF2* mosaicism are likely to carry the mutation:
      1. Risk of transmission to offspring will be less than the expected one in two (50%) for an inherited mutation.
      2. Children who inherit the mutation from a mosaic parent will probably have more severe disease than will the parent because the mutation will be present in all their somatic cells.

Clinical Features

1. Young adulthood (age 20–30 years) (Asthagiri et al. 2009):
   1. Hearing loss from a vestibular schwannoma, often unilateral initially
   2. Accompanied symptoms
      1. Tinnitus
      2. Dizziness
      3. Imbalance
   3. A significant proportion of cases (20–30%) present with:
      1. Headaches and/or seizures from an intracranial meningioma
      2. Pain, muscle weakness, and/or paresthesia from spinal tumor
      3. Cutaneous tumor-induced symptoms
2. Children (up to 30%):
   1. May present with the same symptoms as adults
   2. More frequently present with the following:
      1. Visual disturbance:
         1. Cataract
         2. Hamartomas
         3. Intracranial tumors
      2. Skin tumors
      3. Mononeuropathy:
         1. Facial paresis
         2. Foot drop
      4. Symptomatic spinal cord tumors
      5. Non-vestibular intracranial tumors
3. Lesions associated with NF2:
   1. Neurological lesions (Borofsky and levy 2013):
      1. Bilateral vestibular schwannomas (90–95%) (the hallmark of NF2, a disease exhibits considerable phenotypic variability) and other cranial nerve schwannomas (24–51%): hearing loss, dizziness, headaches, diplopia, and facial weakness (the most common presenting clinical symptoms)
      2. Intracranial meningiomas and glioma (50–60%)
      3. Spinal tumors, most frequently ependymomas (63–90%):
         1. Extramedullary tumors (55–90%)
         2. Intramedullary tumors (18–53%)
      4. Peripheral neuropathy ($\leq$66%)
   2. Ophthalmological lesions:
      1. Cataracts (60–81%)
      2. Epiretinal membranes (12–40%)
      3. Retinal hamartomas (6–22%)
   3. Cutaneous lesions:
      1. Skin tumors (59–68%)
      2. Skin plaques (41–48%)
      3. Subcutaneous tumors (43–48%)
      4. Intradermal tumors (rare)
   4. Segmental neurofibromatosis type 2 presenting multiple schwannomas confined to one limb (Castellanos et al. 2015)

4. Diagnostic criteria for NF2 including the NIH criteria (National Institutes of Health Consensus Development Conference 1988) with additional criteria (Manchester criteria which expanded the previous NIH diagnostic criteria and were designed to include patients with neither a family history of NF2 nor bilateral vestibular schwannomas, but who had multiple schwannomas or meningiomas) (Evans et al. 2005; Evans 2009a, b; Baser et al. 2002b; Asthagiri et al. 2009):
    1. Major criteria:
        1. Bilateral vestibular schwannomas
        2. First-degree family relative with NF2 plus unilateral vestibular schwannoma or two NF2-associated lesions (meningioma, glioma, neurofibroma, schwannoma, or cataract)
    2. Additional criteria:
        1. Unilateral vestibular schwannoma plus any two NF2-associated lesions (meningioma, glioma, neurofibroma, schwannoma, or cataract)
        2. Multiple meningiomas plus unilateral vestibular schwannoma or two other NF2-associated lesions (glioma, neurofibromas, schwannoma, or cataract)
5. The Baser criteria for diagnosis of NF2 (Baser et al. 2011):
    1. First-degree relative with NF2 diagnosed by these criteria: 2 (if present at or before the age of 03), 2 (if present after the age of 30)
    2. Unilateral vestibular schwannoma: 2 (if present at or before the age of 03), 1[a] (if present after the age of 30)
    3. Second vestibular schwannoma: 4 (if present at or before the age of 03), 3[a] (if present after the age of 30)
    4. One meningioma: 2 (if present at or before the age of 03), 1 (if present after the age of 30)
    5. Second meningioma (no additional points for $>$ 2meningiomas): 2 (if present at or before the age of 03), 1 (if present after the age of 30)
    6. Cutaneous schwannoma (*one or more*): 2 (if present at or before the age of 03), 1 (if present after the age of 30)
    7. Cranial nerve tumor (excluding vestibular schwannoma) (*one or more*): 2 (if present at or before the age of 03), 1 (if present after the age of 30)
    8. Mononeuropathy: 2 (if present at or before the age of 03), 0 (if present after the age of 30)
    9. Cataract (*one or more*): 2 (if present at or before the age of 03), 2 (if present after the age of 30)
    10. A diagnosis of definite NF2 is established if the total number of points is $\geq$6 ([a]points are not given for unilateral or second vestibular schwannoma if age at diagnosis is $>$70 years)
    11. NF2 mutation testing is indicated if the total number of points is 4 or 5:
        1. A diagnosis of definite NF2 is established if a constitutional pathogenic *NF2* mutation is found on mutation testing
        2. If no constitutional pathogenic *NF2* mutation is found on mutation testing:
            1. A diagnosis of mosaic NF2 is established if mosaicism for a pathogenic *NF2* mutation is found in the blood or no detectable pathogenic *NF2* mutation is found in the blood, but the same pathogenic *NF2* mutation is found in two separate NF2-associated tumors.
            2. Otherwise, a temporary diagnosis of possible NF2 is made, pending further clarification. Clarification may occur if the patient is established to have a different condition (e.g., schwannomatosis or multiple meningiomas) by standard diagnostic criteria or if evolution of the patient's disease over time permits establishing a diagnosis of definite NF2 or mosaic NF2 according to the criteria given above.
6. Patient populations at risk for NF2 (Evans et al. 2005):

1. First-degree relative with NF2 (affected parent, sibling, or children)
2. People younger than age 30 years with a unilateral vestibular schwannoma or meningiomas
3. People with multiple spinal tumors (schwannomas, meningiomas)

7. Recommended intervals for screening children of an affected parent (Evans et al. 2005):
   1. Ophthalmological examination yearly from infancy.
   2. Neurological examination yearly from infancy.
   3. Audiology with auditory brain stem evoked potentials yearly from infancy.
   4. Presymptomatic genetic testing: one test from 10 years of age.
   5. Cranial MRI at 10–12 years of age.
   6. Spinal MRI at 10–12 years of age (every 2–3 years).
   7. For presymptomatic genetic testing, cranial MRI, and spinal MRI, screening may start earlier than age 10 years in severely affected families and families in which early detection of disease would aid family preparation for future events related to NF2.
8. Variable expressivity of NF2 among individuals:
   1. Varying size, location, and number of tumors.
   2. Although these tumors are not malignant, their anatomical location and multiplicity lead to great morbidity and early mortality.
   3. The average age of death is 36 years.
   4. Actuarial survival from the time of establishing the correct diagnosis is 15 years.
   5. Survival is improving with earlier diagnosis and better treatment in specialty centers (Baser et al. 2002a; Evans et al. 2005).
   6. Under recognized in children in whom skin tumors and ocular findings may be the first manifestations (NF2 is usually considered an adult-onset disease).
9. Penetrance: 100%.
10. Differential diagnosis:
    1. Main differential diagnosis of NF2: schwannomatosis (multiple schwannomas without the vestibular schwannomas that are diagnostic of NF2)
    2. Multiple non-cranial schwannomas: Some patients turn out to have mosaic NF2 (Moyhuddin et al. 2003; Evans et al. 2007).
    3. Neurofibromatosis 1
11. Prognosis is adversely affected by:
    1. Early age at onset
    2. A higher number of meningiomas
    3. Having a truncating mutation

Diagnostic Investigations

1. Clinical and family history (Evans 2009a).
2. Physical examination including cutaneous and ophthalmic (slip lamp).
3. Craniospinal MRI.
4. Hearing evaluation, including BAER.
5. Chromosome analysis: Gross chromosomal changes are rare but may reveal a variety of chromosome abnormalities:
   1. Cytogenetically visible deletions encompassing the NF2 gene: may cause mental retardation and multiple congenital abnormalities (Barbi et al. 2002):
      1. Ring chromosome 22 (Tsilchorozidou et al. 2004).
      2. Can cause multiple meningiomas and vestibular schwannomas fulfilling NF2 diagnostic criteria, NF2 locus itself is usually present within the ring, but the ring itself is frequently loss as a result of instability.
      3. Apparently balanced chromosomal translocations disrupting the *NF2* gene causing NF2.
      4. Fluorescence in situ hybridization (FISH) to identify smaller deletions that remove multiple exons of the NF2 gene or the whole gene.

6. Molecular genetic analysis:
    1. Sequence analysis/mutation scanning of *NF2* gene (Evans et al. 2007):
        1. In 73% of families with NF2, sequence analysis identified a mutation in a member of the second generation.
        2. In simplex cases (a single occurrence in a family), the mutation detection rate is approximately 60%.
        3. Approximately 25–33% of mutations are not detected as a result of somatic mosaicism.
        4. Mutations with mosaicism levels >10% can be detected in lymphocyte DNA.
        5. Identification of the remainder of mosaic mutations usually requires testing of tumor material.
    2. Deletion/duplication analysis:
        1. Systematically detects whole exon deletions and duplications.
        2. Most large deletions and, less commonly, duplications of single exons or multiple exons can be detected by multiple ligation-dependent probe amplification (MLPA).
    3. Linkage analysis:
        1. In families in whom no disease-causing mutation is identified, and at least two family members of different generations are affected.
        2. Modified linkage analysis using both constitutional and tumor DNA can exclude NF2 in those children of a simplex case who have not inherited the allele lost in the tumor.
7. Presymptomatic genetic testing is an integral part of the management of NF2 families:
    1. At-risk relatives whose genetic status is unknown can be tested for presence of the *NF2* mutation (either constitutional or somatic mosaic) identified in an affected relative.
    2. In the rare instance in which an *NF2* mutation cannot be identified, linkage analysis can be used in families with at least two affected family members of different generations, or tumor DNA can be used to clarify the genetic status of children of a simplex case.

Genetic Counseling

1. Recurrence risk: presence of an affected parent in approximately 50% of individuals with NF2 (other 50% have NF2 as the result of a de novo mutation; 20–33% of simplex cases without family history are mosaic for an *NF2* mutation) (Evans 2009a):
    1. Patient's sib:
        1. Affected parent: a 50% risk
        2. Asymptomatic parents: a low risk since the age of onset of symptoms is relatively uniform within families:
            1. A single case of germ line mosaicism in a clinically normal parent has been reported.
            2. Somatic mosaicism which may include germ line mosaicism is found in 25–33% of individuals with NF2 who are simplex cases.
    2. Patient's offspring:
        1. The risk of disease transmission is 50% in the second generation and beyond.
        2. The risk of transmission in people with new NF2 mutations is less than 50% due to mosaicism, in which only a proportion of cells have the mutated *NF2* gene (Evans et al. 1998; Kluwe and Mautner 1998).
2. Prenatal diagnosis and preimplantation genetic diagnosis: possible for at risk pregnancies, provided prior identification of the disease-causing mutation in the family.
3. Management:
    1. Surgery remains the focus of current management:
        1. Surgical removal of symptomatic cranial and spinal tumors
        2. More difficult to determine the timing of removal of vestibular schwannomas
    2. Stereotactic radiosurgery, most commonly with the gamma knife, may be an alternative to surgery.
    3. Important to balance the use of microsurgery and radiation treatment, which can have a role in patients who have particularly aggressive tumors, or who are poor surgical risks, or who refuse surgery.

4. Hearing preservation and augmentation with hearing aids or auditory rehabilitation with a cochlear or auditory brainstem implants (Matthies et al. 2014; Schwartz 2014).
5. Watchful waiting with careful surveillance and occasionally radiation treatment have a role.
6. Patients should be assessed in a multidisciplinary center with experience in managing NF2 (Szudek et al. 2012):
    1. Goal of treating vestibular schwannomas: to maximize the duration of useful hearing while minimizing morbidity to the facial nerve and brainstem
    2. Treatment options for vestibular schwannomas: traditional approach of initial observation or tumor resection with attempted hearing preservation
    3. Choice of treatment: depends on patient factors and preferences as well as the available surgical expertise

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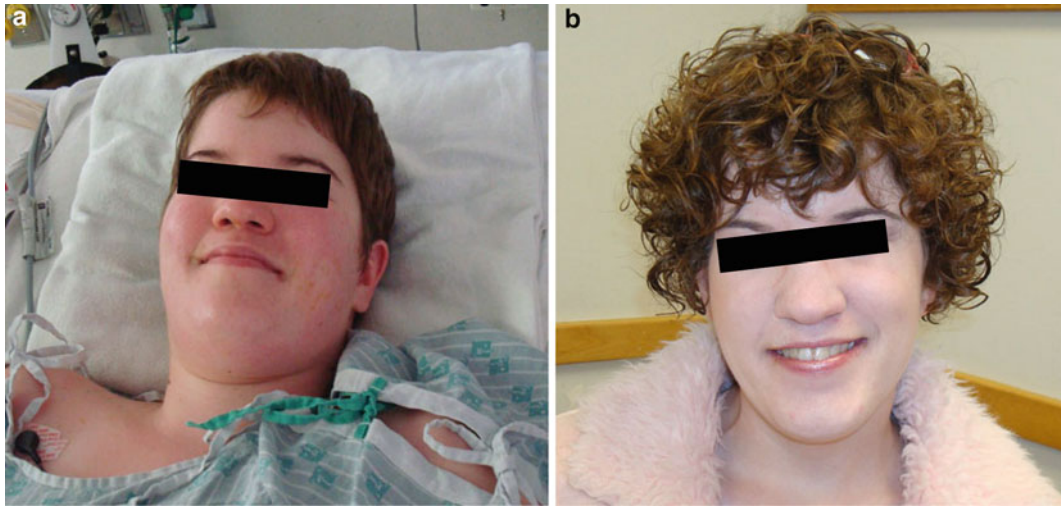

Fig. 1 (**a**, **b**) A 23-year-old female had resection of anterior fossa meningioma 2 years previously. She complained worsening headaches with intermittent vomiting and blurry vision recently. She underwent a posterior fossa craniectomy and resection of a large cervical medullary tumor, consistent with a spindle cell tumor (schwannoma). She also has history of bilateral hearing loss and balance dysfunction. Molecular genetic testing revealed a truncating mutation in the *NF2* gene (c.553delG) confirming the diagnosis of NF2 in this patient

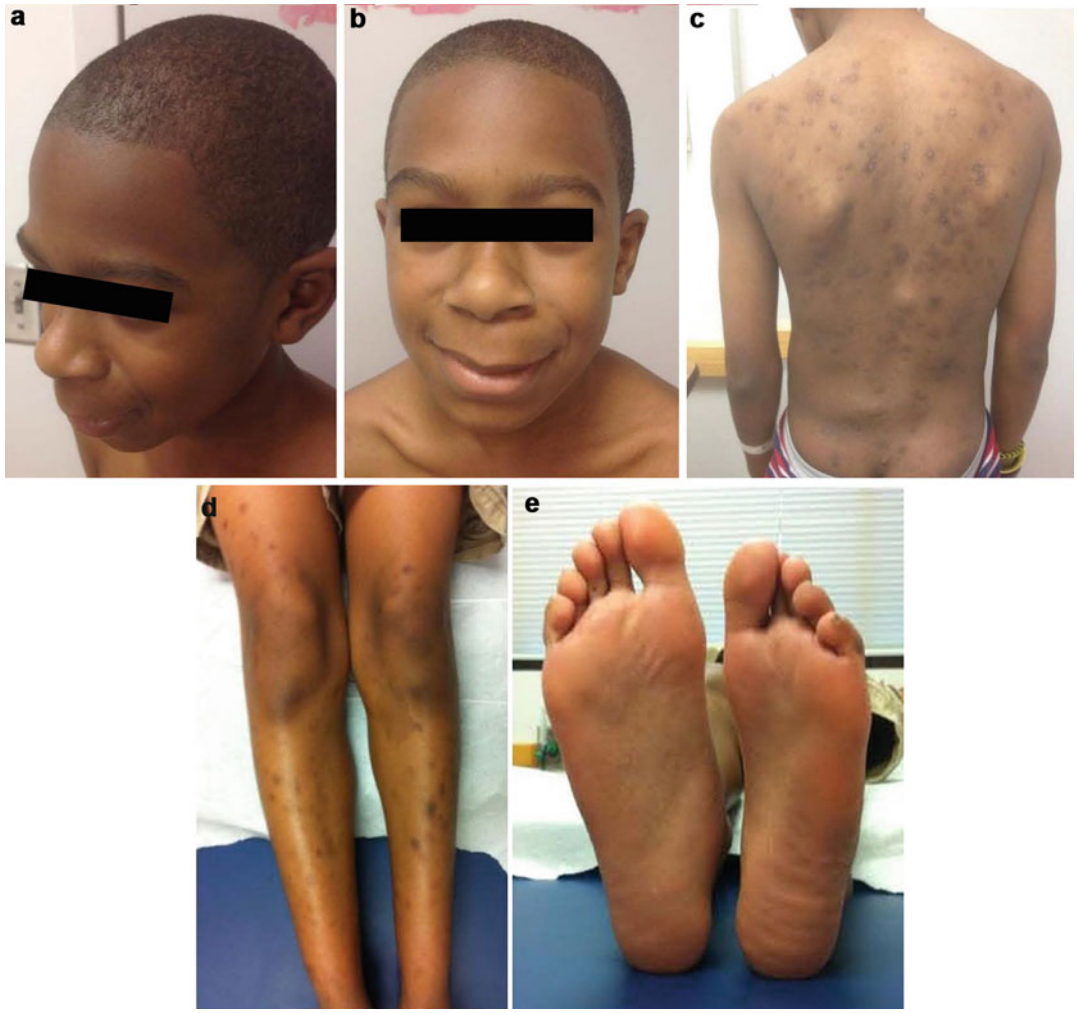

Fig. 2 (**a**–**e**) An 11-year-old African-American boy was reevaluated for possible neurofibromatosis 2. Family history, pregnancy history, and birth history were noncontributory. He had mild developmental delay. He was thought to have neurofibromatosis 1 (*NF1*) because of multiple café-au lait spots on his back and legs and several soft tissue masses. The detail examination showed soft diffuse subcutaneous mass on the right supraorbital region (**a**) and upper lip (**b**). Multiple café-au-lait spots were noted primarily on the trunk, appeared to be much darker than the usual Café-au-lait spots and some were excoriated (**c**). There were several separate large, soft, diffuse subcutaneous lesions. He also had numerous hyperpigmented macules on the back, chest, and legs (**d**). No axillary or inguinal freckling was noted. His left foot was smaller than the right (**e**) as well as left calf size. The comprehensive NF1 mutation analysis was negative. MRI of the brain showed an enhancement adjacent to the VIII cranial nerve suspicious of bilateral acoustic neuroma. The boy presented recently with headache, a small cataract of the right eye, and mild hearing impairment. Mutation analysis of *NF2* gene identified a heterozygous mutation in the *NF2* gene (c.1000-?_1446+?del) (deletion of *NF2* exons 11–12). This finding confirms the diagnosis of *NF2* in this patient (Collaboration with Dr. Susonne Ursin)

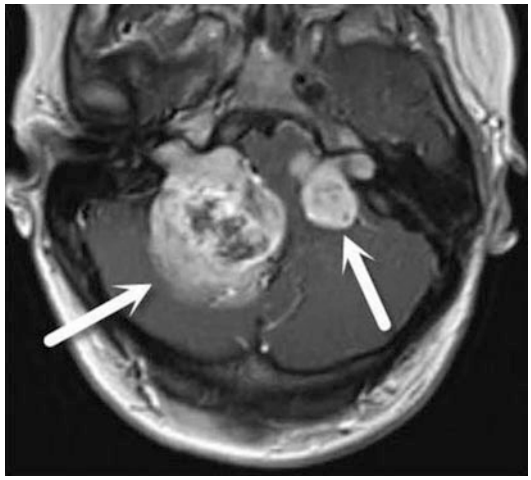

Fig. 3 Post contrast MRI image of brain on a 16-year-old female presenting with hearing loss demonstrates avidly enhancing extra-axial masses bilaterally in the posterior fossa (*arrows*). These masses are herniating into and causing expansion of the internal auditory canal without any bony destruction consistent with bilateral acoustic schwannomas. Mass effect on the brainstem and cerebellum is also identified (Courtesy of Dr. Grace Guo and Dr. Arabinda Choudhary)

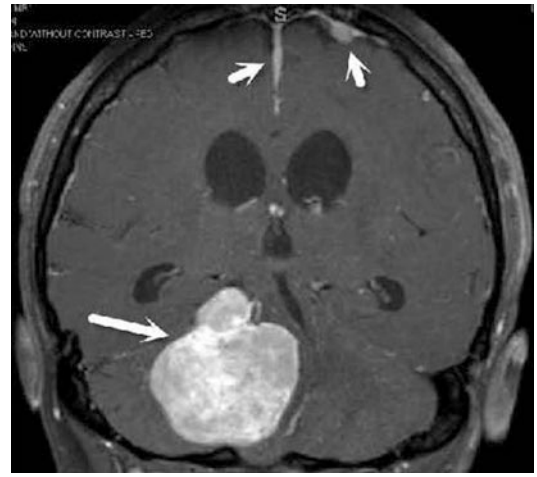

Fig. 4 Her other post contrast MRI image of brain also demonstrates avidly enhancing extra-axial masses bilaterally in the posterior fossa (*large arrow*). Mass effect on the brainstem and cerebellum is also identified. Smaller enhancing dural masses are also identified along the left interhemispheric fissure and overlying the left parietal lobe consistent with meningiomas (*small arrows*) (Courtesy of Dr. Grace Guo and Dr. Arabinda Choudhary)

Niemann-Pick Disease

Contents

Niemann-Pick disease has been used to designate a heterogeneous group of autosomal recessive lysosomal lipid storage disorders (acid sphingomyelinase deficiency) (types A and B), with common features of hepatosplenomegaly and sphingomyelin storage in reticuloendothelial and parenchymal tissues, with or without neurological involvement. Niemann-Pick type C disease (NP-C) evolved from that of a sphingomyelin storage disorder to that of a cholesterol storage disorder (Pentchev et al. 1994).

Synonyms and Related Disorders

Acid sphingomyelinase deficiency; Niemann-Pick disease types A, B, C

Genetics/Basic Defects

1. Niemann-Pick disease types A and B
    1. A rare lysosomal storage disease.
    2. Inherited as autosomal recessive traits.
    3. Result from allelic mutations in the sphingomyelin phosphodiesterase (*SMPD*) genes, located within the chromosomal region 11p15.4.
    4. Caused by deficient activity of acid sphingomyelinase (ASM).
    5. The acid sphingomyelinase defect leads to the accumulation of sphingomyelin in the cells of the liver, spleen, bone marrow, lungs, and, in some patients, brain (Schneider and Kennedy 1967; Marathe et al. 1998; Rodriguez-Lafrasse and Vanier 1999; Schuchman and Desnick 2001a, b).
2. Niemann-Pick disease type C (Vanier 2010)
    1. Biochemically, genetically, and clinically distinct from type A disease and type B disease
    2. Caused by autosomal recessive inheritance of mutations in two genes, *NPC1* (18q11.2) in 95% of cases or *NPC2* (14q24.3) in about 4% of cases, resulting in a disruption of intracellular cholesterol transport and accu-

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mulation of excessive amounts of cholesterol within liver and spleen and other lipids in the brain

Clinical Features

1. Niemann-Pick disease type A (Vanier 2010; Adolina 2014)
   1. A severe neurodegenerative disease with little or no enzyme activity.
   2. Ashkenazi Jewish predilection (gene frequency estimated to be 1:100).
   3. Overall frequency of types A and B: 1:250,000 (Meikle et al. 1999).
   4. Onset in infancy.
      1. Abdominal enlargement due to hepatosplenomegaly
      2. Feeding difficulties
      3. Macular cherry-red spot
   5. Progressive loss of acquired motor skills.
   6. Peripheral neuropathy (Gumbinas et al. 1975; Landrieu and Saïd 1984).
      1. Hypotonia
      2. Absent reflexes
   7. Increased accumulation of sphingomyelin in ganglion cells of the central nervous system leads to neurologic disturbances and mental retardation generally resulting in death by 3 years of age (McGovern et al. 2006).
2. Niemann-Pick disease type B (Guillemot et al. 2007; McGovern et al. 2013)
   1. A milder disease with the same gene defect as type A but has more residual enzyme activity
   2. Panethnic
   3. Characterized by phenotypic heterogeneity
   4. Broad range of severity
   5. Ocular manifestations (primary retinal including macular halos and cherry-red maculae) (Lowe et al. 1986; McGovern et al. 2004a)
   6. Onset in preteen years with the enlargement of the liver and spleen (hepatosplenomegaly)
   7. In adulthood, infiltrative pulmonary disease and ataxia are the major complications
   8. Other features
      1. Hyperlipidemia
      2. Liver dysfunction
      3. Cardiac disease
      4. Excessive bleeding and bruising
      5. Recurrent respiratory infections
      6. Retinal stigmata
      7. Growth retardation/developmental delay
      8. Skeletal manifestations
         1. Osteoporosis
         2. Osteopenia
      9. Peripheral neuropathy
   9. Absence of central nervous system involvement in most patients
   10. Serious morbidities: clinically significant hepatic, cardiac, and pulmonary disease especially in pediatric population
   11. Major causes of death: pneumonia/respiratory failure
3. Niemann-Pick disease type C (Patterson et al. 2012)
   1. Perinatal fetus.
      1. Fetal hydrops
      2. Fetal ascites
   2. Neonates/infants.
      1. Prolonged neonatal cholestatic icterus appearing in the first days or weeks of life (most cases resolve spontaneously by 2–4 months of age), usually associated with progressive hepatosplenomegaly in approximately 50% of patients (Vanier et al. 1988; Kelly et al. 1993; Yerushalmi et al. 2002)
      2. Ascites and severe liver disease resulting from infiltration of the liver
      3. Respiratory failure resulting from infiltration of the lungs
      4. Infants with severe early infantile neurologic onset form
         1. Hepatosplenomegaly almost invariably present
         2. Central hypotonia
         3. Developmental delay of motor milestones
         4. Loss of acquired motor skills, followed by pronounced spasticity with pyramidal tract involvement
         5. Intentional tremor frequently present

3. Mid-to-late childhood: classic presentation occurs during this period.
    1. Insidious onset of ataxia
    2. Vertical supranuclear gaze palsy (a clinical hallmark, often the initial sign)
    3. Dementia
    4. Action dystonia
    5. Seizures
    6. Dysarthria
    7. Dysphagia
    8. Develop pyramidal signs and spasticity at a late stage
    9. Eventual disabling
    10. Death usually occurring in the late second or third decade from aspiration pneumonia
4. Adults.
    1. Dementia
    2. Psychiatric signs
        1. Psychosis including paranoid delusions, auditory or visual hallucinations, and interpretative thoughts
        2. Depressive syndrome
        3. Behavioral problems with aggressiveness
        4. Social isolation
        5. Others

Diagnostic Investigations

1. Radiology.
    1. Type A: chest X-ray and CT scan for demonstrating interstitial lung disease.
    2. Type B:
        1. Chest X-ray and CT scan demonstrate interstitial lung disease (presence of "crazy paving" sign: ground-glass opacities, intermixed thickened interlobular septa and intralobular lines) (Mendelson et al. 2007).
        2. MRI of the brain: may show pronounced cerebellar and mild supratentorial atrophy (Obenberger et al. 1999).
    3. Type C: MRI at late stages of the illness may reveal marked atrophy of the superior/anterior cerebellar vermis, thinning of the corpus callosum, mild cerebral atrophy, and increased signal in the periatrial white matter reflecting secondary demyelination; MRS (magnetic resonance spectroscopy) may be more sensitive than standard MRI (Tedeschi et al. 1998).
2. Pulmonary function test. The lack of correlation between functional pulmonary impairment and the findings at radiography and thin-section CT may be due to the pathologic basis of the lung abnormalities in type B Niemann-Pick disease.
3. Biochemical/histological analyses (Mendelson et al. 2007; Schuchman 2007; Cruse 2013).
    1. NPD type A
        1. Absence of residual acid sphingomyelinase activity and subsequent lysosomal accumulation of sphingomyelin (Graber et al. 1994)
        2. Decreased high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, and increased LDL cholesterol (McGovern et al. 2004b)
        3. Large lipid laden foam cells: observed in the reticuloendothelial system of the spleen, bone marrow, lymph nodes, blood vessels, peripheral nerve Schwann cells, central nervous system, and retinal cells (Wenger et al. 1981)
        4. Electron microscopy: reveals lysosomal inclusions and myelin inclusions in peripheral nerves, indicating a severe myelinopathy (Landrieu and Saïd 1984)
    2. NPD type B
        1. Demonstration of reduced ASM activity in isolated leukocytes and/or cultured skin fibroblast
        2. High triglycerides and LDL cholesterol
        3. Low HDL cholesterol (most consistent laboratory finding)
        4. Thrombocytopenia secondary to hypersplenism in most patients
        5. Liver involvement: infiltration of foamy histiocytes, ballooning of hepatocytes, and fibrosis (Takahashi et al. 1997)
    3. NPD type C (Patterson et al. 2012)
        1. Impaired cholesterol esterification

2. Positive filipin staining in cultured fibroblasts
4. Molecular genetic analysis
   1. NPD types A and B: identification of *SMPD1* gene mutation
   2. NPD type C: molecular testing of *NPC1* and *NPC2* detects disease-causing mutations in approximately 94% of individuals with NPD type C

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis
   1. Type A or B
      1. Measure sphingomyelinase activity in amniotic fibroblasts (Wenger et al. 1978; Vanier 2002)
      2. Molecular genetic testing if both disease-causing *SMPD1* alleles have been identified in an affected family member (McGovern and Schuchman 2011)
   2. Type C (Patterson et al. 2012)
      1. Chorionic villus sampling at 10–12 weeks or fetal cells obtained by amniocentesis at 15–18 weeks: available for pregnancies at 25% risk for type C.
      2. Biochemical testing can be done only when the proband has the typical biochemical phenotype.
      3. Molecular genetic testing: possible when the two disease-causing *NPC1* or *NPC2* mutations have been identified in the proband.
3. Carrier testing: available by molecular testing if the *NPC1* or *NPC2* gene mutation has been identified in the proband
4. Management (Vanier 2010)
   1. Symptomatic management
      1. Antiepileptic drugs for seizures.
      2. Anticholinergic agents for dystonia and tremor.
      3. Physiotherapy for spasticity and prevention of contractures.
      4. Melatonin may be used to treat insomnia.
      5. Special schooling.
      6. Proper management of infections.
      7. Gastrostomy for feeding difficulties.
   2. Bone marrow transplantation
      1. Regression of hepatomegaly and lung infiltration (Hsu et al. 1999).
      2. Unfortunately neurologic status continues to deteriorate.
   3. Liver transplantation with cirrhosis does not influence the course of neurologic deterioration (Gartner et al. 1986).
   4. A rationale supporting early hematopoietic stem cell transplantation in NPC2 patients because the NPC2 protein is soluble, secreted, and recaptured (Verot et al. 2007; Bonney et al. 2010).
   5. Miglustat.
      1. A controlled clinical trial was initiated in neurologically symptomatic patients, first in adolescents and adults (12 years and above) (Patterson et al. 2007), then in children (4–12 years). Overall, the disease course stabilized in 72% of patients treated for 1 year or more.
      2. In January 2009, the European Union has extended the indication of miglustat to the treatment of progressive neurological manifestations in adult and pediatric patients with NP-C, and the drug is now approved for this indication in several other countries. This represents the first specific treatment for NP-C.
      3. An international, multicenter observational cohort study in 66 patients treated off-label with miglustat (Iturriaga et al. 2006; Pineda et al. 2009) further showed a significant reduction in the annual rate of progression of the disease in a majority of patients. Late-onset forms generally appeared as the best responders. A further case series from Spain has been documented (Pineda et al. 2010).
      4. Longer term studies will be important to better evaluate the disease progression

following the stabilization phase (Jacklin et al. 2010).

5. It has been recommended to treat patients as soon as they show neurological manifestations of any type.
6. Miglustat, however, is not expected to have an effect on the systemic manifestations of NP-C.

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Fig. 1 This is an 18-year-old Caucasian female who was seen because of abnormal neurologic symptoms. Early developmental milestones were on target. At 1 year of age, she was noted to walk with an unusual gait. She began staggering and waggling, accompanied with pronate wrists and "stiff arms." As she gets older, she started to have slurring speech, drooling, and choking when drinking or eating. She was also noted to have vertical gaze palsy especially with downward motion, seizures, ataxia, and loss of previously attained speech. The ophthalmology evaluation revealed inferior and superior rectus paralysis and monitor myopia. Her brother has similar clinical symptoms. He has abnormal cholesterol esterification studies with less than 10% of normal cultured fibroblast control assay results. Niemann-Pick type C mutation analysis from his fibroblast culture revealed a heterozygous sequence change in exon 8: c.1211G > A (DNA change of p.2903A > G), which is a known pathogenic mutation. He also has a heterozygous sequence change in exon 19: c.2903A > G. The significance of this sequence change is unknown. Fibroblasts from this patient displayed depressed but not absent cholesterol esterification (20% of normal control cells). Filipin staining of free cholesterol was also seen although not as dramatic as a bona fide Niemann-Pick type C patient. Her Niemann-Pick type C mutation analysis revealed the same heterozygous sequence changes in exon 8 and exon 19. The molecular findings of this patient and her brother are consistent with Niemann-Pick disease type C (Courtesy of Dr. Susonne Ursin)

Noonan Syndrome

Contents

Noonan syndrome (NS) is a relatively common but genetically heterogeneous autosomal dominant malformation syndrome. The incidence of Noonan syndrome is estimated to be 1 in 1,000–1 in 2,500 live births (Tartaglia et al. 2001).

Synonyms and Related Disorders

Female pseudo-Turner syndrome; Male Turner syndrome; Turner phenotype with normal karyotype

Genetics/Basic Defects

1. Inheritance (Allanson 1987; Tartaglia et al. 2010)
    1. Autosomal dominant inheritance
    2. Many affected individuals with de novo mutations
    3. Affected parent recognized in 30–70% of families
2. Caused by mutations in the *PTPN11* (Tartaglia et al. 2001), *SOSI*, *KRAS*, *NRAS*, *RAF1*, *BRAF*, and *MEK1* (*MAP2K1*) genes: accounting for approximately 70% of affected individuals
    1. The gene *PTPN11* (protein tyrosine phosphatase, nonreceptor type 11), mapped on 12q24.1, encoding the protein tyrosine phosphatase SHP-2.
        1. Heterozygous point mutations in the gene *PTPN11* identified in the following:
            1. Families showing linkage to the *NS1* locus in 12q24
            2. Some sporadic cases with NS
        2. All mutations detected to date: missense mutations (Kosaki et al. 2002)
        3. The majority of mutations found in exons 3 and 8, which correspond to the interacting regions of the N-SH2 and protein tyrosine phosphatase domains of the gene (Maheshwari et al. 2002)
        4. Genotype-phenotype correlation of *PTPN11* mutations (Tartaglia et al. 2002; Zenker et al. 2004)
            1. Increased frequency of *PTPN11* mutations observed in individuals with Noonan syndrome with pulmonary stenosis (70%)
            2. Infrequent frequency of *PTPN11* mutations observed in individuals with hypertrophic cardiomyopathy (6%)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. SHP-2 (encoded by *PTPN11*), SOS1, BRAF, RAF1, and MEK1 positively contribute to RAS-MAPK signaling and possess complex autoinhibitory mechanisms that are impaired by mutations.
3. Similarly, reduced GTPase activity or increased guanine nucleotide release underlies the aberrant signal flow through the MAPK cascades promoted by most *KRAS* mutations.

3. Mutation in *SHOC2*
   1. Encodes a cytoplasmic scaffold positively controlling RAF1 activation.
   2. Has been discovered to cause a closely related phenotype previously termed Noonan-like syndrome with loose anagen hair.
   3. This mutation promotes aberrantly acquired *N*-myristoylation of the protein, resulting in its constitutive targeting to the plasma membrane and dysregulated function.
4. *PTPN11*, *BRAF*, and *RAF1* mutations
   1. Also account for approximately 95% of LEOPARD syndrome.
      1. A condition which resembles NS phenotypically
      2. Characterized by multiple lentigines dispersed throughout the body, café au lait spots, and a higher prevalence of electrocardiographic conduction abnormalities, obstructive cardiomyopathy, and sensorineural hearing deficits
   2. These recent discoveries demonstrate that the substantial phenotypic variation characterizing NS and related conditions can be ascribed, in part, to the gene mutated and even the specific molecular lesion involved.

Clinical Features

1. Clinical features (Collins and Turner 1973; Mendez and Opitz 1985; Allanson 1987; Ranke et al. 1988; Noonan 1994)
   1. Growth
      1. Average length at birth, 47 cm
      2. Generally normal birth weight but can be high due to subcutaneous edema
      3. Prepubertal growth parallel to the third centile (40%) with a relatively normal growth velocity
      4. Pubertal growth spurt often reduced or absent
   2. Craniofacial features: change with age (Allanson et al. 1985)
   3. Ocular abnormalities (observed up to 95% of cases)
      1. Strabismus
      2. Refractive errors
      3. Amblyopia
      4. Nystagmus
      5. Anterior segment and fundal changes
   4. Congenital heart defects (two thirds of cases)
      1. Pulmonary valvular stenosis (50%)
      2. Hypertrophic cardiomyopathy (20–30%): may be present at birth or appears in infancy or childhood
      3. Atrial septal defect (10%)
      4. Asymmetrical septal hypertrophy (10%)
      5. Ventricular septal defect (5%)
      6. Persistent ductus arteriosus (3%)
      7. Other cardiac defects
         1. Pulmonary artery branch stenosis
         2. Mitral valve prolapse
         3. Ebstein anomaly
         4. Single ventricles
   5. Genitourinary abnormalities
      1. Males: ranging from normal prepubertal virilization to delayed fertility and inadequate secondary sexual development associated with deficient spermatogenesis secondary to earlier cryptorchidism (60%)
      2. Females: normal or delayed puberty but fertile in majority of cases
   6. Skeletal abnormalities
      1. Characteristic pectus deformity
      2. Common features
         1. Cubitus valgus (50%)
         2. Hand anomalies including clinobrachydactyly and blunt fingertips (30%)

3. Vertebral and sternal anomalies (25%)
4. Dental malocclusion (35%)

7. Ectodermal abnormalities
   1. Various skin manifestations
      1. Café au lait patches (10%)
      2. Pigmented nevi (25%)
      3. Lentigines (2%)
      4. Keratosis pilaris atrophicans faciei
   2. Several instances of neurofibromatosis and the Noonan phenotype documented
8. Bleeding diathesis (Witt et al. 1988; Artoni et al. 2014)
   1. Twenty percent of patients with the Noonan syndrome had a history of severe bleeding diathesis and another 20% of moderate bleeding diathesis.
   2. Bleeding episodes occurred not only during surgical interventions but also spontaneously.
9. Lymphatic abnormalities (Witt et al. 1987; Ogata et al. 2003)
   1. Congenital dysplasia, hypoplasia, or aplasia of lymphatic channels (20%)
   2. General lymphedema
   3. Peripheral lymphedema
   4. Pulmonary lymphangiectasia
   5. Intestinal lymphangiectasia
   6. Hydrops fetalis
   7. Cystic hygroma
10. Rare associated features
    1. Autoimmune thyroiditis
    2. Pheochromocytoma
    3. Ganglioneuroma
    4. Malignant schwannomas
    5. Congenital contractures
    6. Chiari malformation with syringomyelia
    7. Skin and oral xanthomas
    8. Odontogenic keratosis
11. Behavioral and developmental abnormalities
    1. Failure to thrive in infancy (40%)
    2. Motor developmental delay (26%)
    3. Learning disability with specific visual-constructional problems and verbal-performance discrepancy (15%)
    4. Language delay (20%) secondary to perceptual motor disabilities, mild hearing loss (12%), or articulation abnormalities (72%)
    5. Intelligence
       1. IQ: 64–127 with a median of 102
       2. IQ: ten points below that of unaffected family members
       3. Mild mental retardation reported in up to 35% of cases

2. Changing phenotype with age (Allanson 1987)
   1. Newborn period
      1. Marked edema
         1. Contributing to a normal-to-high birth weight
         2. Rapid reduction after birth simulating failure to thrive
      2. Excess nuchal skin
      3. Sloping and broad forehead
      4. Apparent ocular hypertelorism
      5. Downslanting palpebral fissures
      6. A deep philtrum
      7. Mild retrognathia
      8. Posteriorly angulated ears with a thick helix
   2. Neonatal period to 2 years
      1. Head
         1. Relatively large appearance
         2. Flat malar eminence
         3. Bitemporal narrowing accentuated by lateral supraorbital fullness
         4. "Coarse" and occasional asymmetric facial appearance
      2. Eyes
         1. Prominent and round
         2. Ocular hypertelorism
         3. Telecanthus
         4. Lessening downslanting of the palpebral fissures
         5. Occasional strabismus
         6. Thick eyelid hooding the upper iris
         7. Sharp arched eyebrows
      3. Nose
         1. Depressed nasal root
         2. Low nasal bridge
         3. Wide nasal base
         4. Bulbous nasal tip
         5. Anteverted nares

6. Short columella
4. Deep philtrum
5. Arched upper lip with high and wide peaks of the vermilion border
6. Ears
   1. Posteriorly rotated
   2. Occasionally small or square
7. Neck
   1. Short
   2. Less excess skin than in the newborn period
   3. A low posterior hairline
8. Often failure to thrive and hypotonia
9. Occasional hepatosplenomegaly, swarthy skin, and wispy hair
10. 12–18 months of age
    1. Changing body shape with stocky and square upper body
    2. Occasional presence of an umbilical hernia or diastasis recti
    3. The limbs becoming relatively longer and thinner secondary to resolving edema
    4. Blunt fingertips

3. Childhood
   1. Face
      1. Appearance remaining coarse
      2. Becoming more triangular as the chin lengthens
      3. Forehead becoming lower and may be bossed
      4. Flatter malar eminence
   2. Eyes
      1. Less prominent eyes with reduced epicanthus
      2. Increasing ptosis
      3. Increasing lateral supraorbital fullness
      4. Higher nasal root and bridge
   3. Full lips with sublabial protrusion
   4. Neck
      1. Appearing longer
      2. Accentuating webbing
      3. Prominent trapezius
   5. Thorax
      1. Broad
      2. An inverted pyramid shape
      3. Increasing pectus
      4. Upper chest length that increases with relatively low-set nipples and axillary webbing which persist to adulthood
   6. Scapula
      1. Round shape
      2. Winged scapulae
   7. Limbs
      1. Thin
      2. Marked cubitus valgus
      3. Flat feet
   8. Skin
      1. Lentigines
      2. Nevi
      3. Café au lait spots
   9. Often markedly curly or woolly hair
4. Teenage and young adulthood
   1. Facial shape becoming increasingly triangular
   2. Facial features becoming sharper
   3. Less prominent eyes with occasional ptosis
   4. Nose
      1. Thinner
      2. A pinched root
      3. Higher bridge
      4. Wide base
      5. Pointed tip
      6. A longer columella
   5. Eyebrows becoming sparse
5. Older adulthood
   1. Prominent nasolabial folds
   2. Higher anterior hairline
   3. Occasional sloping forehead
   4. Transparent wrinkled skin
6. Prominent abnormalities at all ages
   1. Striking blue or blue-green irides
   2. Increased number of fingertip whorls
   3. Posteriorly angulated ears with a thick helix
   4. Characteristic pectus deformity
      1. Pectus carinatum superiorly
      2. Pectus excavatum inferiorly

3. Disorders clinically related to Noonan syndrome (Jorge et al. 2009; Tartaglia et al. 2010)
   1. LEOPARD syndrome (Please see the chapter of “LEOPARD syndrome”)
   2. Cardiofaciocutaneous syndrome

1. A rare sporadic multiple congenital anomalies/mental retardation syndrome characterized by:
    1. Failure to thrive
    2. Severe feeding problems
    3. Developmental delay
    4. Short stature
    5. Distinguished face
    6. Abnormalities of the skin, gastrointestinal tract, and CNS
    7. Cardiac defects (pulmonary stenosis, hypertrophic cardiomyopathy)
2. Genetically heterogeneous, with mutations in the *KRAS*, *BRAF*, *MEK1*, and *MEK2* genes occurring in approximately 60–90% of affected individuals

3. Costello syndrome
    1. Clinical features
        1. Prenatal overgrowth
        2. Followed by postnatal feeding difficulties and severe failure to thrive
        3. Distinctive "coarse" facial features
        4. Mental retardation
        5. Short stature
        6. Cardiac defects (pulmonary stenosis, hypertrophic cardiomyopathy)
        7. Musculoskeletal (joint laxity) and skin abnormalities
    2. Caused by germline missense mutations in the *HRAS* proto-oncogene
    3. Other causative genes: *KRAS*, *BRAF*, and *MEK1*

4. Neurofibromatosis-Noonan syndrome (NFNS) (Abuelo and Meryash 1988)
    1. Most individuals with NFNS harbor an *NF1* mutation and that a single mutation can be sufficient to engender the trait.
    2. Double heterozygosity for *NF1* and *PTPN11* mutations rarely causes NFNS, and it is not yet clear how frequently mutations in other NS disease genes co-occur with *NF1* defects in the disorder.
    3. These findings support the view that NFNS is genetically distinct from NS and emphasize the extreme phenotypic variability associated with lesions in the *NF1* gene.
    4. The identification of specific *NF1* alleles recurring in NFNS, the evidence that these alleles cosegregate with the condition in families, and the observation of a peculiar mutational spectrum strongly suggest that the term "NFNS" does characterize a phenotypic variant of NF1, which manifests with a lower incidence of plexiform neurofibromas, skeletal anomalies, and internal tumors, in association with hypertelorism, ptosis, low-set ears, and congenital heart defects.
    5. Some of the mutations identified in patients with NFNS have also been reported in NF1 without any feature suggestive of NS.

5. Legius syndrome
    1. Previously known as neurofibromatosis type 1-like syndrome.
    2. An autosomal dominant disorder.
    3. Clinical features.
        1. Multiple axillary freckling
        2. Café au lait spots
        3. Macrocephaly
        4. NS-like facial dysmorphism in some individuals
    4. Caused by loss-of-function mutations of the *SPRED1* gene, which encodes a negative modulator of RAS-MAPK signaling (Brems et al. 2007).
    5. *SPRED1* mutational analysis of sporadic or familial cases with a diagnosis of NF1 or with a phenotype suggestive of the disorder indicates that mutations account for approximately 0.5–1% of *NF1* mutation-negative cases.

Diagnostic Investigations

1. Growth curves for height for males and females with Noonan syndrome now available (Witt et al. 1986; Noonan et al. 2003)
2. Echocardiography for previously described congenital heart defects (Burch et al. 1993)
3. Electrocardiography

1. A wide QRS complex
2. Left axis deviation
3. Giant Q wave
4. A negative pattern in the left precordial leads

4. Radiography: pectus deformity
5. Renal ultrasound for renal anomalies
6. Coagulation studies, mainly platelet function abnormalities in 90% of patients (Artoni et al. 2014)
7. Chromosome analysis: normal karyotype
8. Molecular genetic testing available clinically
   1. Mutations in the gene *PTPN11* identified in 50% of patients (familial and sporadic cases)
   2. Germline mutations
      1. Detected in 59% of patients with familial Noonan syndrome
      2. Detected in 37% of individuals with sporadic Noonan syndrome
   3. Target next-generation sequencing (NGS): Molecular testing of RASopathies by targeted NGS could allow an early and accurate diagnosis of Noonan syndrome and related disorders, enabling a prompt diagnosis especially for those patients with mild, nonspecific, or atypical features, in whom the detection of the causative mutation usually requires prolonged diagnostic timings when using standard routine. This approach strongly improved genetic counseling and clinical management (Lepri et al. 2014).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Fifty percentage if a parent is affected
      2. If both parents had only possible or no signs of Noonan syndrome, an empiric recurrence risk is 5% subsequent to the birth of the first child with Noonan syndrome (Sharland et al. 1993)
   2. Patient's offspring: 50% affected
2. Prenatal diagnosis (Allanson and Roberts 2011)
   1. Ultrasonography (Achiron et al. 2000) for pregnancies at 50% risk: no definitive ultrasonographic diagnostic criteria early in gestation.
      1. Septated cystic hygroma
      2. Scalp edema
      3. Polyhydramnios
      4. Facial features
         1. Posteriorly angulated, apparently low-set ears
         2. Depressed nasal bridge
      5. Pleural and pericardial effusions
      6. Cardiac defects
         1. Pulmonic stenosis
         2. Hypertrophic cardiomyopathy
      7. Ascites
      8. Hydrops fetalis
   2. Molecular genetic testing of fetal DNA extracted from amniocentesis or CVS for *PTPN11* mutations. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
   3. Preimplantation genetic diagnosis: may be available for families in which the disease-causing mutation has been identified.
3. Management (Allanson 2001)
   1. Plotting of growth parameters on growth charts for Noonan syndrome.
   2. Ophthalmological care.
   3. Cardiac management of congenital heart defects and hypertrophic cardiomyopathy.
   4. Hearing evaluation and management.
   5. Physical and occupational therapies for hypotonia.
   6. Speech therapy for articulation deficiencies.
   7. Infant stimulation program for developmental delay.
   8. Multidisciplinary developmental intervention program.
   9. Hearing aids for sensorineural hearing loss.
   10. In case of bleeding episodes or surgical interventions in patients with platelet function abnormalities, recommend administration of vitamin K in patients with low levels of FVII and prolonged PT, general hemostatic agents such as tranexamic acid and desmopressin,

and, in the most severe cases, platelet transfusion (Artoni et al. 2014).

11. Orthopedic management of musculoskeletal abnormalities.
12. Growth hormone treatment of short stature (Kirk et al. 2001): final height not improved substantially in most patients. When long-term GH therapy is intended to promote growth in children with NS, it has to be considered in relation to the genotype, the effective promotion of growth, and the potentially increased tumor risk (Binder 2009).
13. Successful pregnancy possible in women with Noonan syndrome.

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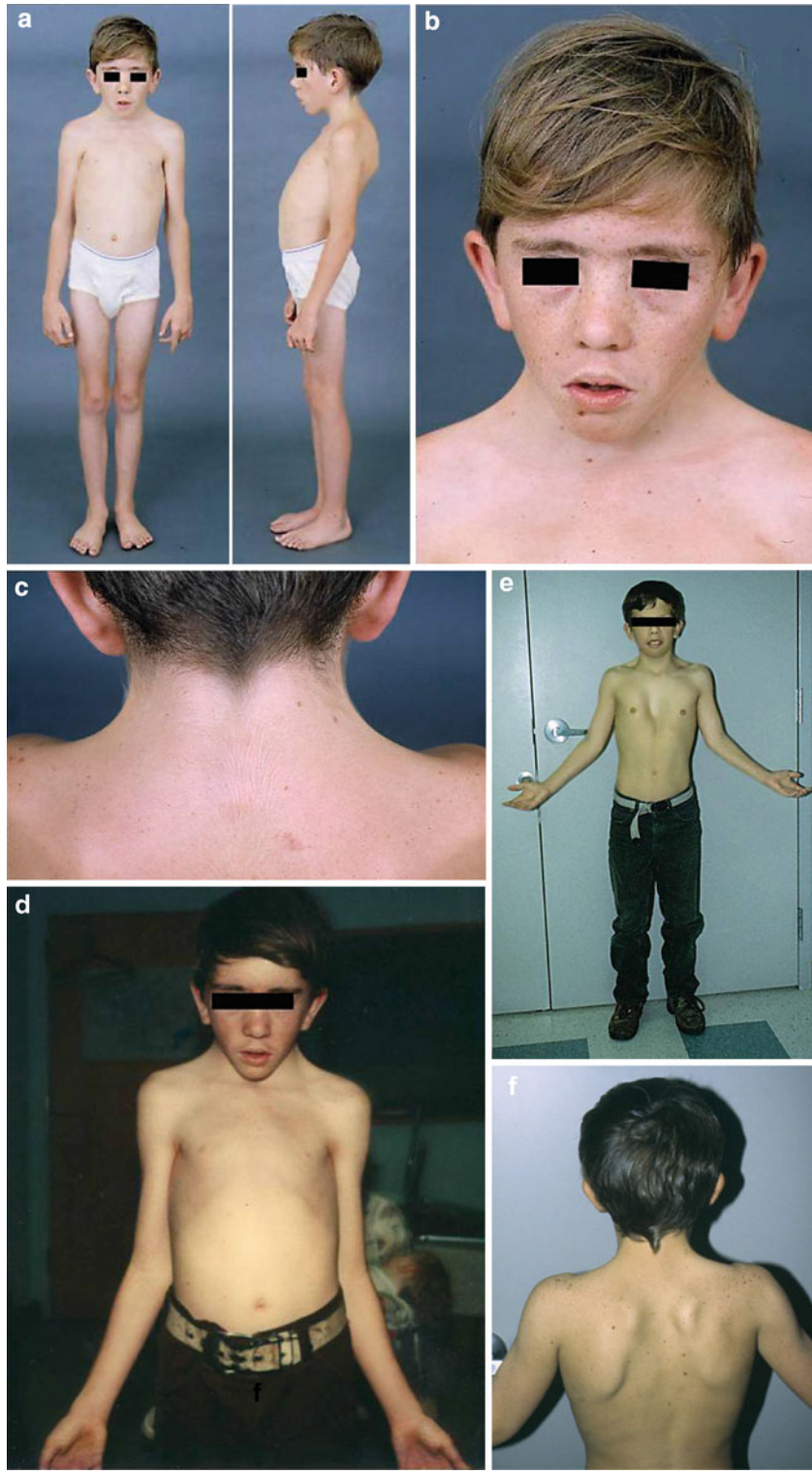

Fig. 1 Two boys (**a**–**d**; **e**–**f**) with Noonan syndrome showing various features: downslanting palpebral fissures, hypertelorism, short and webbed neck with a low posterior hairline, pectus, and cubitus valgus

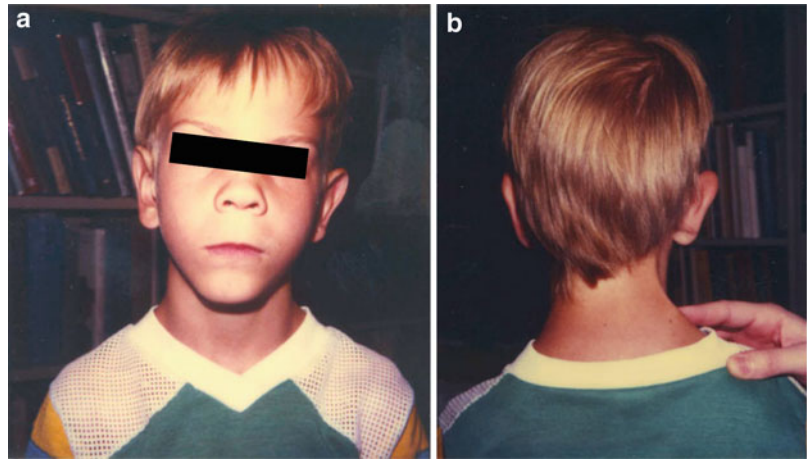

Fig. 2 (**a**, **b**) A boy with Noonan syndrome showing characteristic facial features and webbed neck

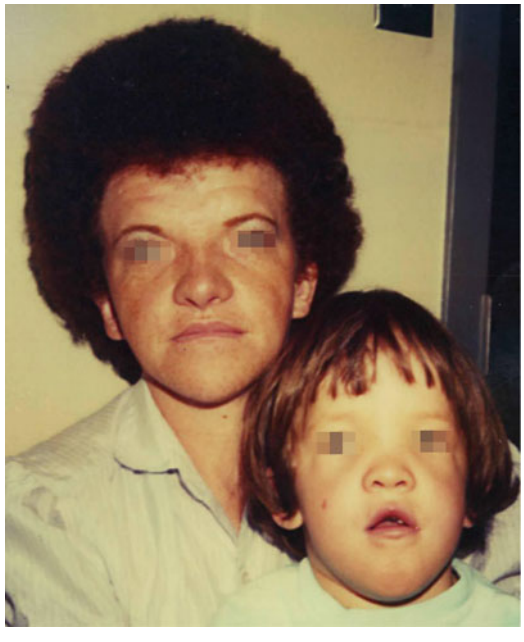

Fig. 3 Familial Noonan syndrome in a mother and a daughter

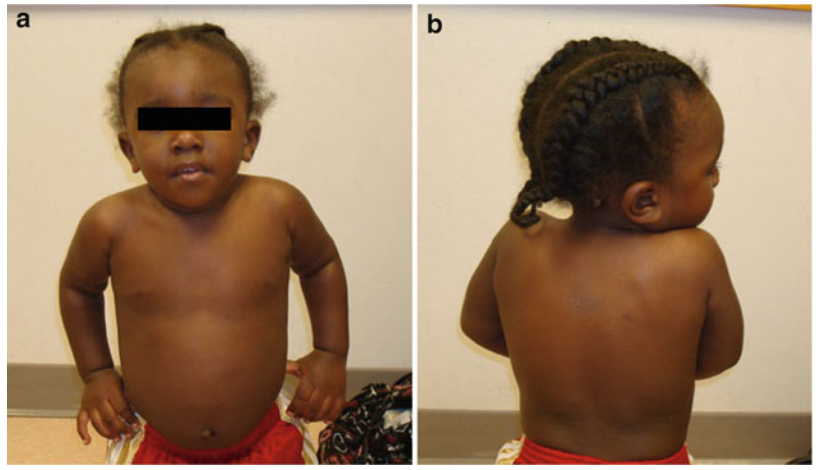

Fig. 4 (**a**, **b**) A 21-month-old boy was evaluated for possible Noonan syndrome because of antimongoloid slant of the palpebral fissures, depressed nasal bridge, slightly low-set ears, short neck, a shield-like chest with distally displaced nipples, and pulmonary stenosis. PTPN11 select exon analysis revealed a heterozygous G > A nucleotide substitution in exon 3, resulting in the replacement of a glycine codon (GGT) with a serine codon (AGT) at amino acid position 60 of the tyrosine phosphatase SHP-2 protein (p.Gly60Ser or G60S) (c.178G > A)

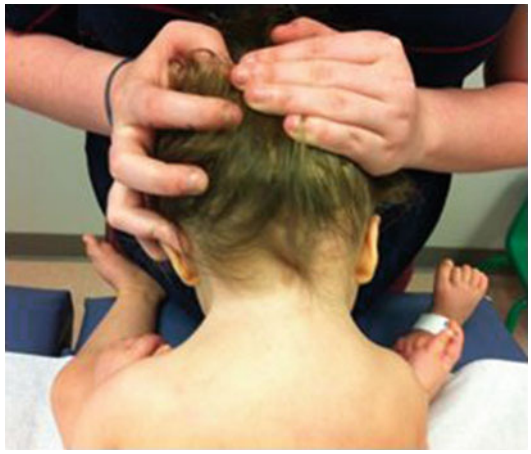

Fig. 5 A 12-year-old Caucasian female was evaluated for short stature and failure to thrive as an infant, a repaired AV canal, repaired intestinal malrotation, developmental delay, and dysmorphic features. Physical examination revealed small for her age (weight 27.3 kg, 0%tile, length 141.5 cm, 1%tile, head circumference 49 cm, <2%tile) with mild webbing of the neck, a broad forehead, and downslanting palpebral fissures. Her internipple distance is 17.5 (~75% tile) and appears to be wide. Chromosome microarray analysis showed normal female microarray profile. Molecular genetic analysis showed heterozygous for the T73I mutation in the *PTPN11* gene, consistent with the diagnosis of a disorder in the Noonan syndrome spectrum (Courtesy of Dr. Susonne Ursin)

Oblique Facial Cleft Syndrome

Contents

Oblique facial clefts are extremely rare congenital anomalies occurring in about 1/100 to 12/1,000 of facial clefts (Rintala et al. 1980).

Synonyms and Related Disorders

Mandibular process clefts; Naso-ocular clefts; Oculomaxillofacial dysplasia with oblique facial cleft; Oroaural clefts; Oro-ocular clefts; Tessier clefts

Genetics/Basic Defects

1. Genetic heterogeneity (Richieri-Costa and Gorlin 1994).
    1. Sporadic in most cases
    2. A disruptive event resulting from amniotic band rupture sequence considered as a main etiological agent (Coady et al. 1998; Kara and Ocsel 2001)
        1. Twenty-six percent of nonsyndromal craniofacial cleft displays congenital limb anomalies.
        2. Thirteen percent of nonsyndromal craniofacial cleft shows evidence of limb ring constrictions.
    3. Occasional association with malformation syndrome (e.g., Fryns anophthalmia-microphthalmia-oblique clefting syndrome)
    4. Rare autosomal recessive inheritance
2. Classification of facial clefts: A universally accepted classification scheme that fully encompasses, accurately describes, and integrates all the various types of orofacial and craniofacial clefts does not exist (Stellzig et al. 1997; Eppley et al. 2005).
    1. The American Association for Cleft Palate Rehabilitation (1962) divided facial clefts into four major groups according to the anatomic location:
        1. Mandibular process clefts
        2. Naso-ocular clefts
        3. Oro-ocular clefts
        4. Oroaural clefts
    2. Boo-Chai (1990) proposed a subdivision of the oro-ocular group into
        1. Medial (Type I)
        2. Lateral (Type II)
    3. Tessier (1976) presented an anatomic classification of the facial clefts by using numbers 0–14 anticlockwise to point the location of the cleft when the orbit is used as the central point.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Commonly used by surgeons because it is purely descriptive and makes no pretense at causation and developmental relationships.
2. Proven validity in analyzing complex facial deformities.
3. Careful examination in confirming the diagnosis and in managing the patients.
4. The Tessier classification includes numbered clefts from 0 (midline cleft of the lip and nose) to 30 (clefting of lower face or a mandibular cleft).
5. Tessier cleft numbers 4, 5, and 6 are oro-ocular clefts.
6. Tessier cleft numbers 7, 8, and 9 are lateral facial or commissural clefts.
7. The oblique clefts: indicated by Tessier cleft numbers 3 through 5 and 9 (Darzi and Chowdri 1993; Eppley et al. 2005).
8. Tessier number 3 cleft (oral-nasal-ocular cleft): (da Silver Freitas et al. 2010)
    1. A paranasalmedial orbitomaxillary cleft running across the lacrimal segment of the lower eyelid and over the lacrimal groove.
    2. The frontal process of the maxilla may be totally absent, as well as the medial wall of the maxillary sinus. It passes around the nasal ala in the nasolabial groove to finally cross the lip and the alveolus like a "harelip."
    3. It represents one of the most difficult and challenging malformations to correct for the reconstructive surgeon.

3. Classification of orofacial clefts (Tolarová and Cervenka 1998)
    1. Isolated anomaly (61.63%)
        1. Cleft lip
        2. Cleft lip and palate
        3. Cleft palate
        4. Atypical facial cleft
    2. Sequence (3.9%)
        1. Robin sequence
        2. Holoprosencephaly sequence
        3. Frontonasal dysplasia sequence
        4. Amyoplasia congenital disruption sequence
    3. Chromosome aberrations (8.79%)
        1. Trisomy 21 syndrome
        2. Trisomy 13 syndrome
        3. Trisomy 18 syndrome
        4. Other trisomies
        5. Other chromosomal aberrations
    4. Monogenic syndromes (6.02%)
        1. Autosomal dominant
            1. Stickler syndrome
            2. Craniosynostosis syndromes
            3. Van der Woude syndrome
            4. Others
        2. Autosomal recessive
            1. Smith-Lemli-Opitz syndrome
            2. Meckel syndrome
            3. Others
        3. X-linked dominant
    5. Known environmental cause (0.2%)
        1. Fetal alcohol syndrome
        2. Dilantin embryopathy
        3. Congenital syphilis
    6. Associations (0.79%)
        1. CHARGE association
        2. VATER association
    7. Multiple congenital anomalies (MCA) (18.5%)
        1. MCA of malformation origin
        2. MCA of deformation origin
        3. MCA of malformation and malformation origin
        4. MCA of other combinations
    8. Conjoined twins
4. Oblique clefts (Kubaček and Pěnkava 1974)
    1. Considered as late or secondary defects resulting from outgrowth of one or more bone centers in membranous bones
    2. Including certain types of Tessier classification (1976): oblique clefts corresponding to the numbers 3–6 distally or "southward" and 8–11 proximally or "northward" from the orbit in the extreme forms (Rintala et al. 1980)
    3. Arbitrary classification in some instances
    4. Presence of intermediate forms of facial clefts

Clinical Features

1. Clinical variability
2. Oblique facial clefts (Boo-Chai 1970; Key 1973)
   1. Naso-ocular clefts
      1. Whole stretch from the lip through the nose to the eyelid and orbit
      2. Nasolacrimal duct always involved
      3. Defective and upwardly dislocated ala nasi
   2. Oro-ocular clefts
      1. Type I (medial): cleft medial to infraorbital region of the nasolabial groove to end in the inner canthus or the lower eyelid
      2. Type II (lateral): cleft extending from the angle of the mouth upward to the orbit ending in the lateral canthus or in a coloboma in the midportion of the lower eyelid
      3. Twice as frequent as the naso-ocular types
   3. Bilateral clefts in 20–35% of cases (Sakurai et al. 1966; Sano et al. 1983)
   4. Presence of complete or incomplete forms
   5. Possible involvement of palate and extending into the temporal region
3. Concordant clinical signs
   1. Short stature
   2. Sparse eyebrows
   3. Sparse eyelashes
   4. Lower lid coloboma
   5. Abnormal nose (Schweckendiek 1974)
   6. Involvement of the nasolacrimal duct
   7. Malar hypoplasia
4. Other variable clinical signs
   1. Mental retardation
   2. Anophthalmia/microphthalmia (Schlenker et al. 1979; Tsu et al. 1991; Warburg et al. 1997)
   3. Hemimelia (possibly resulting from in utero vascular accident in some cases)
5. Associated anomalies
   1. Amniotic bands (Mayou and Fenton 1981; Eppley et al. 1998)
      1. Amniotic band affecting premaxillary-nasal-ocular areas of the midface producing oblique tissue disruptions
      2. Intrauterine amputation
      3. Constriction rings
      4. Distal lymphedema
      5. Distal pseudosyndactyly
      6. Remnant of amniotic band still attached to the lesion
   2. CNS abnormalities
      1. Encephalocele
      2. Hydrocephaly
   3. Aplasia cutis congenita
   4. Talipes equinovarus

Diagnostic Investigations

1. Radiography for craniofacial anomalies
2. Three-dimensional CT reconstruction scan for visualization of the extent and location of the cleft (David et al. 1989)
3. MRI of the brain for CNS anomalies
4. Blood for chromosome analysis to rule out chromosome etiology (Dasouki et al. 1988)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Recurrence risk not increased since most cases are sporadic, especially in a case where amniotic band rupture sequence is considered to be the etiological factor
      2. Recurrence risk possibly increased in occasional cases of autosomal recessive inheritance
   2. Patient's offspring: not increased
2. Prenatal diagnosis: possible by ultrasonographic documenting oblique facial cleft associated with other commonly associated anomalies (CNS anomaly, anophthalmia, and findings of amniotic band disruption sequence)

3. Management
   1. Early orthopedic treatment
      1. To achieve both the proper alignment of the maxillary segments and a reduction of cleft width in cases of unilateral cleft lip, alveolus, and palate
      2. Presurgical orthopedic devices to approximate the distorted segments and to facilitate lip closure in the treatment of maxillary clefts
   2. Surgical repair of facial cleft (Chiong et al. 1981)
      1. General principle
         1. Accurate approximation of each tissue layer
         2. Meticulous layered closure to prevent loss of anatomical continuity and a depressed scar along the site of the operative procedure
         3. Multiple Z-plasty when the repair crosses lines of minimal skin tension or when there is loss of length
      2. Closure of the cleft and reconstruction of the underlying bony deficiencies at a very early age
      3. Followed by subsequent correction of orbital hypertelorism between the ages of 2 and 5 years
      4. Followed by orthognathic correction of maxillary and mandibular deformities in the teens
   3. Management of Tessier number 3 clefts
      1. Eyelid, nose, and upper lip deformities should be treated in sequential stages, positioning the medial canthus, ala, and upper lip, using the contralateral side as the reference (da Silver Freitas et al. 2010).
      2. Tessier number 3 clefts can be associated with multiple other craniofacial anomalies making reconstruction challenging. Soft tissue and bony reconstruction must be considered separately, and a variety of tools may be employed to accomplish each goal (Allam et al. 2014).
   4. Multidisciplinary approach to early intervention

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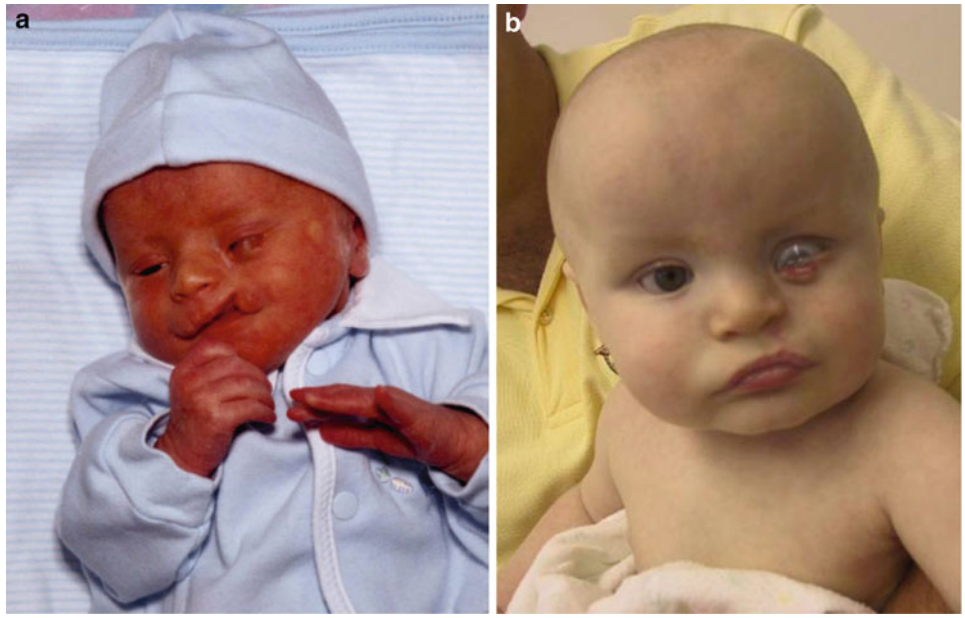

Fig. 1 (**a**, **b**) An infant with oblique facial cleft syndrome (at birth and postoperative) showing unilateral oro-ocular cleft with cleft beginning at the angle of the mouth and ending in a coloboma of the lower eyelid and corneal opacity

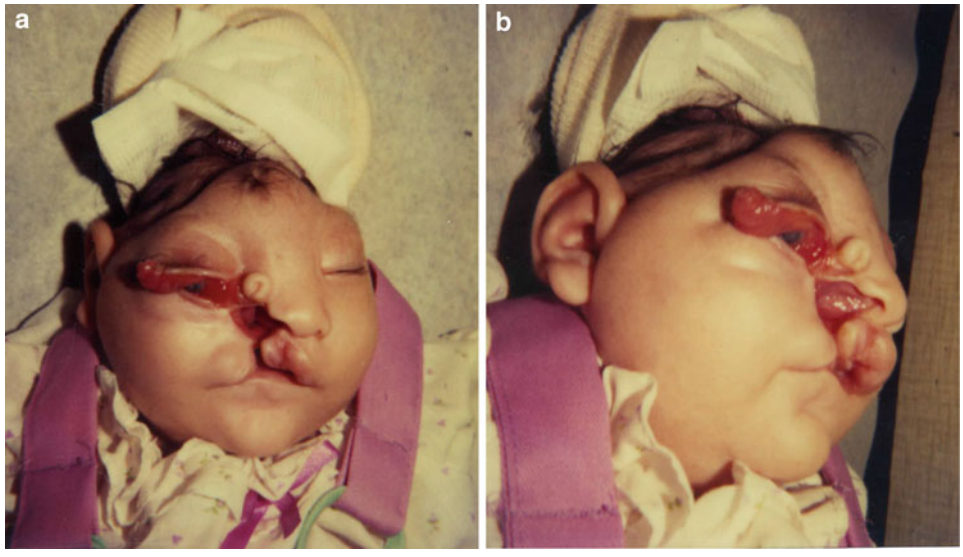

Fig. 2 (**a**, **b**) An infant with oblique facial cleft syndrome showing extensive unilateral oro-naso-ocular cleft and encephalocele

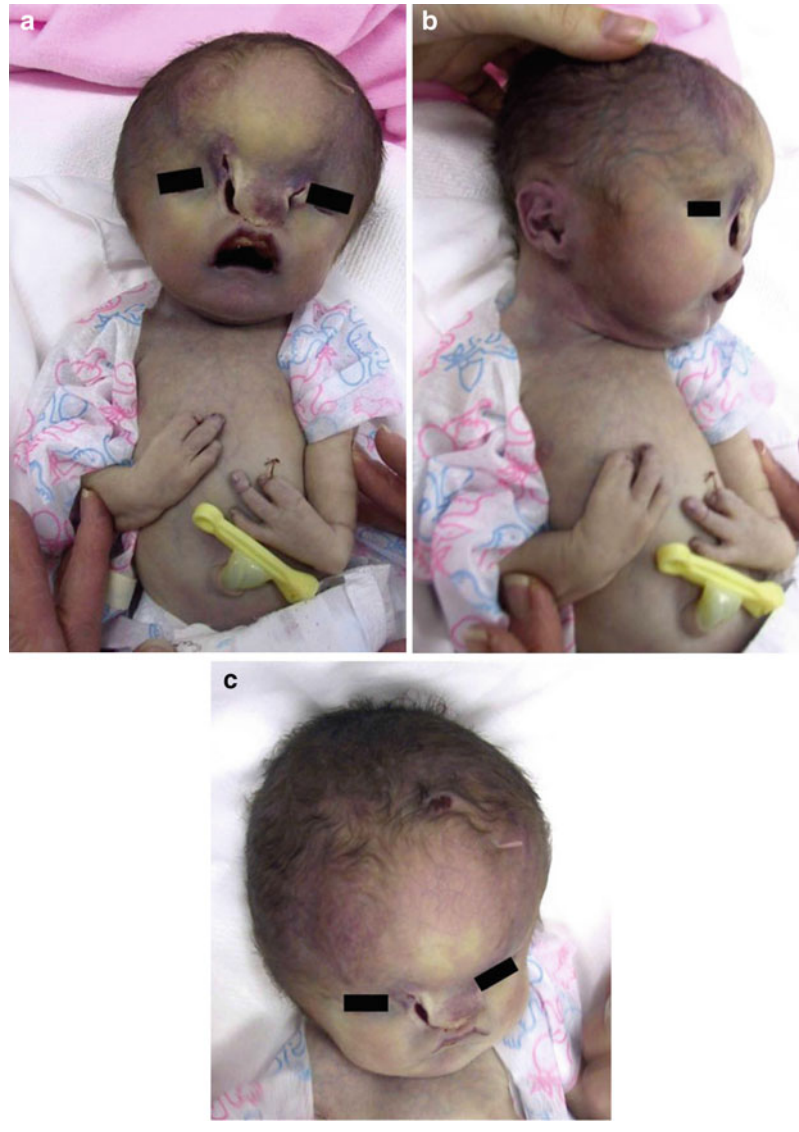

Fig. 3 (**a**–**c**) A newborn with oblique facial cleft syndrome associated with amniotic band syndrome and cutis aplasia congenita of the scalp showing bilateral frontonasal clefts, scalp defect, pseudotail, hypertelorism, anophthalmia, clubhands, digital amputation, constriction bands, and an amniotic band still attached to the left finger. The infant also had hydrocephalus, atrial septal defect, and clubfoot

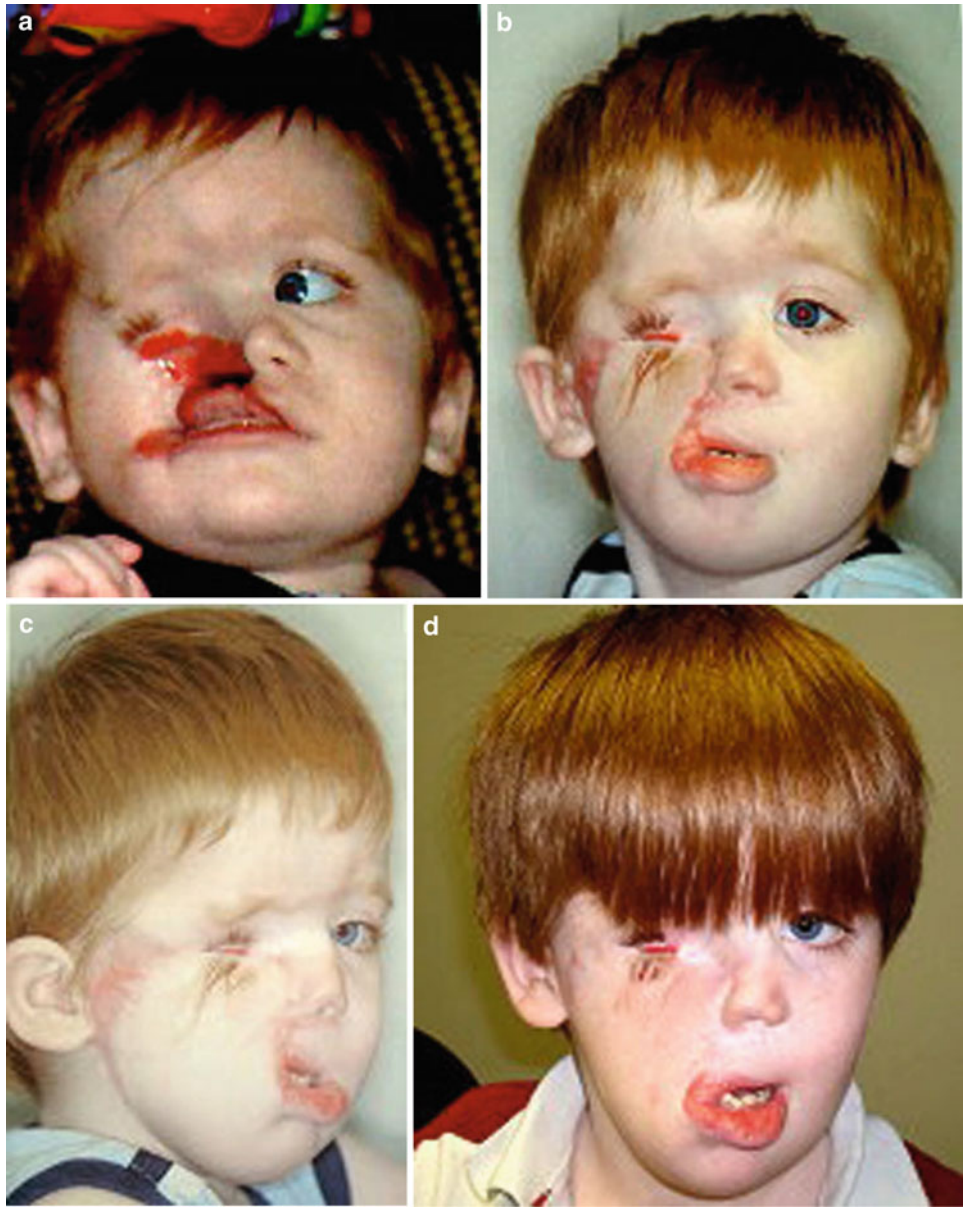

Fig. 4 (**a**–**d**) A 4-year-and-11-month-old boy was seen for Tessier complex orofacial cleft. He was born without right eyeball, absent right nostril, and large oblique orofacial cleft. The photographs show before and after operations

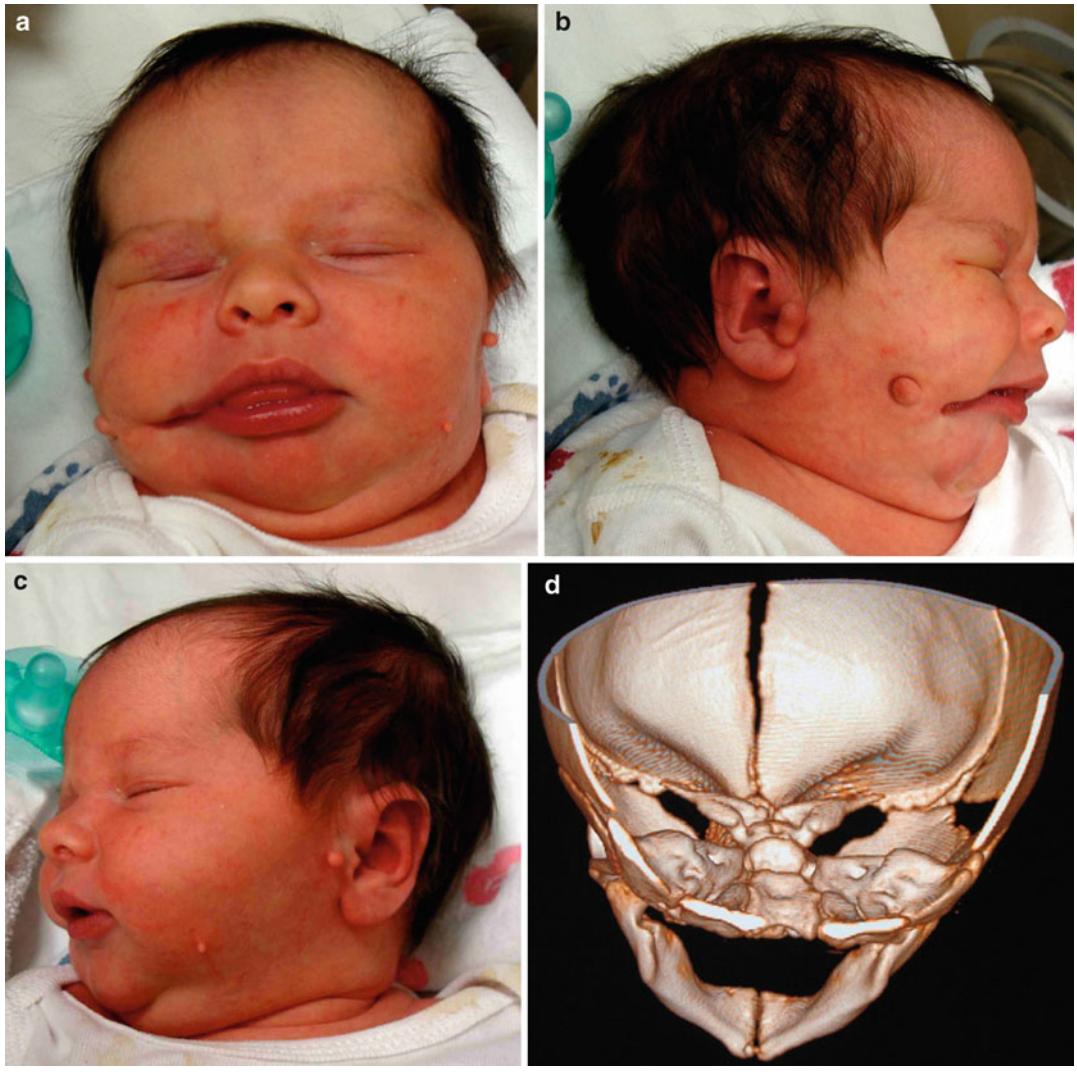

Fig. 5 (**a**–**d**) An infant with Tessier number 7 cleft with a 3D reconstruction CT

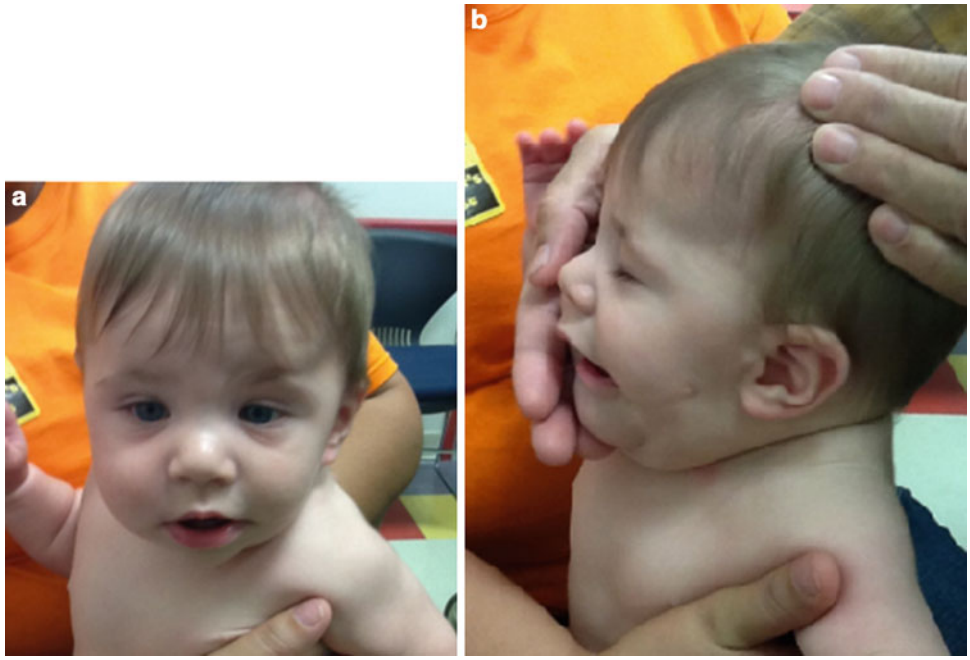

Fig. 6 (**a**, **b**) This 6-month-old boy was evaluated for oblique facial cleft syndrome. He has clefting of the left mouth angle contiguous with a long linear depression/scar connecting to left preauricular tag, which was surgically removed

Oligohydramnios Sequence

Contents

Oligohydramnios is defined as deficiency of amniotic fluid, i.e., decrease in the volume of amniotic fluid. It may result from decreased urinary production or excretion or fluid loss from rupture of membranes. The incidence is estimated to be 0.5–8% of all pregnancies.

Synonyms and Related Disorders

Anhydramnios; Chronic abruption–oligohydramnios sequence; Oligohydramnios; Potter sequence; Potter syndrome; Renal agenesis; Renal tubular dysgenesis

Genetics/Basic Defects

1. Associated maternal conditions (Peipert and Donnenfeld 1991)
    1. Uteroplacental insufficiency
        1. Antiphospholipid antibodies
        2. Chronic hypertension
        3. Collagen vascular diseases
        4. Diabetic vasculopathy
        5. Maternal hypovolemia
        6. Preeclampsia/pregnancy-induced hypertension
    2. Drugs
        1. Prostaglandin synthetase inhibitors
        2. Angiotensin-converting enzyme inhibitors
    3. Placental
        1. Abruption
        2. Twin-to-twin transfusion
    4. Maternal hydration status
2. Associated fetal conditions
    1. Renal malformations (Newbould and Barson 1994)
        1. Bilateral agenesis (34%)
        2. Bilateral cystic dysplasia (34%)
        3. Unilateral cystic dysplasia/agenesis (9%)
        4. Meckel syndrome
        5. Infantile polycystic kidneys
        6. Infantile nephronophthisis can present in utero with oligohydramnios sequence (limb contractures, pulmonary hypoplasia, and facial dysmorphisms) or postnatally with renal manifestations that progress to end-stage renal disease before age 3 years (Stokman et al. 2016)
        7. Renal tubular dysgenesis (Lacoste et al. 2006)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Probably an under recognized disorder.
2. An autosomal recessive disorder.
3. Should be considered for fetuses who present early oligohydramnios, normal or nearly normal kidneys on ultrasound examination, and skull ossification defects.
4. Abnormal renal renin expression confirms the diagnosis and may point toward the gene involved in cases with *REN* null mutations (Gribouval et al. 2012).

8. Posterior urethral valves.
9. Renal hypoplasia.
10. Horseshoe kidney.

2. Other congenital anomalies
   1. Amniotic band syndrome
   2. Branchio-oto-renal syndrome
   3. Cystic hygroma
   4. Encephalocele
   5. Endocardial fibroelastosis
   6. Holoprosencephaly
   7. Hypophosphatasia (homozygous dominant form)
   8. MURCS association
   9. Sacral agenesis (caudal regression)
   10. Sirenomelia
   11. VATER association
   12. Others
3. Chromosome abnormalities
   1. Trisomy 13
   2. Trisomy 18
4. Twin-to-twin transfusion syndrome ("stuck twin syndrome") (Mahony et al. 1990; Bromley et al. 1992)
   1. A complication of monochorionic diamniotic twinning
   2. One twin stucked because of severe oligohydramnios and compressed by the significant polyhydramnios associated with its co-twin
   3. Perinatal mortality associated with severe oligohydramnios/polyhydramnios sequence in a monochorionic twin pregnancy before 28 weeks: 70–100%
5. Intrauterine growth retardation
6. Intrauterine fetal demise
7. Postmaturity possibly caused by a decline in placental function
8. Premature rupture of membranes: the most common cause of oligohydramnios
   1. Preterm (Spong 2001): Preterm premature rupture of the fetal membranes complicated by oligohydramnios may have significant impact and sequelae on pregnancy outcome.
   2. Prolonged (Rib et al. 1993).
      1. Major maternal morbidity: chorioamnionitis.
      2. The overall perinatal survival was 47%, but in infants exceeding 24 weeks' gestation or 500-g weight, the survival increased to 75%.
      3. No significant limb abnormalities, facial anomalies, growth retardation, or pulmonary hypoplasia occurred in the study population.
      4. Long-term follow-up demonstrated that 28% of infants exhibited major neurologic or developmental deficits.
      5. Lung hypoplasia: diagnosed after rupture of the membranes of $\geq$7 days with onset before 29 weeks of gestation (Rotschild et al. 1990). Gestational age at onset of rupture of the membranes is the best single predictor of occurrence of pulmonary hypoplasia (Vergani et al. 1994).
9. Idiopathic

3. Dynamic of amniotic fluid (Sherer 2002)
   1. Presence of amniotic fluid throughout gestation
      1. Enables normal development of the fetal respiratory, gastrointestinal, and urinary tracts and musculoskeletal system
      2. Continued fetal growth in a nonrestricted, sterile, and thermally controlled environment
      3. Amniotic fluid volume is gestational-age dependent
   2. Factors contributing to the formation and removal of amniotic fluid

1. Formation
    1. Fetal urination
    2. Tracheal secretions
    3. Intramembranous pathway including transfers between amniotic fluid and fetal blood perfusing the fetal surface of the placenta, fetal skin, and umbilical cord
    4. Transmembranous pathway involving direct exchange across the fetal membranes between amniotic fluid and maternal blood within the uterus
2. Removal: fetal swallowing
3. Significance of oligohydramnios
    1. A sign of potential fetal compromise
    2. Associated with an increased incidence of adverse perinatal morbidity and mortality, especially in conjunction with the following:
        1. Structural fetal anomalies
        2. Fetal growth restriction
        3. Postdates pregnancies
        4. Maternal disease

Clinical Features

1. Consequences of severe fetal constraints secondary to early and prolonged oligohydramnios.
    1. Potter facies (Potter 1946): associated with renal agenesis and any other cause of severe oligohydramnios
        1. Hypertelorism
        2. Deep crease under the eyes
        3. Epicanthal folds
        4. Flat nose
        5. Receding chin
        6. Low-set, aberrantly folded ears
    2. Lung hypoplasia
        1. Respiratory insufficiency
        2. Death
    3. Limb positional anomalies
        1. Arthrogryposis
        2. Spade-like hands
        3. Talipes equinovarus
    4. Genitourinary abnormalities (Mandel et al. 1992)
    5. Intrauterine growth retardation: one of the most common complications associated with sever oligohydramnios
2. Thirty cases of arthrogryposis associated with long-standing oligohydramnios were identified among 2,500 cases of arthrogryposis (1.2%) and were reviewed for clinical features and natural history (Hall 2014).
    1. None had renal agenesis or renal disease.
    2. Twenty-two had a history of known rupture of membranes.
    3. Only 50% had pulmonary hypoplasia at birth and only two died (7%).
    4. Sixty percent (18/30) seemed to have their multiple congenital contractures primarily on the basis of compression related to the long-standing oligohydramnios and responded well to physical therapy.
    5. On average they did not have intrauterine growth restriction.
    6. "Potter" facies and remarkable skin changes were present in all.
    7. An excess of males was observed in spite of the lack of genitourinary anomalies.
3. Presence of fetal abnormalities in cases associated with severe oligohydramnios (Shipp et al. 1996).
    1. 50.7% in the second trimester
    2. 22.1% in the third trimester
    3. Rate of aneuploidy: at least 4.4%
4. Correlation of the rate of survivors and the gestation when the severe oligohydramnios is diagnosed (Shipp et al. 1996).
    1. 10.2% survivors in the second trimester
    2. 85.6% survivors in the third trimester
5. First and early-second trimester oligohydramnios: a predictor of poor fetal outcome (Barss et al. 1984; Mercer and Brown 1986), except in iatrogenic oligohydramnios post chorionic villus biopsy (Bronshtein and Blumenfeld 1991).
6. The prognosis of early onset renal oligohydramnios is poor. Predictive determinants of survival are (Grijseels et al. 2011).
    1. Gestational age at diagnosis

2. Nature of renal anomaly (hydronephrosis vs other)
3. Presence of associated anomalies

7. 88% of the fetuses with severe oligohydramnios or anhydramnios had lethal outcomes, compared with 11% in the mild/moderate group (Moore et al. 1989).
8. The incidence of adverse outcomes was approximately 15% in preterm small for gestational age (SGA) infants. SGA infants born with oligohydramnios may be at increased risk for cerebral palsy or death (14.7%) compared to those with normal amniotic volume (Sasahara et al. 2016).
9. Renal oligo- and anhydramnios: both renal and pulmonary dysfunction lead to a poor outcome in those patients (Klaassen et al. 2007; Kemper and Mueller-Wiefel 2007; Grijseels et al. 2011; Spiro et al. 2015).
10. Chronic abruption–oligohydramnios sequence (Kobayashi et al. 2014): a clinical condition with lasting vaginal bleeding and oligohydramnios because of chronic placental abruption, which seems to cause preterm labor and neonatal chronic lung disease.

Diagnostic Investigations

1. Ultrasonography
   1. Ultrasonographic modalities to assess oligohydramnios
      1. Single deepest vertical pocket (range, <0.5–<3 cm)
      2. Two-diameter pocket (vertical X horizontal <15 cm)
      3. Amniotic fluid index (AFI) (range, <5–<8 cm)
   2. Defines oligohydramnios
      1. Amniotic fluid index less than 7 cm
      2. Absence of a fluid pocket of 2–3 cm in depth
   3. Variable effects of oligohydramnios on the biparietal diameter and the cephalic index: rapid and marked effect that oligohydramnios can have on the shape of the fetal head and cephalic index can be normal despite an abnormal cranial configuration (Hill et al. 1984)
   4. Assesses fetal growth
   5. Pulmonary hypoplasia (Laudy and Wladimiroff 2000)
   6. Visualizes fetal kidneys, collecting system, and bladder
   7. Improves fetal structures by amnioinfusion
2. Role of diagnostic and therapeutic transabdominal amnioinfusion in oligohydramnios (Fisk et al. 1991)
3. Chromosome analysis for aneuploidy
4. Autopsy for verification of etiology

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: depends on etiology
   2. Patient's offspring: depends on etiology
2. Prenatal diagnosis
   1. Ultrasonography
   2. Amniocentesis
3. Management
   1. Maternal bed rest.
   2. Maternal hydration.
   3. Serial amnioinfusions to prevent pulmonary hypoplasia (complications including preterm labor, amnionitis, and perinatal deaths).
   4. The risks of maintaining the fetus in utero must be weighed against the morbidities and mortalities of premature delivery.
   5. Bilateral renal disease with oligohydramnios indicates significant global fetal renal dysfunction and is a risk factor for the development of pulmonary hypoplasia. This is in striking contrast to the dramatic progress that has been made in neonatal intensive care including pulmonary management.
   6. Recent advances in treatment of infants and children with chronic kidney disease and end-stage renal disease have improved prognosis and also for infants with renal insufficiency considerably (Klaassen et al. 2007).

7. Therapeutic amnioinfusion for chronic abruption–oligohydramnios sequence: a possible prevention of the infant respiratory disease (Morita et al. 2014).
8. In term or post-term pregnancies, isolated oligohydramnios is associated with increased risk of obstetric interventions, but outcomes are similar to those of pregnancies with normal AF (Rossi and Prefumo 2013).

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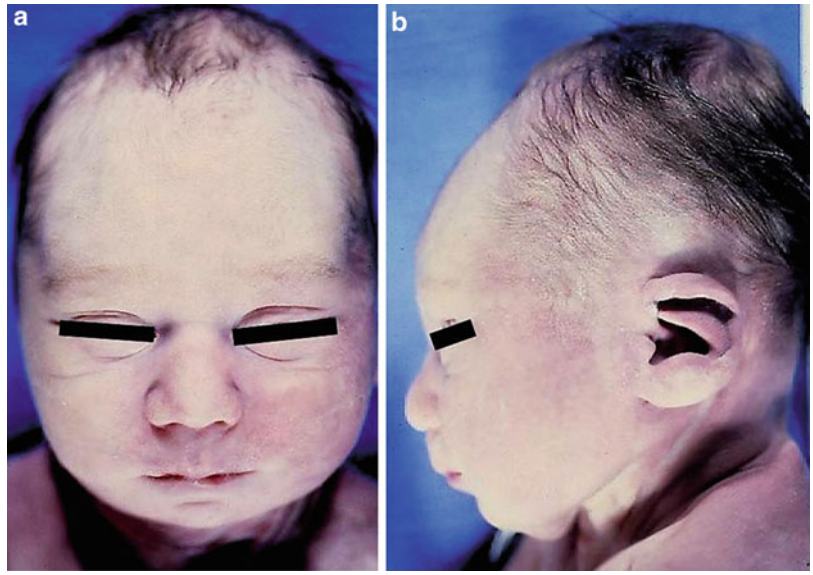

Fig. 1 (**a**, **b**) An infant with renal agenesis and oligohydramnios showing characteristic Potter facies

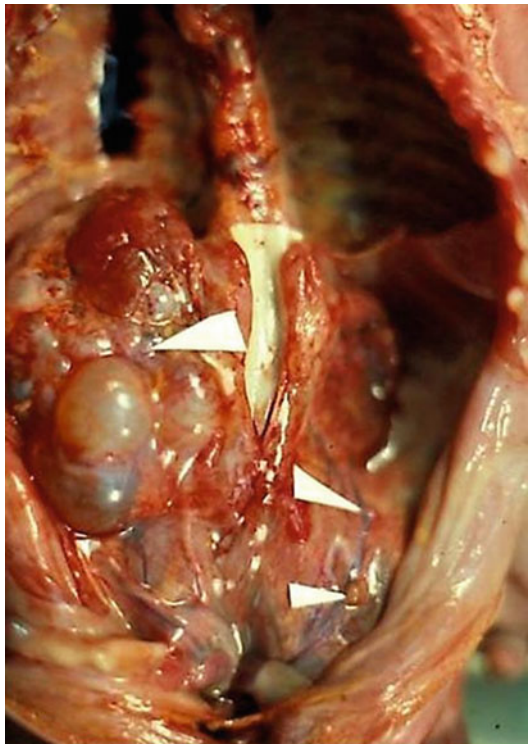

Fig. 2 Multicystic/dysplastic kidneys (*arrows*) causing oligohydramnios

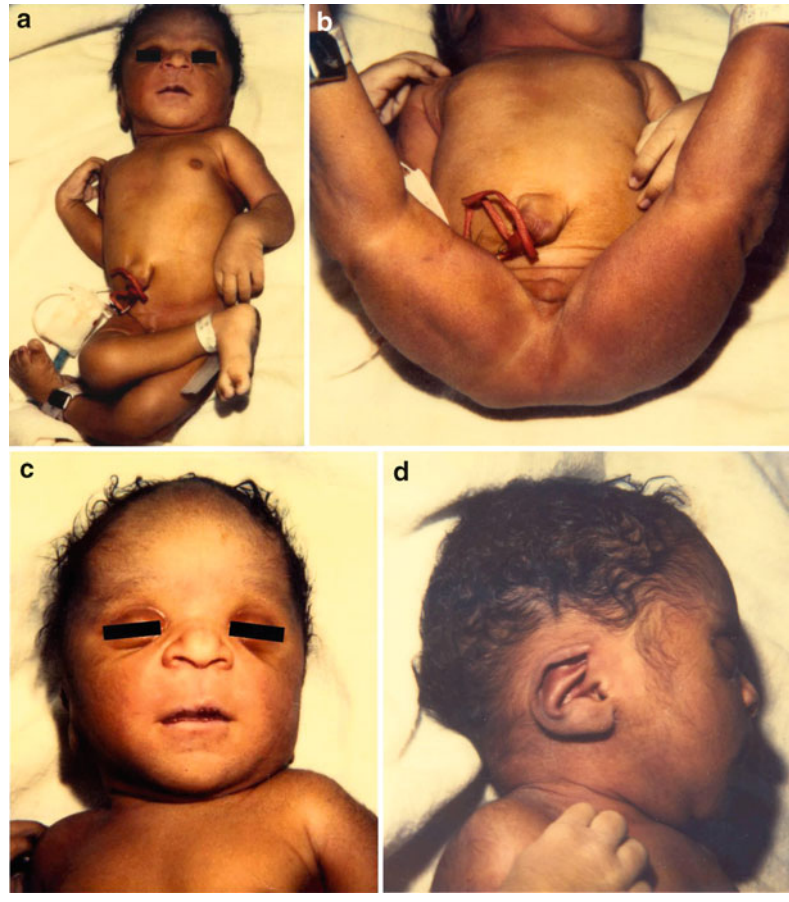

Fig. 3 (**a**–**d**) An infant with caudal regression showing Potter facies (**a**, **c**, **d**), anal atresia (**b**), arthrogryposis, and talipes equinovarus (**a**)

Omphalocele

Contents

Omphalocele is a congenital herniation of viscera into the base of the umbilical cord, covered by a membranous sac. The incidence of omphalocele is approximately 1 in 4000 births (Baird and MacDonald 1981).

Synonyms and Related Disorders

Gastroschisis; OEIS complex; Omphalocele, autosomal dominant; Omphalocele, autosomal recessive; Omphalocele, diaphragmatic hernia, and radial ray defects; Omphalocele, X-linked; Omphalocele-cleft palate syndrome; Shprintzen omphalocele syndrome

Genetics/Basic Defects

1. Embryogenesis
    1. Failure of the cranial, caudal, and lateral folds to fuse before myotome invasion is the most likely explanation for the failure of physiologically herniated midgut returning to the abdomen during the first trimester.
    2. Exomphalos (omphalocele) (Duhamel 1963)
        1. Upper celosomia (herniae of the abdominal wall or ventral herniae)
            1. Omphalocele and defect of sternum, diaphragm, pericardium, and heart
            2. Omphalocele, diaphragmatic hernia, and ectopia cordis abdominalis
            3. Omphalocele and diaphragmatic hernia
        2. Middle celosomia: omphalocele alone
        3. Lower celosomia
            1. Omphalocele and bladder exstrophy
            2. Omphalocele, hindgut agenesis, vesicointestinal fissure, and bladder exstrophy
2. Inheritance
    1. Usually sporadic
    2. Single-gene disorders associated with omphalocele (Chitayat et al. 1997)
        1. Autosomal recessive disorders
            1. Agonadism with multiple internal malformation
            2. Agonadism, XY, with mental retardation, short stature, retarded bone age, and multiple extragenital malformations
            3. Craniostenosis-mental retardation syndrome of Lin and Gettig (1990)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Hydrocephalus with associated malformation
5. Hydrolethalus syndrome
6. Omphalocele-cleft syndrome, lethal (Czeizel 1983)
7. Malpuech facial clefting syndrome
8. Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS): also known as exstrophy of the cloaca occurring in about 1 in 100,000–400,000 pregnancies (Carey et al. 1978). Its mostly sporadic occurrence has etiologic heterogeneity with a role for environmental causes and selected genes (Keppler-Noreuil 2001)
9. Omphalocele-cleft palate
10. Opitz C syndrome

2. Autosomal dominant disorders
   1. Beckwith-Wiedemann syndrome
   2. Omphalocele (Kanagawa et al. 2002)
   3. Shprintzen omphalocele syndrome (Shprintzen and Goldberg 1979)
3. X-linked recessive disorders
   1. Cranioorodigital syndrome
   2. Melnick-Needles osteodysplasty
   3. Omphalocele (Havalad et al. 1979)
   4. Simpson-Golabi-Behmel syndrome
   5. Thoracoabdominal syndrome

3. Other malformation syndromes associated with omphalocele (Barisic et al. 2001)
   1. Caudal regression
   2. Cornelia de Lange syndrome
   3. Amniotic band syndrome
   4. Limb body wall complex
   5. Megacystic microcolon
   6. Schisis association
   7. Skeletal dysplasias
4. Chromosome disorders associated with omphalocele (25%) (Frolov et al. 2010)
   1. Partial trisomy 1q (Chen et al. 1979)
   2. Trisomy 3q (Yatsenko et al. 2003)
   3. Trisomy 13
   4. Trisomy 18
   5. Trisomy 21
   6. Trisomy 16
   7. Add(15)
   8. Turner syndrome
   9. Del(4q)
   10. Del(9)(p22)
   11. Del(18p)
   12. Del(21p)
   13. Diploid-triploid mixoploidy: omphalocele with absent radial ray (Lin et al. 1998)
   14. Inv(2)(p11q12)
   15. Inv(3)(p13q11)
   16. Inv(16)(p11.1q11.2)
   17. 47,XXX

Clinical Features

1. General features
   1. Prematurity
   2. IUGR
2. Herniated sac
   1. Size ranging from 2 to 10 cm
   2. Covering avascular sac consists of fused layers of peritoneum and amnion
   3. Contents of hernia include thoracic and abdominal viscera
      1. Liver
      2. Large intestine
      3. Small intestine
      4. Stomach
      5. Gall bladder
      6. Urinary bladder
      7. Pancreas
      8. Spleen
      9. Internal genitalia
   4. The sac may be torn or ruptured (10–20%)
   5. Necrotizing enterocolitis and malabsorption only if sac is ruptured
3. Umbilical cord inserting into the apex of the sac
4. At increased risk for associated anomalies or syndromes (45–67%)
   1. Cleft lip/palate: Reports of the two cases of co-occurrence of omphalocele and cleft palate raise the possibility of a new syndrome (Upadhyay et al. 2016)
   2. Gastrointestinal abnormalities
      1. Diaphragmatic hernia
      2. Midgut volvulus

3. Meckel diverticulum
4. Intestinal atresia
5. Intestinal duplication
6. Intestinal malrotation
7. Colonic agenesis
8. Imperforate anus

3. Congenital heart defects
4. Neural tube defects
5. Genitourinary: exstrophy of the bladder
6. Skeletal defects (Loder and Guiboux 1993)
   1. Limb deformity
   2. Spinal deformity
7. Beckwith-Wiedemann syndrome
   1. Macroglossia
   2. Hypoglycemia
   3. Organomegaly
   4. Gigantism
8. Epigastric omphalocele associated with pentalogy of Cantrell (Cantrell et al. 1958)
   1. Cardiac abnormalities
      1. Ventricular septal defect most common
      2. Occasional diverticulum of the left ventricle
   2. Sternal cleft
   3. Epigastric omphalocele
   4. Anterior diaphragmatic hernia
   5. Ectopia cordis

5. Prognosis depending on (Mayer 1980; Langer 1996; Kilby et al. 1998):
   1. Size of the omphalocele (Christison-Legay et al. 2011)
      1. Better prognosis with smaller defects (10% of all omphaloceles diagnosed on prenatal US) (Heider et al. 2004): better prognosis (Tucci and Bard 1990)
      2. Large omphalocele (up to 60% of infants with a large omphalocele) (Koivusalo et al. 1999; Biard et al. 2004)
         1. Intractable respiratory insufficiency
         2. Recurrent lung infections or asthma
         3. Gastroesophageal reflux
         4. Feeding difficulty with failure to thrive
   2. Presence or absence of the associated anomalies, especially cardiac defects
   3. Presence of chromosome anomalies: Abnormal karyotypes were significantly associated with the absence of liver from the omphalocele sac and sonographically detectable concurrent malformations (Nyberg et al. 1989)
   4. Gestation at delivery
6. Comparison of characteristics of omphalocele and gastroschisis (please see the chapter on "▶ Gastroschisis") (Christison-Legay et al. 2011; Ledbetter 2012)
   1. Omphalocele
      1. Sac: present
      2. Associated anomalies: Common
      3. Location of the defect: umbilicus
      4. Herniated abdominal organs: bowel and sometimes liver
      5. Maternal age: average
      6. Mode of delivery: cesarean/vaginal
      7. Surgical management: not urgent
      8. Prognostic factors: associated anomalies
   2. Gastroschisis
      1. Sac: absent
      2. Associated anomalies: uncommon
      3. Location of the defect: right of umbilicus
      4. Herniated abdominal organs: Bowell
      5. Maternal age: younger
      6. Mode of delivery: vaginal
      7. Surgical management: urgent
      8. Prognostic factors: condition of bowel

Diagnostic Investigations

1. Routine blood work
2. Abdominal radiography
3. Abdominal ultrasound
4. Echocardiography
5. Chromosome analysis
6. Initiate studies for associated single-gene disorder or malformation syndrome

Genetic Counseling

1. Recurrence risk: depends on the mode of transmission and associated chromosome anomalies
2. Prenatal Diagnosis

1. Elevated maternal serum alpha-fetoprotein (MSAFP): MSAFP screening sensitivity was greater for gastroschisis than for omphalocele at any given cutoff (Palomski et al. 1988)
2. Prenatal 2D ultrasonography
    1. Maternal polyhydramnios
    2. A circumscribed mass containing liver and/or intestines at the cord insertion site
    3. Covering sac composed of amnion and peritoneum
    4. Ruptured omphalocele: a rare complication
    5. Identifies other malformations and allows diagnosis of recognizable syndromes such as pentalogy of Cantrell and prune belly syndrome
3. Prenatal 3D ultrasonography (Bonilla-Musoles et al. 2001)
    1. A useful complement to 2D ultrasonography
    2. Improved definition of omphalocele
    3. Identifies other malformations and allows diagnosis of recognizable syndromes such as pentalogy of Cantrell and prune belly syndrome
    4. Allows isolation and better evaluation of the anomalous structure of interest when there is oligohydramnios or fetal contact with the uterine wall or placenta
4. Ultrasound findings in fetal abdominal wall defects (Prefumo and Izzi 2014)
    1. Omphalocele
        1. Covering membrane: yes
        2. Site of defect: umbilical insertion
        3. Umbilical cord insertion: omphalocele membrane
    2. Gastroschisis (please see the chapter on "► Gastroschisis")
        1. Covering membrane: no
        2. Site of defect: right of umbilical insertion
        3. Umbilical cord insertion: normal insertion
    3. Umbilical hernia
        1. Covering membrane: yes
        2. Site of defect: no umbilical ring defect
        3. Umbilical cord insertion: normal insertion
    4. Pentalogy of Cantrell
        1. Covering membrane: yes
        2. Site of defect: above umbilical insertion
        3. Umbilical cord insertion: omphalocele membrane
        4. Additional findings: anterior diaphragmatic hernia, sternal clefting, ectopia cordis, and intracardiac defect
    5. OEIS complex
        1. Covering membrane: yes
        2. Site of defect: umbilical insertion
        3. Umbilical cord insertion: omphalocele membrane
        4. Additional findings: bladder exstrophy, imperforate anus, and spina bifida
    6. Body-stalk anomaly (please see the chapter on "► Body Stalk Anomaly")
        1. Covering membrane: herniated organs in extraembryonic coelom
        2. Site of defect: whole anterior abdominal wall
        3. Umbilical cord insertion: cord absent or shortened
        4. Additional findings: kyphoscoliosis, cranial defects, and limb defects
    7. Bladder exstrophy (please see the chapter on "► Bladder Exstrophy")
        1. Covering membrane: not applicable
        2. Site of defect: below umbilical insertion
        3. Umbilical cord insertion: low insertion
        4. Additional findings: nonvisualization of bladder, lower abdominal bulge (exstrophied bladder), small penis with anteriorly displaced scrotum (if male), and widening of the iliac crests
    8. Cloacal exstrophy (please see the chapter on "► Cloacal Exstrophy")
        1. Covering membrane: not applicable
        2. Site of defect: below umbilical insertion

3. Umbilical cord insertion: low insertion
4. Additional findings: renal anomalies, neural tube defect, omphalocele, vertebral anomalies, nonvisualization of the bladder, distended bladder, hydrocolpos, dilated or echogenic bowel, umbilical cord cyst, separated pubic bones, and "elephant trunk" sign

5. Prenatal US detection rate at discovery of omphalocele by type of malformation (Barisic et al. 2001)
   1. Isolated (62%)
   2. Syndromic (86%)
   3. Chromosomal (83%)
   4. Multiple (90%)
6. Absence of liver in the omphalocele predicts an abnormal karyotype (Benacerraf et al. 1990): Prenatal US diagnosis would suggest an abnormal karyotype in these fetuses
7. Fetal echocardiography for evaluation of cardiac anomalies: an association between large omphalocele and inferior vena cava with azygos continuation to the superior vena cava (Mlczoch and Carvalho 2015)
8. Fetal MRI (Mann et al. 2008; Nakagawa et al. 2013)
   1. On MRI, a mass consisting of herniated viscera covered by a peritoneal–amniotic membrane is apparent in the anterior abdominal wall of the fetus.
   2. The umbilical cord is inserted into the apex of the surrounding membrane.
   3. The sac of omphalocele commonly contains the liver and small bowel.
   4. The ascites, large bowel, stomach, and spleen can also be present.
   5. Useful for viewing anatomical details where visualization is limited by maternal body habitus or amniotic fluid volume (Pumberger et al. 2003).
   6. Volumetric calculations of lung volume (Cannie et al. 2006).
   7. Evaluation of abdominal contents (Takada et al. 2006).
9. Amniocentesis
   1. Elevated amniotic fluid alpha-fetoprotein
   2. Positive acetylcholinesterase
10. Chromosome analysis
    1. Amniocentesis
    2. CVS
    3. Fetal blood sampling

3. Management (Mann et al. 2008)
   1. Mode of delivery: Owing to the potential intrapartum risk of dystocia (Paidas et al. 1994), sac rupture, and trauma to abdominal viscera, delivery of fetuses with giant omphaloceles should be by cesarean section.
   2. Attempts at primary repair: difficult due to a small abdominal cavity resulting from extraabdominal location of the viscera in utero.
   3. Emergency care
      1. Insertion of an orogastric tube
         1. To decompress the stomach
         2. To prevent swallowed air from causing bowel distention
      2. Cover the intact omphalocele sac with a sterile dressing and protect it from injury or rupture: Rupture of the sac increases the risk of infection and can lead to intestinal or hepatic trauma but, worse, destroys options for delayed closure strategies
      3. Use of a silastic silo to reduce the viscera over time. The silo is attached to the skin with nonabsorbable suture and is hung above the abdomen to use gravity to help reduce the viscera. The silo is tightened each day as the viscera reduce. Once all of the viscera have been reduced, the silo is removed and the fascia and skin are closed (Kelly and Ponsky 2013)
      4. Administer intravenous fluids and parenteral antibiotics
      5. Assess cardiorespiratory status and additional anomalies
   4. Pulmonary hypoplasia can be severe in these neonates with giant omphalocele and may require prolonged mechanical ventilation and tracheostomy (Edwards et al. 2007; Islam 2012)

5. Pulmonary hypertension (PH) was observed in 37% of giant omphalocele (GO) patients. PH represents a significant complication of GO, and management of pulmonary dysfunction is a critical consideration in improving clinical outcomes in these patients (Partridge et al. 2014)
6. The advent of total parenteral nutrition (TPN) was an important factor in decreasing the mortality, and with a better knowledge of the mechanical ventilation of the neonate the results are better and involve the survival of a greater number of patients with serious associated malformations (Yazbeck et al. 1986)
7. Direct primary closure of the abdominal wall for small omphalocele (2 cm)
8. Use of silver sulfadiazine dressing changes for initial nonoperative management of giant omphaloceles: safe and effective bridge to delayed closure (Lee et al. 2006)
9. Staged closure: using a Dacron-reinforced Silastic silo as a temporary housing for the bowel for medium to large omphalocele
10. Giant omphalocele can be safely repaired in the neonatal period without opening the amniotic sac. Intestinal malrotation should be excluded and Ladd's procedure can be performed laparoscopically at a later stage (Pacilli et al. 2005)

Management of a giant omphalocele with non–cross-linked intact porcine-derived acellular dermal matrix (Strattice) combined with vacuum therapy (Travassos et al. 2015)

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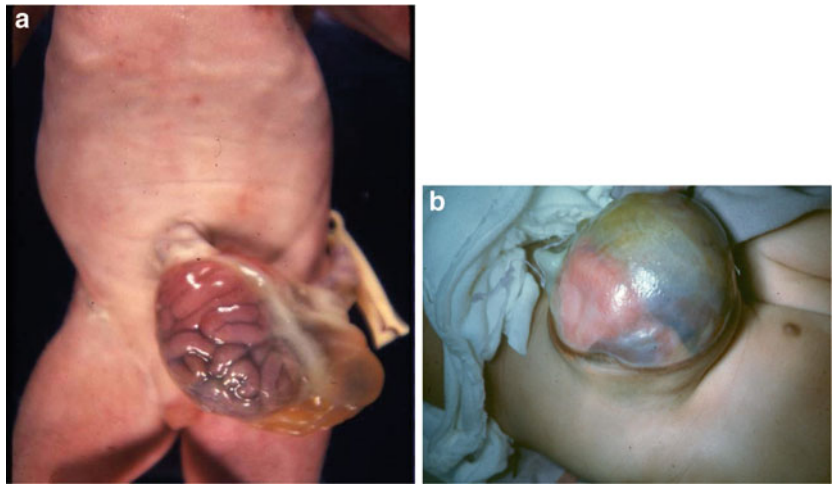

Fig. 1 (**a**, **b**) Two infants with omphalocele showing a sac containing bowel and other abdominal contents

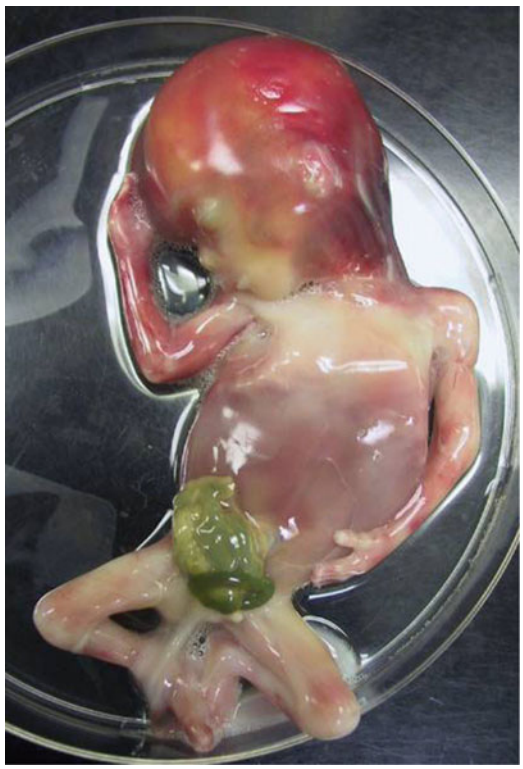

Fig. 2 A 16-week-old fetus with omphalocele showing a sac containing bowel

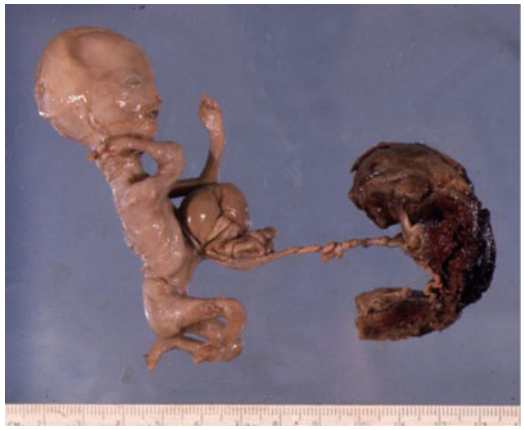

Fig. 3 A fetus with omphalocele showing the umbilical cord attaching to the apex of the sac

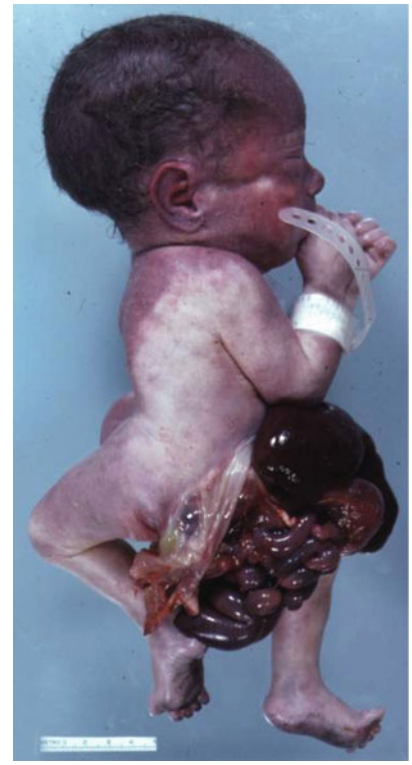

Fig. 4 A neonate with a large ruptured omphalocele. The remnant of omphalocele sac is visible between the herniated viscera and the abdominal wall. The infant had body-stalk anomaly

Opitz Trigonocephaly Syndrome

Contents

Opitz trigonocephaly syndrome, also known as C syndrome, is a malformation syndrome characterized by trigonocephaly, severe mental retardation, hypotonia, variable cardiac defects, redundant skin, and dysmorphic facial features including upslanted palpebral fissures, epicanthal folds, depressed nasal bridge, and low-set posteriorly rotated ears (Kaname et al. 2007) (Fig. 1).

Synonyms and Related Disorders

Bohring–Opitz syndrome; C-like syndrome; C syndrome; Opitz C syndrome; Trigonocephaly syndrome

Genetics/Basic Defects

1. Evidence suggests onset of gene action in the primary field during the establishment of the progenitor fields of major organ systems including central nervous system, cardiac anomalies, a bona fide primary connective tissue dysplasia, and craniofacial-axial midline involvement and possibly involving a defect of the sonic hedgehog (SHH)/PTC/GLI3 pathway (Opitz et al. 2006)
2. Caused by mutation in the *CD96* gene (Kaname et al. 2007)
    1. 46,XY,t(3;18)(q13.13;q12.1) was observed in a patient with C syndrome (Chinen et al. 2006).
    2. The *CD96* gene, located at 3q13.13 breakpoint, was disrupted by the translocation in exon 5, probably leading to premature termination or loss of expression CD96 protein.
    3. No deletions or duplications were detected from surveyed copy number variation for the whole genome in this patient.
3. Inheritance: autosomal recessive
4. Phenotypic overlap with Bohring–Opitz syndrome (caused by heterozygous mutation in the *ASXL1* gene on chromosome 20q11.21) (Fisher et al. 2003)

Clinical Features

1. Prenatal history (Opitz et al. 2006)
    1. May document an apparently normal pregnancy
    2. Anhydramnios in case of severe urogenital anomalies

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Central nervous system
    1. Mental retardation: generally moderate to severe, but normal intelligence has been reported (Lalatta et al. 1990; Stratton et al. 1990)
    2. Brain anomalies (Zampino et al. 1997)
        1. Agenesis of the corpus callosum
        2. Cerebellar vermis hypoplasia
        3. Cerebral atrophy/ventriculomegaly
        4. Megacysterna magna
        5. Generalized reduction in white matter
        6. Dandy–Walker malformation
        7. Occipital meningocele
    3. Hypotonia in most affected infants
    4. Seizures: may develop
3. Growth
    1. Short stature
    2. Failure to thrive
4. Craniofacial phenotype: complex and highly characteristic
    1. Cranial features
        1. Trigonocephaly with prominence of metopic suture
        2. Hypotelorism: in case of premature fusion of the metopica
        3. Hypertelorism: frequent and indicates a primary deficiency of the frontal lobes without premature fusion of the metopic suture
        4. Progressively smaller head size to microcephaly
        5. Becoming dolichocephalic skull shape
    2. Facial features
        1. Upward slant of palpebral fissures
        2. Thick epicanthic folds
        3. Squint
        4. Depressed bridge and broad tip of the nose
        5. Short, thick nasal septum and columella
        6. Variable length of the upper lip with flat philtrum and thin vermilion borders
        7. Micrognathia
    3. Oral features
        1. Broad alveolar ridges with rugose anterior palatal mucosa
        2. Highly arched/cleft palate with upper midline thick buccogingival frenulum with subsequent diastema
        3. There may be multiple additional, mostly upper buccogingival frenula
        4. Increased width of upper central incisors
    4. Other features
        1. Posteriorly angulated auricles with multiple minor, mostly modeling defects and deficient cartilage
        2. Hearing loss (Nacarkucuk et al. 2003)
        3. Capillary hemangiomata: may be confined to the midline of the face (upper lip, nose, glabella, forehead) but also involve upper lids
5. Neck: short and appears to be an effect of residual nuchal lymphedema
6. Connective tissue dysplasia
    1. Generalized and extremely stretchy skin over trunk
    2. Wrinkling of skin over distal limbs
7. Limbs
    1. Short, especially rhizo/acromelic segments
    2. Hypermobile elbows with crepitus
    3. Polydactyly, usually postaxial of 1, 2, 3, or 4 limbs, with variable degrees of syndactyly of toes
    4. Fingers: short with thumbs described at times as “spatulate,” Rubinstein–Taybi like, or digitalized
    5. Knee joints: tend to be hypermobile, rarely dislocated as in the spectacular examples of Opitz et al. (1969)
    6. Distal phalanges: may be deficient
8. Back: usually straight with sacral dimple and at times with hirsutism
9. Trunk: may appear short secondary to platyspondyly
10. Chest
    1. Deformed with thin, deformed ribs
    2. Short sternum with reduced number of ossification centers but more normal length of manubrium and xiphisternum
11. Cardiovascular malformation

    1. Common cardiac anomalies: tetralogy of Fallot, ASD, VSD, and PDA
    2. Vascular anomalies
12. Other features
    1. Umbilical hernia
    2. Omphalocele: at times
    3. Inguinal herniae
    4. Enlarged clitoris
    5. Small penis
    6. Cryptorchidism
    7. Diaphragmatic hernia
13. Phenotypic overlap with Bohring–Opitz syndrome (or C-like syndrome): with more severe features than C syndrome (Bohring et al. 1999)
14. A very high mortality rate: almost 50% of patients die within the first year of life (Opitz et al. 2006)

Diagnostic Investigations

1. Cytogenetic analysis: to identify any chromosome abnormality
2. Molecular analysis of *CD96* mutation: not available clinically
3. CT of the head for trigonocephaly
4. MRI of the brain for CNS anomalies
5. Echocardiography for congenital heart defects
6. EEG for seizures

Genetic Counseling

1. Recurrence risk according to autosomal recessive inheritance
    (a) Patient's sib: a 25% risk
    (b) Patient's offspring: not increased unless the spouse is also a carrier
2. Prenatal diagnosis: has not been described, although ultrasonography may identify congenital anomalies
3. Management: supportive

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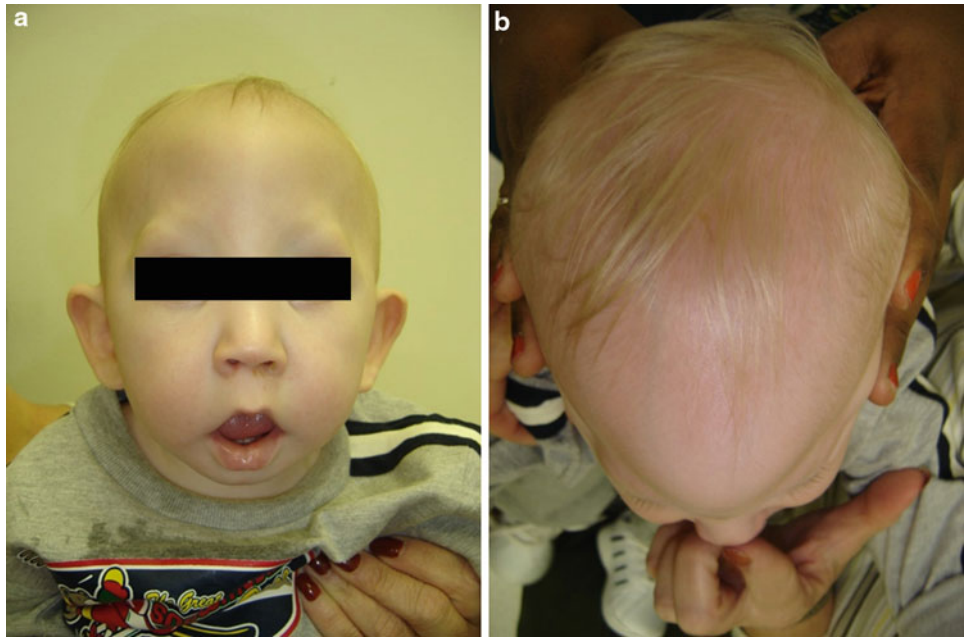

Fig. 1 (**a**, **b**) This 1-year-old Caucasian male infant (**a**) was evaluated for trigonocephaly (**b**) and to rule out Opitz trigonocephaly syndrome. He also has developmental delay, a flat nasal bridge, bilateral epicanthal folds, retromicrognathia, low-set ears, posteriorly rotated ears, bilateral preauricular pit, bicuspid aortic valve, G-tube placement due to poor suck reflex, presacral pit, and hyperextensible joints

Oral-Facial-Digital Syndrome

Contents

In 1941, Mohr reported a family in which the propositus had oral (high-arched palate, lobate tongue with papilliform outgrowths), facial (broad nasal root, hypertelorism), and digital (syndactyly, brachydactyly, polydactyly of the hands and feet) findings. This report was the first description of an oral-facial-digital syndrome (OFD). Mohr concluded that the condition was due to sex-linked recessive sublethal gene. A later report of the same family identified a similarly affected individual born to consanguineous parents, thus leading to the conclusion that the condition was inherited as an autosomal recessive trait, now known as OFD II or Mohr syndrome.

A similar phenotype, described by Papillon-Leage and Psaume in 1954, was identified as an X-linked dominant trait, now known as OFD I. After the identification of OFD I and OFD II, the phenotype spectrum was further expanded with extra oral-facial-digital manifestations, leading to the definition of the new types (Toriello 1988; Al-Qattan and Hassanain 1997). To date, 13 types have been distinguished based on the characteristic clinical manifestations. The oral-facial-digital syndromes result from the pleiotropic effect of a morphogenetic impairment affecting almost invariably the mouth, face, and digits.

Synonyms and Related Disorders

OFD I (papillon-Leage-Psaume syndrome); OFD II (Mohr syndrome); OFD III (Sugarman syndrome); OFD IV (Baraitser-Burn syndrome or Mohr-Majewski syndrome); OFD V (Thurston syndrome); OFD VI (Varadi-Papp syndrome); OFD VII (Whelan syndrome); OFD VIII (Edwards syndrome); OFD IX (Gurrieri syndrome); OFD X (Figuera syndrome); OFD XI (Gabrielli syndrome); OFD XII (Moran-Barroso syndrome); OFD XIII (Degner syndrome); OFD XIII (Degner syndrome); OFD XIV; Orofaciodigital syndrome (OFD)

Genetics/Basic Defects

1. OFD I (Papillon-Leage-Psaume syndrome) (Wahrman et al. 1966): X-linked dominant (lethal in males): *OFD1* is the only gene currently known to be associated with oral-facial-digital syndrome type I. Caused by mutation in the OFD1 protein gene (Rakkolainen et al. 2002; Romio et al. 2003)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. OFD II (Mohr syndrome): autosomal recessive
3. OFD III (Sugarman syndrome): autosomal recessive
4. OFD IV (Mohr-Majewski syndrome, Baraitser-Burn syndrome): autosomal recessive, caused by mutation in the TCTN3 gene
5. OFD V (Thurston syndrome): autosomal recessive, caused by mutation in the DDX59 gene
6. OFD VI (Varadi-Papp syndrome): autosomal recessive, caused by mutation in the C5ORF42 gene
7. OFD VII (Whelan syndrome): autosomal or X-linked dominant
8. OFD VIII (Edwards syndrome): X-linked recessive
9. OFD IX (Gurrieri syndrome): X-linked recessive
10. OFD X (Figuera syndrome): autosomal dominant
11. OFD XI (Gabrielli syndrome): isolated cases
12. OFD XII (Moran-Barroso syndrome): autosomal recessive
13. OFD XIII (Degner syndrome): autosomal recessive
14. OFD XIV: autosomal recessive, caused by mutation in the C2CD3 gene on chromosome 11q13 (Thauvin-Robinet et al. 2014)

Clinical Features

1. OFD I (Papillon-Leage-Psaume syndrome) (Gorlin and Psaume 1962; al-Qattan and Hassanain 1997; Ferrante et al. 2001; Thauvin-Robinet et al. 2006; Gurrieri et al. 2007; Papagrigoraskis et al. 2010; John et al. 2013; Toriello and Franco 2013)
    1. Characterized by anomalies of the face, oral cavity, and digits with a high degree of phenotypic variability even within the same family, possibly due to different degrees of somatic mosaicism resulting from random X-inactivation
    2. Abnormalities of the oral cavity: primarily affecting the tongue, palate, and teeth
        1. Lobed tongue often described as bifid or trifid.
        2. Tongue nodules, usually hamartomas or lipomas, also occur in at least one third of individuals.
        3. Ankyloglossia attributable to a short lingual frenulum common
        4. Cleft hard or soft palate, submucous cleft palate, or highly arched palate: occurring in more than 50% of affected individuals.
        5. Trifurcation of the soft palate reported.
        6. Alveolar clefts and accessory gingival frenula are common. These fibrous bands are hyperplastic frenula extending from the buccal mucous membrane to the alveolar ridge, resulting in notching of the alveolar ridges.
        7. Dental abnormalities include missing teeth (most common), extra teeth, enamel dysplasia, and malocclusion.
    3. Craniofacial abnormalities
        1. Median pseudoclefting of the upper lip
        2. Irregular margin of the lips
        3. Facial asymmetry
        4. Downslanting palpebral fissures
        5. Ocular hypertelorism
        6. Telecanthus
        7. Micrognathia
        8. Broadened nasal ridge
        9. Hypoplasia of the malar bones and nasal alar cartilages
        10. Frontal bossing
        11. Vanishing milia of the face and ears, usually disappear before the third year of life
        12. Dryness, brittleness, and/or alopecia of the scalp hair
    4. Digital abnormalities
        1. Brachydactyly.
        2. Syndactyly of varying degrees.
        3. Clinodactyly of the fifth finger.
        4. The third (i.e., middle) finger showing variable radial or ulnar deviation.

5. Duplicated hallux (great toe) occurs in fewer than 50% of affected individuals but if present is usually unilateral.
6. Preaxial or postaxial polydactyly of the hands occurring in 1–2% of affected individuals.
7. Radiographs of the hands often demonstrate fine reticular radiolucencies, described as irregular mineralization of the bone, with or without spicule formation of the phalanges.

5. Other associated anomalies
   1. CNS anomalies (Towfighi et al. 1985; Holubu et al. 2005):
      1. Microcephaly
      2. Intracerebral cysts
      3. Agenesis of the corpus callosum
      4. Cerebellar agenesis with or without Dandy-Walker malformation
      5. Type 2 porencephaly (schizencephalic porencephaly)
      6. Pachygyria and heterotopias
      7. Hydrocephalus
      8. Cerebral or cerebellar atrophy
      9. Berry aneurysms
   2. Intelligence: about 50% of individuals with OFD1 with some degree of mental retardation or learning disability.
   3. Polycystic kidney disease (Connacher et al. 1987; Donnai et al. 1987; Feather et al. 1997): occurring in fewer than 50% of individuals with OFD1. Renal cysts can develop from both tubules and glomeruli, most often in adulthood.

2. OFD II (Mohr syndrome) (Mohr 1941; Rimoin and Edgerton 1967; Goldstein and Medina 1974; Silengo et al. 1987; Gillerot and Koulischer 1988; Prpic et al. 1995; Balci et al. 1999; Hsieh and Hou 1999)
   1. Oral anomalies
      1. Lobulated/cleft tongue
      2. Tongue hamartomas
      3. Duplicated frenulum
      4. Absent central incisors
   2. Facial anomalies: bifid nasal tip
   3. Digital anomalies (Michels et al. 1985)
      1. Hands: clinodactyly, syndactyly, polydactyly
      2. Feet: preaxial or postaxial polydactyly, synpolydactyly, of both big toes
   4. CNS anomalies
      1. Hydrocephalus
      2. Porencephaly
      3. Mental retardation
   5. Features overlapping with OFD I
      1. Orofacial manifestations: tongue nodules, midline clefts of the lip, thick frenula, and dystopia canthorum
      2. Digital manifestations: clinobrachydactyly, syndactyly, and polydactyly
   6. Subtle clinical differences between types I and II
      1. Greater thickness of the alveolar ridge than in type I, which is normal in type II.
      2. Presence of hair and skin abnormalities in type I.
      3. Presence of bilateral polysyndactyly of the halluces in type II rather than unilateral polysyndactyly, which is usually found in type I.
      4. Conductive hearing impairment may occur in type II.
      5. Central nervous system can also be affected in this form mainly with porencephaly and hydrocephaly.
   7. Distinctive difference in the mode of inheritance: OFD type II is caused by mutations of an as yet unidentified autosomal recessive gene versus X-linked dominant inheritance in OFD type I.
   8. Expanding phenotype spectrum in OFD type II: congenital heart defects such as atrioventricular canal and endocardial cushion defects.
   9. A Y-shaped central metacarpal, usually considered typical of OFD type VI, has also been reported in patients with clinical characteristics falling within the OFD II spectrum, suggesting the existence of transitional OFD types that may turn out to be

allelic forms once the genetic defects of all OFD types are discovered.

3. OFD III (Sugarman syndrome) (Sugarman et al. 1971; Sugarman 1983; Smith and Gardner-Medwin 1993)
   1. Oral anomalies
      1. Lobulated tongue with hamartoma
      2. Cleft palate
      3. Extra small teeth
   2. Facial anomalies
      1. Hypertelorism
      2. Broad nose
      3. Choanal atresia
      4. Low-set ears
   3. Digital anormalies
      1. Hands: oligodactyly, syndactyly
      2. Feet: postaxial polydactyly
   4. CNS anomalies
      1. Dandy-Walker malformation
      2. Cerebellar anomalies
      3. Ceaseless seesaw (continuous alternating) winking of the eyelids
      4. Myoclonic jerks
      5. Mental retardation
   5. Other features: short sternum, hyperconvex nails
4. OFD IV (Mohr-Majewski syndrome, Baraitser-Burn syndrome) (oral-facial-digital syndrome with tibial defects) (Burn et al. 1984; Baraitser et al. 1986; Nevin and Thomas 1989; Meinecke and Hayek 1990; Nevin et al. 1992; Ades et al. 1994; Digilio et al. 1995; Toriello et al. 1997; Moerman and Fryns 1998; Tuysuz et al. 1999)
   1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
   2. Minor facial anomalies: hypertelorism, broad nose, epicanthal folds, micrognathia, low-set ears
   3. Digital anomalies: hands (polydactyly), feet (preaxial and postaxial polydactyly, clubfoot)
   4. Mesomelic limb shortening limited to tibial defects (tibial dysplasia)
   5. Other features: joint dislocations, pectus excavatum, short stature
   6. Expansion of phenotypic spectrum
      1. Occipitoschisis
      2. Brain malformation (porerncephaly, cerebral atrophy)
      3. Hearing loss
      4. Ocular colobomas
      5. Hypoplastic epiglottis
      6. Intrahepatic cyst
      7. Renal cysts
      8. Anal atresia
      9. Joint dislocations
5. OFD V (Thurston syndrome) (Thurston 1909; Khoo and Saad 1980; John et al. 2013)
   1. The mildest form within the OFD group
   2. Oral anomalies
      1. Median cleft lip
      2. Duplicated frenulum
      3. Enamel hypoplasia
      4. High-arched palate
      5. Supernumerary teeth
   3. Postaxial polydactyly of the hands and feet
   4. Normal intelligence
   5. Reported exclusively in individuals of Indian ethnicity
6. OFD VI (Varadi-Papp syndrome) (Varadi et al. 1980; Muenke et al. 1990, 1991; Toriello 1993; Stephens et al. 1994; Wey et al. 1994; Doss et al. 1998)
   1. Distinguished features
      1. First report in endogamic gypsies
      2. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip, deep palate
      3. Facial anomalies: microphthalmia, micrognathia
      4. Digital anomalies
         1. Clinodactyly and syndactyly of the hands
         2. Y-shaped metacarpals/metatarsals: forked third or fourth metacarpals/metatarsals, indicating central polydactyly
      5. Expanded phenotype spectrum
         1. Penile agenesis (Yildirim et al. 2002).
         2. Abnormal clavicles.

3. Vermis hypoplasia/aplasia.
4. Dandy-Walker anomaly.
5. Absent pituitary gland (Al-Gazali et al. 1999).
6. Hypothalamic hamartoma with precocious puberty, which is almost constantly found in Pallister-Hall syndrome, an autosomal dominant condition characterized by postaxial polydactyly, imperforate anus, and hypothalamic hamartoma. The phenotypic overlap between OFD VI and Pallister-Hall syndrome has been noted, and lumping of the two conditions as the same entity has been proposed.
7. GLI3 mutations identified in Pallister-Hall syndrome suggest that GLI3 analysis should also be carried out in patients with OFD VI to find out if these two conditions are allelic.
8. A single report of neuropathologic findings in OFD VI showed disruption or dysgenesis of glial architecture, suggesting a primary glial cell defect. This observation is interesting in light of the recent discovery that OFD I is caused by a failure of the ciliary system, which is involved in cellular migration during embryogenesis.

6. Represents a rare phenotypic subtype of Joubert syndrome and related disorders

7. Diagnostic criteria (Poretti et al. 2012)
   1. Molar tooth sign (a neuroanatomical feature characterized by thickened, elongated, and horizontally located superior cerebellar peduncles and an abnormally deep interpeduncular fossa) and one or more of the following:
   2. Tongue hamartoma(s) and/or additional frenula and/or upper lip notch
   3. Mesoaxial polydactyly of one or more hands or feet
   4. Hypothalamic hamartoma

8. OFD VII (Whelan syndrome) (Whelan et al. 1975; Nowaczyk et al. 2003): a single report of mother and daughter
   1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, cleft palate, median cleft lip
   2. Facial anomalies: asymmetry of the face, hypertelorism
   3. Digital anomalies: clinodactyly of the hands
   4. Preauricular skin tag
   5. Hydronephrosis
   6. Possibly same entity as OFD 1 since mother and daughter later developed cystic kidney disease, although mutation analysis for OFD I failed to detect a pathogenic mutation
9. OFD VIII (Edwards syndrome) (Edwards et al. 1988; Toriello 1993)
   1. Oral anomalies: lobulated tongue with hamartoma, median cleft lip, missing teeth
   2. Facial anomalies: telecanthus, broad/bifid nose
   3. Digital anomalies: hands (pre- or postaxial polydactyly), feet (preaxial polydactyly)
   4. Limb anomalies: short tibiae and radii
   5. Other features: delay of developmental milestones, hypoplastic epiglottis
   6. Distinguished from OFD II by X-linked recessive inheritance
10. OFD IX (Gurrieri syndrome) (Gurrieri et al. 1992; Nevin et al. 1994; Nagai et al. 1998)
    1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
    2. Facial anomalies: hypertelorism
    3. Retinal anomaly (colobomata): a distinctive feature
    4. Digital anomalies: hands (brachydactyly, postaxial oligodactyly), feet (usually consist of hallucal duplication detectable radiologically)
11. OFD X (Figuera syndrome) (Figuera et al. 1993)
    1. Oral anomalies: Cleft palate, duplicated frenulum
    2. Facial anomalies: telecanthus

3. Digital anomalies: hands and feet (preaxial polydactyly and postaxial oligodactyly)
4. Limb anomaly: fibular agenesis

12. OFD XI (Gabrielli syndrome) (Gabrielli et al. 1994; Ferrero et al. 2002): in addition to the oral, facial, and digital anomalies, this type is characterized by following craniovertebral anomalies:
    1. Oral anomalies: bifid tongue, duplicated frenulum, median cleft lip, cleft palate, midline cleft extending to ethmoid and crista galli
    2. Facial anomalies: wide nose, bulbous tip, hypertelorism, blepharophimosis, deformed earlobes
    3. Digital anomalies: postaxial polydactyly of the hands and feet
    4. Additional anomalies
        1. Apophysis
        2. Vertebral malformations
            1. Fusion of vertebral arches in C1, C2, and C3
            2. Clefts of vertebral bodies
        3. Conductive deafness, cardiac interventricular septal hypertrophy, mucosal subaortic spur
13. OFD XII (Moran-Barroso syndrome) (Moran-Barroso et al. 1998)
    1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
    2. Myelomeningocele
    3. Stenosis of the aqueduct of Sylvius
    4. Cardiac anomalies
14. OFD XIII (Degner syndrome) (Degner et al. 1999)
    1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
    2. CNS anomalies
        1. Psychiatric symptoms (major depression)
        2. Epilepsy
        3. Brain MRI findings of leukoaraiosis (patched loss of white matter of unknown pathogenetic origin, possibly of ischemic nature, considered to increase the risk of stroke)
15. OFD XIV (Thauvin-Robinet et al. 2014)
    1. Craniofacial: microcephaly, trigonocephaly, facial dysmorphism, telecanthus, upslanting palpebral fissures, retinitis, cleft palate, cleft tongue, lobulated tongue, lingual hamartoma, buccal frenule, absent epiglottis, supernumerary teeth
    2. Genitourinary: micropenis
    3. Skeletal; postaxial polydactyly of hands, broad/duplicated halluces
    4. CNS: severe intellectual disability, corpus callosum hypoplasia, vermian hypoplasia, molar tooth sign, subarachnoid cysts, incomplete myelinization

Diagnostic Investigations

1. Diagnostic approach
    1. First, ascertain oral, facial, and digital findings.
    2. Obtain family history to determine if a mode of inheritance can be established.
    3. In patients with clear X-linked dominant transmission and even in sporadic female patients, it is necessary to rule out mutations in the OFD1 gene.
    4. Additional studies to delineate specific type, given the fragmentary nosology of OFD.
        1. Brain MRI
        2. Abdominal ultrasound
        3. Skeletal survey
        4. Ophthalmologic evaluation
        5. Audiometric test
        6. Chromosome analysis to detect submicroscopic rearrangements by array-CGH analysis
2. Diagnosis of OFD I (Toriello and Franco 2013)
    1. Established at birth in some infants on the basis of characteristic oral, facial, and digital anomalies
    2. Diagnosis is suspected in some patients only after polycystic kidney disease is identified in later childhood or adulthood

3. Molecular genetic testing (sequence analysis and duplication/deletion analysis) of *OFD1*, the only gene currently known to be associated with OFD I: clinically available for confirmatory diagnostic testing and prenatal diagnosis of OFDI
3. Diagnosis of OFD VII (includes unilateral cleft lip and hydronephrosis, only been described in one mother-daughter pair, who were later found to have a mutation in *OFD1*): either allelic to OFD1 or demonstrates variable expression of OFD1

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive (OFD types II, III, IV, V, VI, possibly types XI, XII, XIII)
            1. A 25% risk
            2. A 50% risk of being a carrier
        2. Autosomal dominant (OFD X)
            1. A small recurrence risk if neither parent is affected
            2. A 50% risk if one parent is affected
        3. X-linked dominant with male lethality (OFD I, OFD VII) (Toriello and Franco 2013)
            1. Approximately 75% of affected individuals are simplex cases (no family history of OFD1).
            2. A female proband with OFD1 may have the disorder as the result of a de novo gene mutation; however, the proportion of cases caused by de novo mutations is unknown.
            3. When the mother of an affected female is also affected, the risk to sibs of inheriting the disease-causing *OFD1* allele at conception is 50%; however, most male conceptuses with the disease-causing *OFD1* allele miscarry (Macca and Franco 2009). Thus, at delivery the expected sex ratio of offspring is 33% unaffected females; 33% affected females; 33% unaffected males.
            4. If no family history of OFD1 exists, the risk that the unaffected mother of an affected female will have another female with OFD1 is less than 1%.
        4. X-linked recessive (OFD VIII): risk to the sibs depending on the carrier status of the mother
            1. Mother is a carrier: a 50% of risk of having a male sib with OFD VIII
            2. Mother is not a carrier: a low recurrence risk
    2. Patient's offspring
        1. Autosomal recessive: a low recurrence risk unless the spouse is also affected or a carrier
        2. Autosomal dominant: a 50% risk if the spouse is normal
        3. X-linked dominant with male lethality (Toriello and Franco 2013)
            1. At conception, the risk to the offspring of females with OFD1 of inheriting the disease-causing OFD1 allele is 50%; however, most male conceptuses with the disease-causing allele miscarry.
            2. At delivery, the expected sex ratio of offspring: 33% unaffected females, 33% affected females, and 33% unaffected males.
        4. X-linked recessive
            1. No sons will be affected.
            2. All daughters will be carriers.
2. Prenatal diagnosis
    1. Prenatal ultrasound
        1. Prenatal diagnosis of OFD type II reported in a fetus
            1. Polydactyly with bifid thumbs in both hands
            2. Bilateral polysyndactyly of halluces
            3. Lateral polysyndactyly and bilateral pes equinovarus
        2. Prenatal diagnosis of OFD type IV (Mohr-Majewski) possible: findings showing overlap between OFD type II (Mohr) and lethal short rib-polydactyly syndrome type II (Majewski) (Rosing et al. 2008)

3. Prenatal ultrasound examination of OFD type I (Toriello and Franco 2013) may detect structural brain malformations (Shipp et al. 2000) and/or duplication of the hallux.
2. Molecular genetic analysis: prenatal diagnosis and preimplantation genetic diagnosis for families in which the disease-causing mutation has been identified is clinically available.

3. Management (Toriello and Franco 2013)
1. Surgery
1. Cleft lip/palate
2. Tongue nodules
3. Accessory frenula
4. Polysyndactyly
5. Removal of accessory teeth
6. Orthodontia for malocclusion
2. Management of renal disease and seizures
3. Speech therapy
4. Special education
5. Surveillance
1. Annual monitoring of renal function
2. Speech and hearing assessment if cleft palate is present

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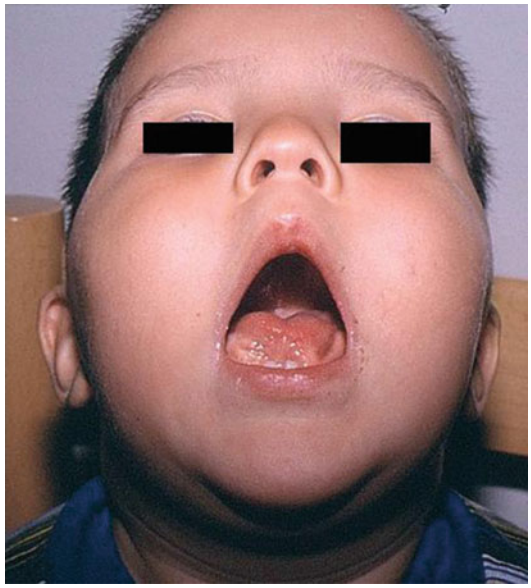

Fig. 1 Patient 1 with OFD I. Note the lingual frenulum and hypoplastic alar nasi

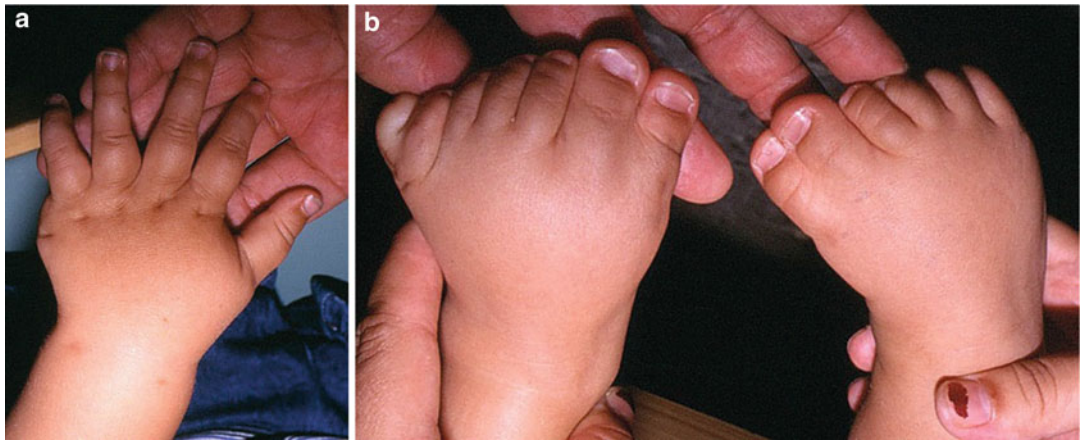

Fig. 2 (**a**, **b**) The patient's bilateral postaxial polydactyly of both hands, duplicated hallux of both feet, and postaxial polydactyly of the left foot

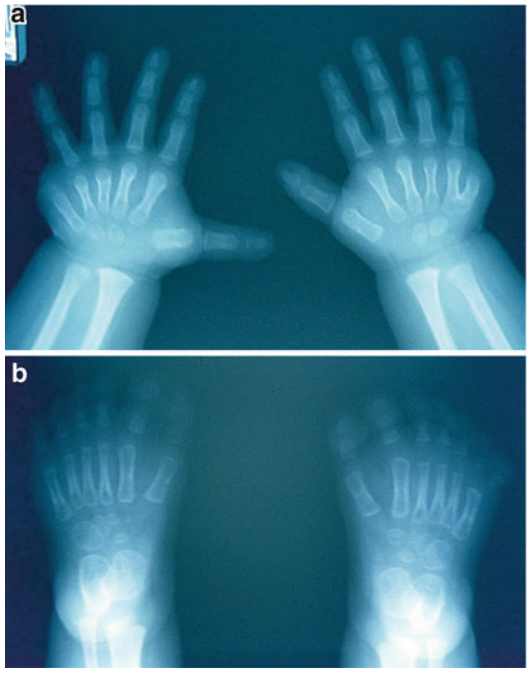

Fig. 3 (**a**, **b**) Radiographs of hands and feet of patient 1

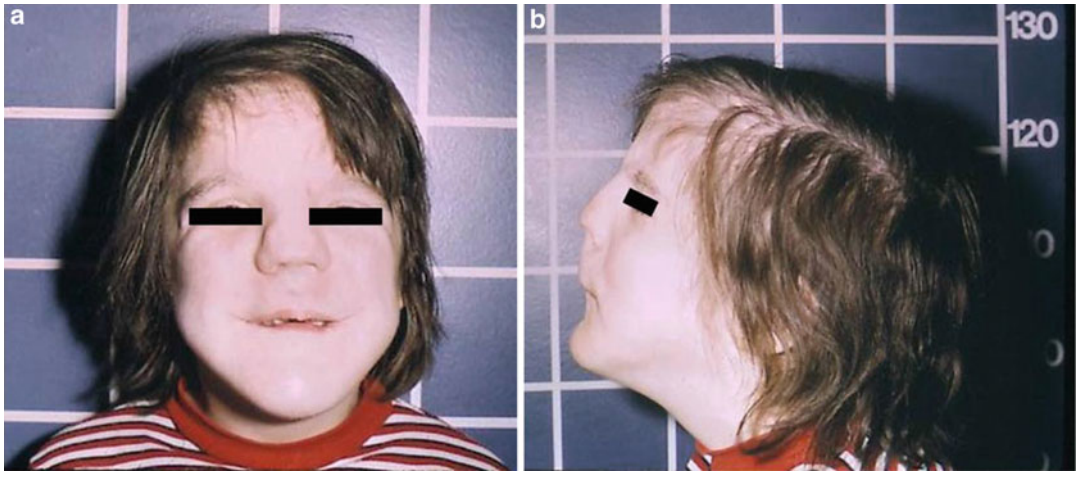

Fig. 4 (**a**, **b**) Patient 2 with OFD II. Note bifid nasal tip, medial cleft of the upper lip, and ocular hypertelorism

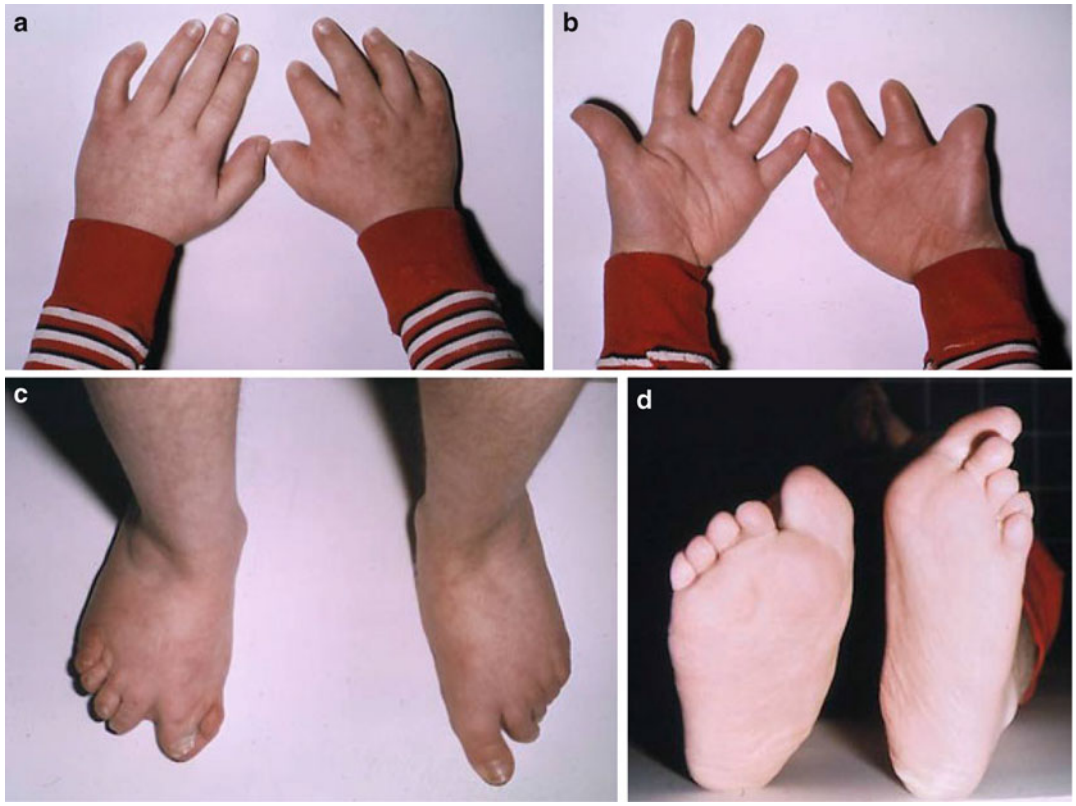

Fig. 5 (**a**–**d**) Note the clinobrachydactyly and syndactyly of the hands and polydactyly of the right hallux

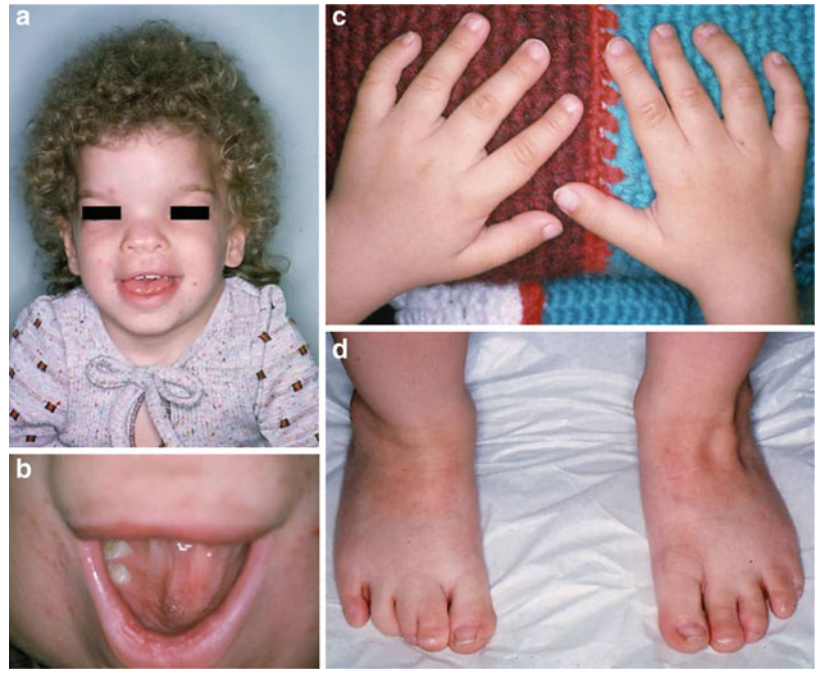

Fig. 6 (**a**–**d**) Patient 3 with OFD II. Note the ocular hypertelorism, bifid tip of the nose, lingual frenulum, and brachysyndactyly

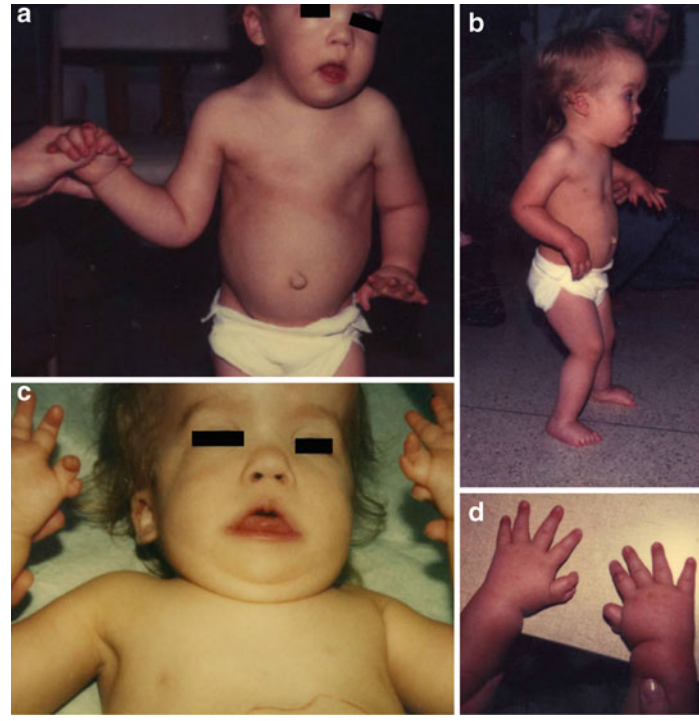

Fig. 7 (**a**–**d**) Patient 4 with unclassified OFD. Note frontal bossing, ocular hypertelorism, strabismus, pseudocleft of the upper lip, preaxial polydactyly of the hands, hepatomegaly, and genu valgum

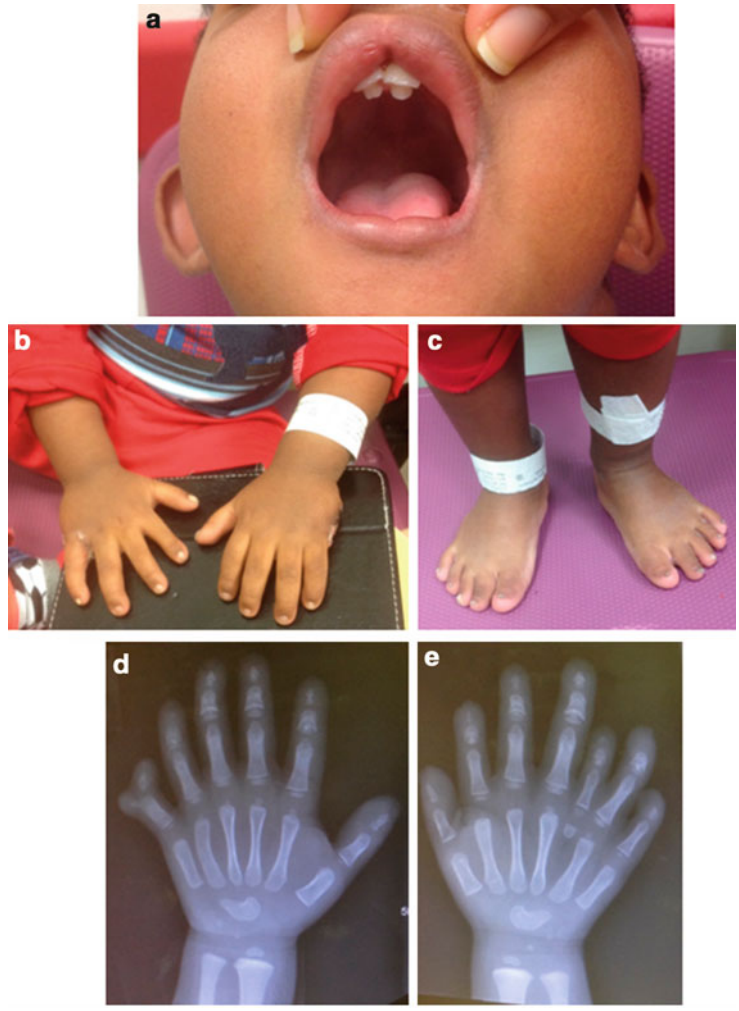

Fig. 8 (**a**–**e**) This 3-year-old Hispanic boy from Panama was seen for abnormal dentition and brachydactyly and polydactyly of both hands. Orofacial features were characterized by slight hypertelorism, flat nasal bridge, and presence of median pseudocleft of the upper lip and double rows of upper central incisors with absence of other teeth (**a**). Radiographic imaging of oromandibular areas with panoramic and cephalometric projection showed no permanent maxillary laterals and complete absence of all central and lateral mandibular teeth (not shown). The fingers were short with postaxial polydactyly of both hands (seven fingers on the right and six fingers on the left with duplicated distal end of the last finger) (Status post incision of polydactylies and post reconstruction of both hands is shown here) (**b**). There was no polydactyly of the toes, but the great toes were slightly broad. Radiograph of left hand (**d**) showed duplication of the fifth ray with dysplasia and hypoplasia of the distal and middle phalanges. Radiograph of the right hand (**e**) showed duplication of the fourth and fifth rays with dysplasia and hypoplasia of the distal and middle phalanges. Dysplastic fusion of the capitate and hamate was present in both wrists (**d, e**)

Osteogenesis Imperfecta

Contents

Osteogenesis imperfecta (OI) is a generalized, hereditary disorder of connective tissue involving bone, tendon, ligament, fascia, and dentin, resulting from mutations affecting the amount or structure of type I collagen. OI affects about 1 in 10,000 individuals.

Synonyms and Related Disorders

Osteogenesis imperfecta with blue sclerae; Osteogenesis imperfecta with normal sclerae; Perinatal lethal osteogenesis imperfecta; Progressively deforming osteogenesis imperfecta with normal sclerae

Genetics/Basic Defects

1. Clinicopathological classification (Glorieux 2008; Basel and Steiner 2009; Fratzl-Zelman et al. 2015): The classification system of Sillence et al. (1979) divides OI into four severity-based types with type IV representing the most clinically diverse group (Cole 1997). It is from this heterogeneous group that types V, VI, VII, and VIII have been identified on the basis of distinct clinical and histological features (Glorieux et al. 2000, 2002; Ward et al. 2002). The most clinically relevant characteristic of all types of OI is bone fragility, the severity of which increases in the order type I < types IV, V, VI, VII, VIII < type III < type II. Heredity follows an autosomal dominant pattern in types I through V and is autosomal recessive in types VI, VII, and VIII. Mutations affecting collagen type I are usually present in types I through IV and types VII and VIII, but are absent in types V and VI. This classification scheme is likely to change as additional information is gathered on newly described forms caused by *CRTAP* and *LEPRE* mutations:
    1. OI I:
        1. Autosomal dominant disorder
        2. Fresh mutation in 15% of cases
        3. The most common and mildest form of osteogenesis imperfecta
        4. Estimated prevalence at between 1 in 10,000 and 1 in 25,000 or may be more frequent because of its relatively mild presentation and the possibility of underdiagnosis

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2. OI II:
    1. Autosomal dominant disorder (new mutations in almost all instances) (Young et al. 1987)
    2. The most severe form, resulting in death in the perinatal period
    3. Autosomal recessive disorder (rare)
    4. Further subdivided into IIA, IIB (same as type III), and type IIC (Cole and Dalgleish 1995)
    5. Estimated frequency of 1 in 20,000–1 in 60,000 births
3. OI III:
    1. Autosomal dominant disorder
    2. Autosomal recessive disorder (uncommon)
    3. The rarest form of OI
    4. Known as the progressive deforming form
4. OI IV:
    1. Autosomal dominant with mutations in *COL1A1* and *COL1A2*
    2. The most clinically diverse group
    3. Represents the moderately severe spectrum of OI
    4. Marked intra-/interfamilial variability of expression
5. OI V (Biggin and Munns 2014):
    1. The first noncollagen OI type to be identified and mutations of the IFITM5 gene have recently been shown to cause this autosomal dominant form of OI (Cho et al. 2012).
    2. The moderately deforming form.
    3. Associated mutations: *IFITM5*.
6. OI VI:
    1. The moderately to severely deforming form
    2. Associated mutations: *SERPINF1*
7. OI VII:
    1. Overlaps with types II and III; milder forms also documented
    2. Associated mutations: hypomorphic expression of *CRTAP*
8. OI VIII:
    1. Overlaps with types II and III; milder forms also documented
    2. Associated mutations: *LEPRE1* (Willaert et al. 2009)
9. OI IX: associated mutations *PPIB* (van Dijk et al. 2009)

2. Molecular basis (Beyers et al. 1991; Minch and Kruse 1998):
    1. Type I collagen:
        1. Found in the skin, bone, tendons, and ligaments.
        2. Composed of three α chains (two α_1 chains and one α_2 chain).
        3. Each α chain forms a helix which consists of three amino acids per turn.
        4. The chains are held together by disulfide bonds at the C-terminal ends of the protein.
        5. There are three amino acids per turn in the helix.
        6. Every third amino acid is glycine, giving a repeat of Gly-X-Y, where X and Y represent other amino acid residues:
            1. About 10% of the X residues are proline.
            2. About 10% of the Y residues are hydroxyproline.
        7. A mutant collagen is produced by missense mutations that result in a substitution of the glycine residue by another amino acid.
    2. OI I:
        1. Affected individuals produce only 50% of the normal amount of type I collagen, produced by the normal allele.
        2. Mechanisms:
            1. Splicing in α_1 gene
            2. Null mutation in α_1 gene
    3. OI II, OI III, and OI IV:
        1. Affected individuals produce only 25% of the normal amount of type I collagen and 75% of mutant or defective collagen.
        2. Mechanism: A missense mutation arises in the α_1 gene resulting in a defective α_1 chain which is incorporated into the final collagen molecule and destroys its function.

3. Severity of the disease:
    1. Related to the position of the missense mutation within the gene and the amino acid substitution that occurs.
    2. Generally, the disease is more severe when the mutation is closer to the C-terminal end of the protein.
4. OI V:
    1. Caused by mutations in *IFITM5*.
    2. Autosomal dominant inheritance.
    3. Defective protein: Bone-restricted ifitm-like protein (BRIL).
    4. Biochemical effects on collagen biosynthesis: BRIL is an osteoblast-specific small transmembrane protein that might regulate early mineralization steps.
    5. Phenotypes.
5. OI VI:
    1. Caused by mutation in *SERPINF1* (Becker et al. 2011).
    2. Alkaline phosphatase may be elevated.
6. OI VII:
    1. Caused by mutation in *CRTAP.*
    2. The disease has been assigned to chromosome 3p22-24.1 (Labuda et al. 2002).
    3. Colocalizing with the gene encoding CRTAP, a cartilage-associated protein, whose expression is 90% reduced in homozygote patients (Morello et al. 2006).
7. OI VIII
    1. Caused by *LEPRE1* mutations
    2. Defective protein: prolyl 3-hydroxylase (P3H1)
8. OI IX:
    1. Caused by *PPIB* mutation
    2. Defective protein: peptidyl-prolyl cis-trans isomerase B (PPIB) (also called cyclophilin B, CyPB)
9. OI X:
    1. Caused by *SERPINH1* mutation
    2. Defective protein: heat-shock protein 47 (HSP47)
10. OI XI:
    1. Caused by *FKBP10* mutation
    2. Defective protein: FKBP65
11. OI-unclassified:
    1. *PLOD2* mutation: lysyl hydroxylase 2 (LH2) (defective protein)
    2. *BMP1* mutation: Bone morphogenic protein 1 (BMP1) (defective protein)
    3. *C-propeptide cleavage site* mutation: C-propeptide cleavage site (defective protein)
    4. *SP7/OSX* mutation: SP7/osterix (defective protein)
    5. *WNT1* mutation: WNT1 (defective protein)
    6. *TMEM38B* mutation: TRIC-B (defective protein)
    7. *CREBL1* mutation: endoplasmic reticulum stress transducer (OASIS) (old astrocyte specifically induced substance) (defective protein)
    8. *PLS3* mutation: actin-binding protein plastin 3 (defective protein)
3. Allelic connective tissue disorders (Basel and Steiner 2009):
    1. Several patients have been described with joint hypermobility and skin laxity, a clinical phenotype more in keeping with Ehlers-Danlos syndrome but who have an increased disposition to fractures.
    2. Mutations not involving the glycine residues within the triple helix of COL1 and mutations involving cysteine residues have been described in a subset of these patients (Malfait et al. 2006, 2007; Cabral et al. 2007).
    3. N-terminal mutations in COL1 appear to result in abnormal protein folding, which leads to a milder OI/Ehlers-Danlos syndrome p (Makareeva et al. 2006).
4. Very few individuals or families share the same mutation, although more than hundreds of unique mutations of the type I collagen genes have been identified.
5. Phenotypic variations among different families and within same family.

Clinical Features

1. OI type I (mild type) (Glorieux 2008):
    1. Fractures:

1. Rarely fracture in utero or in the perinatal period.
2. Usual onset of fractures: when the child begins to walk.
3. A few to more than 50 fractures before puberty.
4. Number of fractures gradually decreases after puberty.
5. Involve any bones of the body, but primarily long bones of the arms and legs, ribs, and small bones of the hands and feet
6. Increasing fractures often after menopause in affected women and in the sixth or eighth decades in affected men.
7. Healing rapidly with evidence of good callus formation and without deformity.

2. Cranial features:
   1. Soft thin calvarium
   2. Wide fontanels
   3. Wormian bones
   4. Frontal and temporal bulging
   5. Occipital flattening
3. Blue sclera (secondary to a thin sclera allowing partial visualization of the choroid):
   1. Readily apparent at birth
   2. Gradually lightens to blue gray in the adulthood
4. Other ocular features:
   1. Occasional embryotoxon (opacity in the peripheral cornea)
   2. Occasional keratoconus or megalocornea
5. Teeth abnormalities:
   1. Rare dentinogenesis imperfecta
   2. Hypoplasia of pulp
   3. Yellow or gray teeth
   4. Susceptible to caries
   5. Irregular placement
   6. Late eruption
6. Hearing loss:
   1. Early onset in about 50% of families beginning in late teens.
   2. Gradually leading to profound hearing loss in the end of fourth or fifth decades secondary to otosclerosis.
   3. Primarily conductive hearing loss in the early phase secondary to fractured and fused bones of the middle ear.
   4. Early hearing loss typically of the high-frequency type resulting in a characteristic bifid compliance curve by tympanometry.
   5. Later hearing loss becoming mixed in type and surgical intervention may be less successful.
7. Skin and joint abnormalities:
   1. Mild joint hypermobility
   2. Easy bruising
   3. Thinner translucent skin
   4. Capillary fragility
   5. Inguinal or umbilical hernia
   6. Flat feet
   7. Joint dislocation
   8. Poorly developed muscles
   9. Decreased thrombocyte function leading to increased bleeding
8. Cardiovascular abnormalities:
   1. Mitral valve prolapse
   2. Aortic valvular insufficiency
   3. Slightly larger than normal aortic root diameter without significant risk of progression to dissection, identified in a small number of patients
   4. Increased bleeding tendency secondary to increased capillary fragility
9. Prognosis:
   1. Usually normal stature but may lose some height in later decades due to spine involvement.
   2. In general, with good orthopedic cares, fractures heal quickly without deformities.
   3. No decrease in fertility or longevity in affected individuals.

2. OI type II (perinatal lethal type) (Sillence et al. 1984):
   1. Lethality during perinatal period resulting from:
      1. Pulmonary insufficiency
      2. Congestive heart failure
      3. Infection

2. Prenatal history:
    1. Intrauterine growth retardation (dwarfism, low birth weight)
    2. Prematurity
    3. Nonimmune hydrops
3. Short-limbed dwarf
4. Characteristic craniofacial features:
    1. Extremely soft calvarium
    2. Dark-blue sclerae
    3. Beaked nose
    4. Micrognathia
5. Chest:
    1. Very small
    2. Beaded ribs
    3. Lung hypoplasia
6. Extremities:
    1. Short and deformed limbs
    2. Bowed legs
7. Hip: flexed and abducted (frog position)
8. Prognosis: death resulting from pulmonary insufficiency, congestive heart failure, or infection:
    1. Usually during the first few hours of life
    2. More than 60% of infants with OI type II during the first day
    3. Eighty percent within the first month
    4. Rare survival beyond a year

3. OI type III (progressively deforming type) (Sillence et al. 1986; Biggin and Munns 2014):
    1. Dwarfism and moderate deformities resulting from in utero fractures, detectable on antenatal ultrasound scan.
    2. The most severe form of OI that is associated with long-term survival.
    3. Craniofacial features:
        1. Typical triangular faces
        2. Relatively large cranium
        3. Grey sclera
    4. Fractures:
        1. Very common
        2. Progressive long bone deformities with growth
        3. Marked deformities of most bones
    5. Significant kyphoscoliosis leading to cardiopulmonary insufficiency, a major cause of early death in these individuals.
    6. Sclerae
        1. Often pale blue at birth
        2. Generally becomes normal hue by puberty
    7. Abnormal dentinogenesis involving both primary and permanent teeth: common.
    8. Hearing loss: common.
    9. Prognosis:
        1. Death resulting from cardiac decompensation, pulmonary insufficiency, or basilar impression with compression of the brain stem
        2. Long-term survival possible with multiple fractures and deformities
        3. Primary objective to lead a satisfying and productive life
        4. Major limitations (severe bone fragility and deformity, muscle weakness, joint contractures that develop from inactivity, progressive scoliosis resulting in life-threatening cardiopulmonary decompensation, marked short stature)
4. OI type IV (moderately severe type) (Biggin and Munns 2014):
    1. Significant intrafamilial and interfamilial phenotypic variation.
    2. Fractures:
        1. Occurring in utero, during labor and delivery, or in the newborn period.
        2. Fractures at birth, not observed in all affected infants.
        3. Some affected infants with only mild femoral bowing.
        4. Early recognition of these fractures is essential to prevent accusation of child abuse when the first fractures occur, and the previous, now healed, fracture (s) is/are detected by routine skeletal survey.
    3. Variable short stature.
    4. Normal white or grayish sclera.
    5. Occasional hearing loss.
    6. Common dentinogenesis imperfecta.
    7. Mild to moderate bone deformity.
    8. Severe kyphoscoliosis may compromise cardiopulmonary function.

9. Prognosis:
    1. Life span near normal in the absence of severe cardiopulmonary complications
    2. Treatment objectives (to minimize the long-term complications of kyphoscoliosis and to assure independence and mobility)
5. OI type V (Biggin and Munns 2014):
    1. Represents 4–5% of the OI population seen in hospitals (Rauch and Glorieux 2004)
    2. Moderate to severe bone fragility (Glorieux et al. 2000)
    3. Does not have blue sclera or dentinogenesis imperfecta
    4. Distinctive clinical features:
        1. Common occurrence of radial head dislocation/subluxation and calcification of the interosseous membrane between the radius and ulna (Lee et al. 2006; Fassier et al. 2007).
        2. Frequent development of hypertrophic calluses at fracture sites.
        3. Early calcification of the interosseous membranes between the bones of the forearm, limiting pronation, and supination.
        4. Normal scleral color.
        5. Presence of a radio-opaque metaphyseal band immediately adjacent to the growth plates on x ray.
        6. Upon histological examination, the bone organization has an irregular mesh-like appearance, clearly distinct from the normal lamellar pattern seen in OI types I and IV (Cheung et al. 2007).
    5. The calcified interosseous membrane often severely limits the pronation/supination of the hand and may lead to secondary dislocation of the radial head.
    6. The hyperplastic callus that may develop after fractures or surgical interventions may mimic osteosarcoma.
6. OI type VI (Biggin and Munns 2014):
    1. Moderate to severe skeletal deformities: may represent in approximately 4% of moderately to severely affected OI patients (Rauch and Glorieux 2004).
    2. Clinically indistinguishable from OI type IV.
    3. Lack blue sclera or dentinogenesis imperfecta and Wormian bones of the skull (Glorieux et al. 2002).
    4. Inheritance: autosomal recessive.
    5. Distinctive histological features: The hallmark is abnormal bone mineralization on histological examination:
        1. A characteristic "fish-scale" pattern of the bone lamellation on bone histology (Glorieux et al. 2002).
        2. The presence of excessive osteoid accumulation on bone-forming surfaces, suggesting a mineralization defect reminiscent of osteomalacia, but there is no abnormality in mineral homeostasis, and growth plate mineralization proceeds normally.
7. OI type VII:
    1. Moderate to severe skeletal deformities and bone fragility.
    2. Lacks blue sclera and dentinogenesis imperfecta.
    3. Coxa vara may be present even in infancy.
    4. Distinctive clinical feature: rhizomelic shortening of the humerus and femur.
    5. "Popcorn" epiphyses often seen in severe forms.
    6. To date, only been observed in a community of Native Americans in northern Quebec, where it exhibits autosomal recessive inheritance.
8. OI type VIII (Shapiro and Sponsellor 2009):
    1. Severe, lethal form
    2. Seen in South African blacks
    3. "Popcorn" epiphyses often seen in severe forms
9. Establishing a diagnosis (Basel and Steiner 2009): The following list of features would be typical in an individual presenting with OI:
    1. Family history of OI or recurrent fractures.
    2. Fractures with minimal or no trauma in the absence of other factors, such as inflicted physical abuse or other known disorders of bone.
    3. Short stature or stature shorter than predicted based on stature of unaffected

family members, often with bone deformity.
4. Blue sclera.
5. Dentinogenesis imperfecta.
6. Progressive, postpubertal hearing loss.
7. Ligamentous laxity and other signs of connective tissue abnormality.
8. Family history of OI, usually consistent with autosomal dominant inheritance.
9. Fractures of varying ages and stages of healing, often of the long bones but may also involve ribs and skull. The metaphyseal chip fractures characteristic of child physical abuse can be seen in a small number of children with OI.
10. "Codfish" vertebrae, which are the consequence of spinal compression fractures, seen primarily in the adult.
11. Wormian bones, defined as "sutural bones that are 6 mm by 4 mm (in diameter) or larger, in excess of 10 in number, with a tendency to arrangement in a mosaic pattern." Wormian bones are suggestive of, but not pathognomonic for, OI. They are present in up to 60% of affected children.
12. Protrusio acetabuli, in which the socket of the hip joint is too deep and the acetabulum bulges into the cavity of the pelvis causing intrapelvic protrusion of the acetabulum.
13. Low bone density detected by dual energy X-ray absorptiometry. There seems to be a correlation between bone mineral density and fracture risk in OI (Huang et al. 2006; Bachrach 2007).

10. Differential diagnosis (Basel and Steiner 2009):
    1. In utero: Prenatal ultrasound examination of severe OI may lead to following skeletal dysplasias which all present with relative macrocephaly and rhizomelic shortening of the limbs (OI type II with ultrasound findings of crumpled long bones and beaded ribs):
        1. Hypophosphatasia
        2. Thanatophoric dysplasia
        3. Campomelic dysplasia
        4. Achondrogenesis
    2. Infancy and childhood:
        1. Nonaccidental trauma (child abuse) (Ricci and Botash 2001)
        2. Infantile hypophosphatasia: See the chapter on "► Hypophosphatasia."
        3. Bruck syndrome:
            1. An autosomal recessive condition.
            2. Bone fragility.
            3. Congenital joint contractures.
            4. Clubfeet.
            5. Normal or blue sclera.
            6. Wormian bones.
            7. It results from defects in the lysyl hydroxylase (PLOD2) that hydroxylates the amino-terminal lysyl residues involved in crosslink formation.
        4. Osteoporosis pseudoglioma syndrome:
            1. Bone fragility and fractures
            2. Other skeletal deformities
            3. Pseudoglioma with blindness in infancy
            4. Other anomalies
            5. Caused by mutations in the gene encoding the lipoprotein receptor-related protein
        5. Cole-Carpenter syndrome:
            1. Bone deformities
            2. Multiple fractures
            3. Ocular proptosis
            4. Shallow orbits
            5. Orbital craniosynostosis
            6. Frontal bossing
            7. Hydrocephalus
        6. Hadju-Cheney syndrome:
            1. Short stature
            2. Failure to thrive
            3. Conductive hearing loss
            4. Dysmorphic features
            5. Early tooth loss
            6. Genitourinary anomalies
            7. Osteopenia
            8. Pathologic fractures
            9. Wormian bones
            10. Failure of suture ossification
            11. Basilar impression
            12. Vertebral abnormalities
            13. Kyphoscoliosis

14. Cervical instability
15. Joint laxity
16. Dislocation of the radial head
17. Long-bowed fibulae
18. Pseudoclubbing
19. Short distal digits
20. Acroosteolysis
21. Hirsutism

7. Gerodermia osteodysplastica:
   1. Dwarfism
   2. Lax skin
   3. Osteoporosis
   4. Wormian bones
   5. Fractures
   6. Vertebral compression
   7. Wizened facial appearance because of facial skin laxity
8. Idiopathic juvenile osteoporosis:
   1. Typically presents in preadolescents with fractures and osteoporosis.
   2. The fracture susceptibility and osteoporosis usually resolve spontaneously with puberty.
   3. The etiology is unknown.
9. Dentinogenesis imperfecta: can occur separately from OI as an isolated familial condition as a result of mutations in the DSPP gene on chromosome 4

11. Importance of diagnosis in the newly affected infant for whom there is no family history (Kleinman 1990):
   1. To facilitate genetic counseling
   2. To reassure the family about prognosis
   3. To remove the concern of child abuse in some families (Steiner et al. 1996):
      1. Fractures considered "highly specific" for child abuse: present in 33% (2/6) of cases with OI:
         1. Metaphyseal fractures
         2. Posterior rib fractures
         3. Scapular spinous process
         4. Sternal fractures
      2. Fractures considered "moderately specific" for abuse: present in 50% (3/6) of cases with OI:
         1. Multiple fractures, especially bilateral
         2. Fractures of different ages
         3. Epiphyseal separations
         4. Digital fractures
         5. Complex skull fractures
      3. Fractures considered "low specificity" for child abuse: present in 17% (1/6) cases of OI:
         1. Clavicular fractures
         2. Long bone shaft
         3. Linear skull fractures
   4. General signs of child abuse:
      1. Multiple fractures as described
      2. Clinical findings highly indicative of child abuse:
         1. Retinal hemorrhage
         2. Cephalohematoma
         3. Subdural hemorrhage
         4. Evidence of bodily abuse (bruises, lacerations, burns)
         5. Evidence of sexual abuse
      3. Incompatible history with physical examination
      4. History of domestic violence, corporal punishment, and child maltreatment
   5. Useful for families to have a letter from the child's physician stating the diagnosis of the osteogenesis imperfecta

Diagnostic Investigations

1. Radiography (Spranger et al. 2002):
   1. OI type I:
      1. None to multiple fractures with little bone deformities
      2. Fractures primarily in long bones (may occur with minimal trauma, decreased dramatically in puberty, increase at later ages, normal healing with callus formation)
      3. Osteopenia (generalized demineralization) which can be documented by densitometry
      4. Thin bones (cortices)
      5. Little trabeculae with fragility
      6. Bowing
      7. Platyspondyly

8. Retarded ossification of the cranial vault with multiple Wormian bones
9. Flattening of vertical axis
10. Widening in the transverse axis of the skull
11. Small facial bones
12. Susceptible to osteoporosis and compression fractures of the vertebrae
13. Pectus carinatum/excavatum

2. OI type II (Thompson et al. 1987; Sillence 1988):
   1. Short-limbed dwarfism
   2. Rhizomelic limb shortening
   3. Severely retarded (virtual absence) calvarial mineralization
   4. Generalized osteoporosis
   5. Multiple fractures with callus formation
   6. Small chest
   7. Beaded and broad ribs
   8. Shortened crumpled long bones especially compressed ("telescoped" or "accordion-like") femurs and/or humeri
   9. Externally rotated and abducted femurs
   10. Bowed lower legs
   11. Angulated tibiae
   12. Usually flexed and abducted hip (frog-leg position)
   13. Flattened acetabulae and iliac wings
   14. Platyspondyly
   15. Type IIA: short and squared tubular bones, continuous beading of the ribs
   16. Type IIB/III: thicker tubular bones, compressed vertebrae, better ossification of the cranial bones, more normally appearing ribs and scapulae
   17. Type IIC: thin, deformed tubular bones, severely twisted long tubular bones
3. OI type III:
   1. Undermineralized calvarium with a large fontanel and Wormian bones
   2. Initially normal or mildly shortening long bones
   3. Fractures present at birth or during the first year of life with evidence of deformity
   4. Thin gracile ribs prone to fracture
   5. Gracile long bones showing evidence of intrauterine fractures with callus formation
   6. Marked angulation or bowing of long bones (especially tibias and femurs, reducing the efficiency of weight bearing and increasing the likelihood of fracture)
   7. "Accordion-like" short and deformed femurs
   8. Later metaphyseal and diaphyseal widening with "popcorn" calcification appearance of cystic metaphyses
   9. Codfish appearance of vertebrae
   10. Fractures with minimal trauma and progressive deformities
   11. Severe and generalized osteopenia
4. OI type IV:
   1. Bowed femurs in the newborn period but tend to straighten with time
   2. Osteopenia/osteoporosis
   3. Thin bones
   4. Fractures with deformities
   5. Scoliosis

2. Bone density analysis:
   1. Still experimental
   2. Dual energy X-ray absorptiometry (DEXA)
3. Bone histology:
   1. Thin cortices
   2. Decreased trabecular bone volume
   3. Smaller apatite crystals
   4. Defective microvascular system
   5. Defective collagen fibril diameter
4. Biochemical analyses (Sillence 1981).
5. Collagen synthesis analyses by cultured fibroblasts from skin biopsy. In OI type I, about half the normal amount of type I procollagen is synthesized.
6. Gene sequence analysis (Basel and Steiner 2009): Genomic DNA can be isolated from peripheral leukocytes in blood or from any other tissue samples:
   1. Sequence analysis of *COL1A1* and *COL1A2* cDNA to detect mutations in the coding sequence and sequence analysis of *COL1A1* and *COL1A2* genomic DNA to detect mutations that alter either sequence

or stability of mRNA identify between 80% and 85% of mutations in the type I collagen genes.
2. The mutations in most families are unique; only a few recurrent mutations (mostly CpG dinucleotides) are seen in more than one family.
3. Mutation detection rate varies by COLA1-related OI type; a comprehensive database of all 850 known mutations has been published along with a genotype-phenotype correlation.
4. For patients in whom no collagen type I mutation is identified, sequencing of *CRTAP* and *LEPRE1* is available commercially and is a reasonable next step in sequential sequencing to identify a mutation.
5. The importance of identifying these mutations is to establish a genetic risk for future offspring as the parents of an affected individual would be at a 25% risk of conceiving another child with the disorder, and it would be imperative for them to be counseled accurately, and adequately, of antenatal services available to them.

Genetic Counseling

1. Recurrence risk for OI I:
    1. Patient's sib: not increased unless a parent is affected or with gonadal mosaicism
    2. Patient's offspring:
        1. Fifty percent affected if an affected parent marrying a normal spouse.
        2. Twenty-five homozygously affected infant (likely to be perinatally lethal or severely affected) if both parents are affected with OI type I.
2. Recurrence risk for OI II:
    1. Patient's sib: an empiric recurrence risk of 2–3% to 6–7% among siblings resulting from parental mosaicism for the mutation that is lethal in the infant who is heterozygous for the same mutation or due to the rare recessive form (Cohn et al. 1990; Cole and Dalgleish 1995; Lund et al. 1996)
    2. Patient's offspring: none surviving beyond infancy
3. Recurrence risk for OI III (also called type IIB):
    1. Patient's sib:
        1. Autosomal dominant form: not increased unless a parent is affected or with gonadal mosaicism
        2. Autosomal recessive form: 25%
        3. An empiric recurrence risk of 7–8% (germinal mosaicism, homozygosity of *COL1A2* mutations, and autosomal recessive inheritance)
    2. Patient's offspring:
        1. Autosomal dominant form: 50%
        2. Autosomal recessive form: not increased unless a spouse is a carrier or affected
4. Recurrence risk for OI IV:
    1. Striking intrafamilial variability making clinical classification difficult for OI IV, OI III, or OI I
    2. Patient's sib: not increased unless a parent carries gonadal mosaicism
    3. Patient's offspring:
        1. Fifty percent when an affected parent marrying a normal spouse
        2. Rare possibility of having children with lethal OI phenotype by a parent with OI IV as a consequence of parental mosaicism for the lethal mutations
5. Prenatal diagnosis (Pepin et al. 1997):
    1. OI type I:
        1. Identification of the mutant allele including segregation studies with an appropriate family structure (Lynch et al. 1991)
        2. Identification of the COL1A1 null-allele in mRNA from the fetus (Nuytinck et al. 1999)
        3. Direct identification of the mutation (CVS at 11–12 weeks gestation)
        4. Recognition of fracture or bowing of long bones by ultrasound
    2. Type II:
        1. Diagnosis by prenatal ultrasonography accomplished between 14 and 18 weeks

gestation (short femurs, fractures, small thoracic cage, minimal calvarial mineralization, or polyhydramnios)
2. Analysis of chorionic villi for the presence of abnormal collagens
3. Analysis of collagens synthesized by cells grown from chorionic villi
4. Direct mutation analysis in families of an identified DNA mutation in a previously affected infant

3. Type III:
1. Diagnosis by prenatal ultrasonography not feasible until 20–22 weeks gestation
2. Direct mutation analysis of collagens synthesized by chorionic villus cells or DNA isolated directly from the tissue

4. Type IV:
1. Linkage analysis with *COL1A2* polymorphisms in the dominant families
2. Direct mutation analysis
3. Analysis of proteins produced by cells grown from CVS biopsies
4. Little value of ultrasound analysis because of the late appearance of short or deformed bones

5. *CRTAP*-related OI and *LEPRE1*-related OI: Prenatal diagnosis is available provided the mutations are previously identified in the family member.

6. Management (Cole 1988, 1993; Lee et al. 2001; Biggin and Munns 2014):
1. Improving bone mass:
1. Use of bisphosphonates (cyclic intravenous pamidronate) to decrease the resorption of bone and to increase the formation of bone (Bembi et al. 1997; Glorieux 2000). Hopefully, early commencement of bisphosphonate treatment will prevent serious deformities (Plotkin et al. 2000).
2. Bisphosphonate therapy does not constitute a cure of OI, but is an adjunct to physiotherapy, rehabilitation, and orthopedic care. These drugs have brought clear improvement to the lives of patients suffering from moderate to severe OI. In contrast, children and adolescents with OI who have few fractures and no functional limitations have less to gain from treatment. It therefore appears advisable not to treat such patients unless clinical benefit can be demonstrated in placebo-controlled studies (Glorieux 2008).
3. Use of bone marrow transplantation as means of introducing normal mesenchymal stromal cells that have the capacity to differentiate into normal osteoblasts (Horwitz et al. 2001).

2. Fractures:
1. Meticulous orthopedic care.
2. Corrective osteotomies.
3. Intramedullary roddings to improve mobility, prevent fractures, and correct and prevent progressive deformity.
4. Avoid unnecessary immobilization.
5. Avoid malunions.

3. Progressive scoliosis in adolescence requires spinal fusion with instrumentation.

4. Orthotics:
1. To stabilize lax joints such as the ankle and subtalar joints
2. To prevent progressive deformities and fractures
3. Commonly used devices include ankle-foot, knee-ankle-foot, and forearm orthoses

5. Recognition and management of hearing loss

6. Care of dentinogenesis imperfecta

7. Psychologic care

8. Physical therapy and comprehensive rehabilitation (Binder et al. 1993)

9. Novel therapies on the horizon:
1. Denosumab: a RANKL antibody that has been shown to reversibly reduce bone resorption in four children with OI VI (Semler et al. 2012).
2. Sclerostin antibody: to stimulate osteoblasts via the canonical Wnt signaling pathway. In a murine model of moderate severe OI, 2 weeks of sclerostin antibody therapy resulted in improved bone mass and reduced long-bone fragility (Sinder et al. 2013).

10. Prenatal and postnatal transplantation of mesenchymal stem cells to treat OI: limited experience (Chan and Götherström 2014; Götherström et al. 2014):
    1. Prenatal transplantation of allogeneic MSC in OI is safe. The cell therapy is of likely clinical benefit with improved linear growth, mobility, and reduced fracture incidence. Unfortunately, the effect is transient. For this reason, postnatal booster infusions using same-donor MSC have been performed with clinical benefit and without any adverse events.

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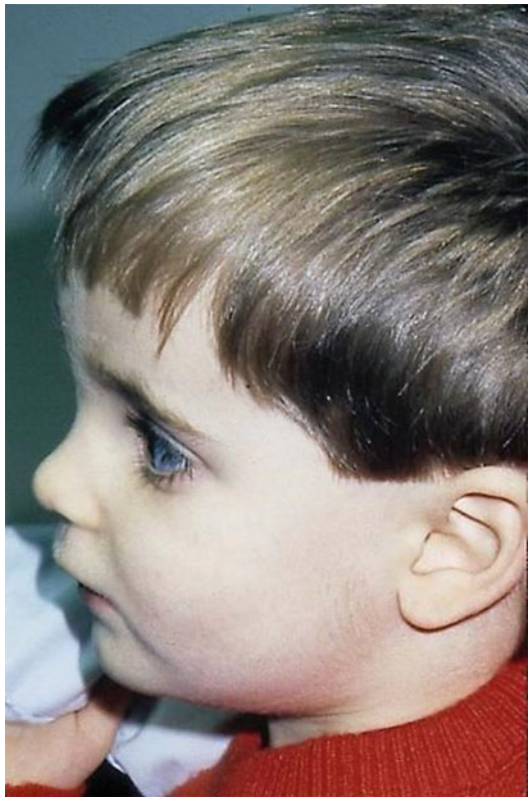

Fig. 1 A boy with osteogenesis imperfecta type I showing blue sclera

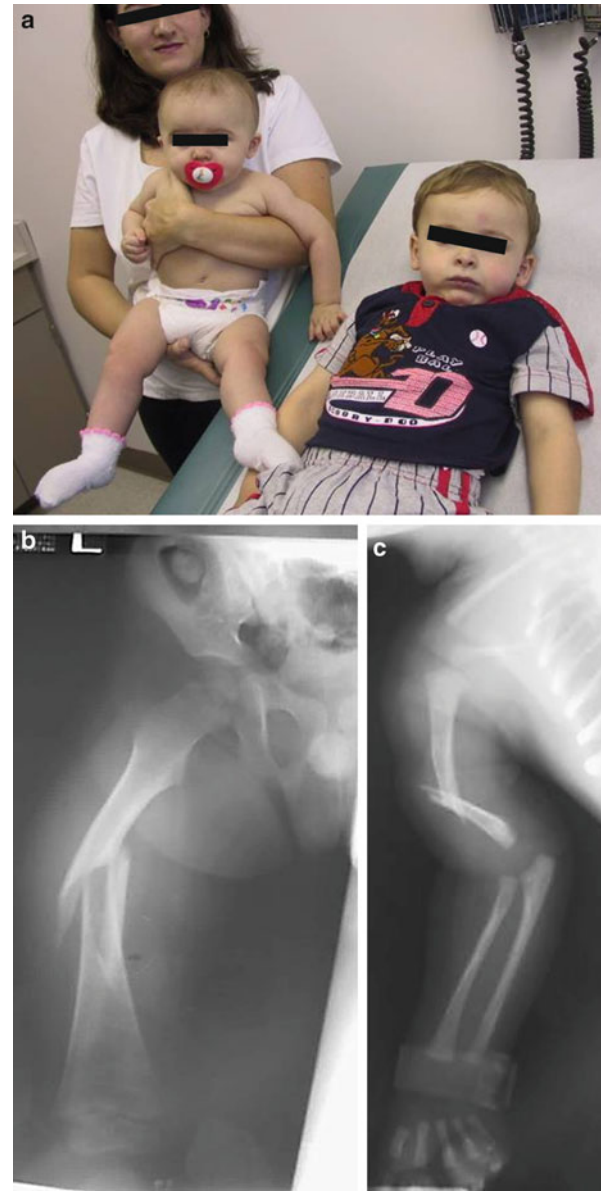

Fig. 2 (**a**–**c**) Familial osteogenesis imperfecta type I in two sibs. Radiographs show fracture of a femur in the boy and that of humerus in the girl. Their father is also affected. Molecular testing revealed c.578^579insC of COL1A1 gene mutation in this family

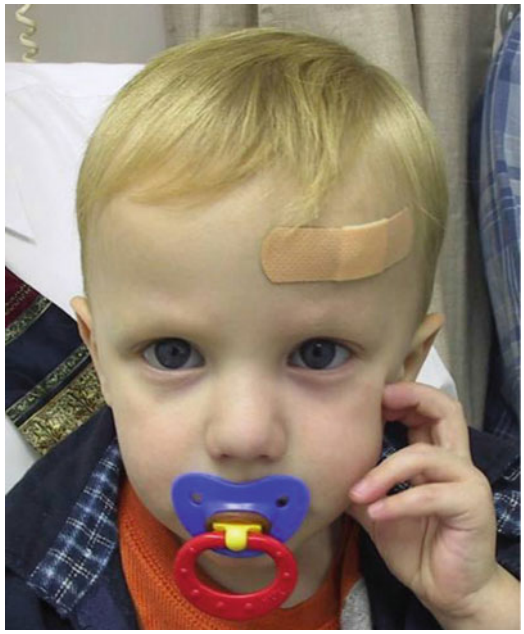

Fig. 3 A 22-month-old boy with osteogenesis imperfecta type I showing blue sclera. He has heterozygous mutation Arg75Stop of the COL1A1 gene by molecular genetic analysis

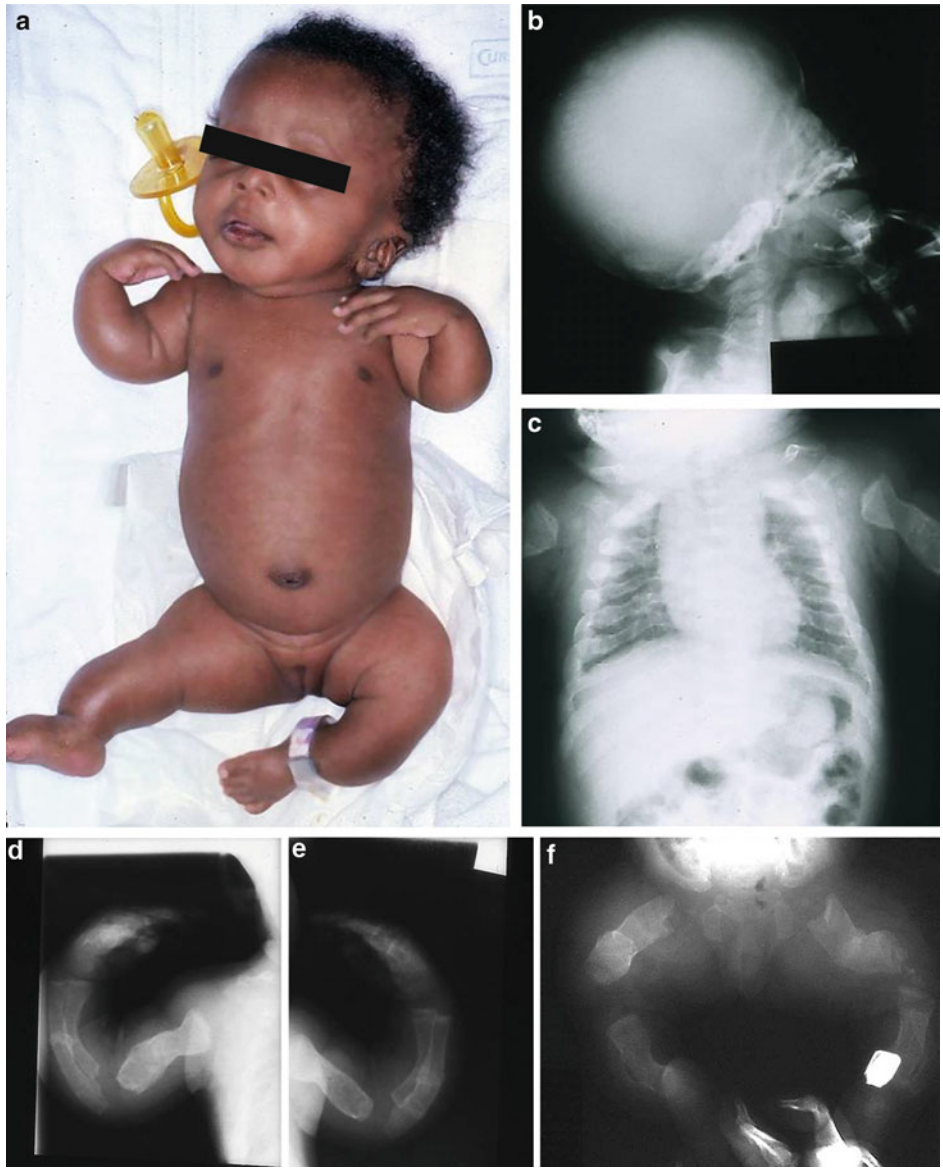

Fig. 4 (**a**–**f**) An infant with osteogenesis imperfecta type II showing severe dwarfism, characteristic craniofacial features, short and deformed limbs, and bowed legs. Radiographs showed short-limb dwarfism, rhizomelic limb shortening, severely retarded calvarial mineralization, multiple fractures with callus formation, beaded and broad ribs, and "telescoped" femurs and humeri

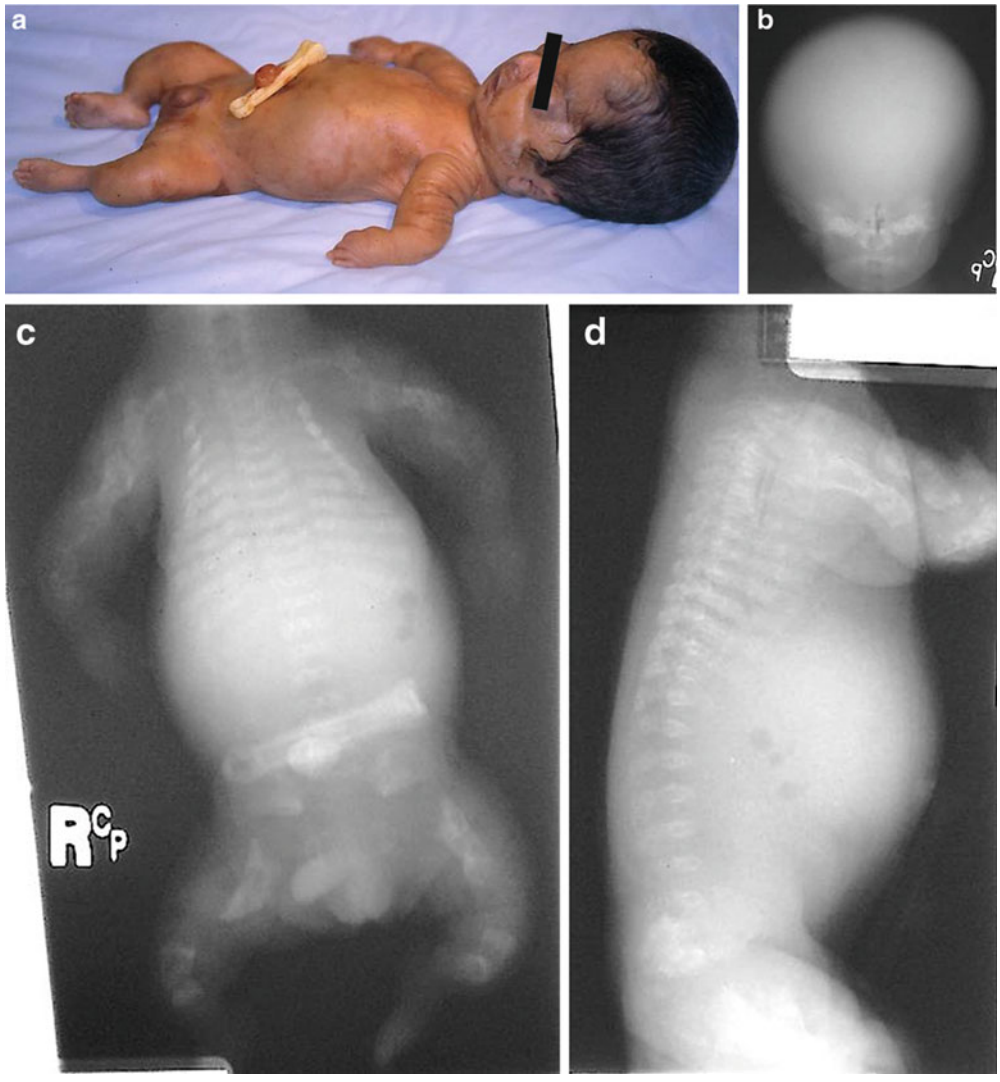

Fig. 5 (**a**–**d**) Another case of osteogenesis imperfecta type II showing the similar features

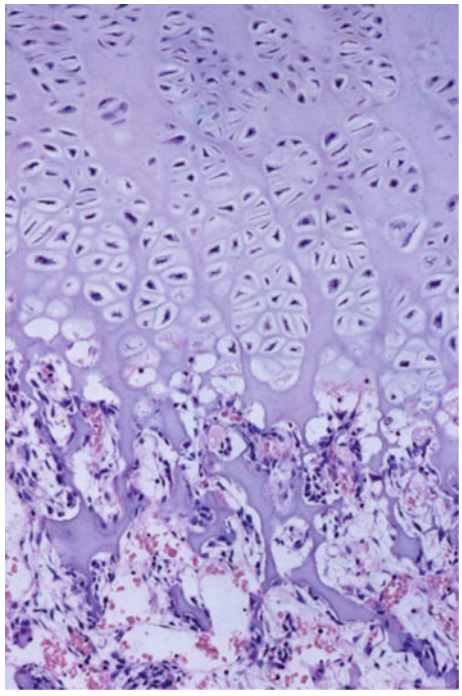

Fig. 6 Photomicrograph of rib of another case with type II osteogenesis imperfecta. The columns of cartilage in the metaphysis are covered by minimal amounts of basophilic primitive woven bone. Normal ossification is absent. The physeal growth zone is moderately disorganized

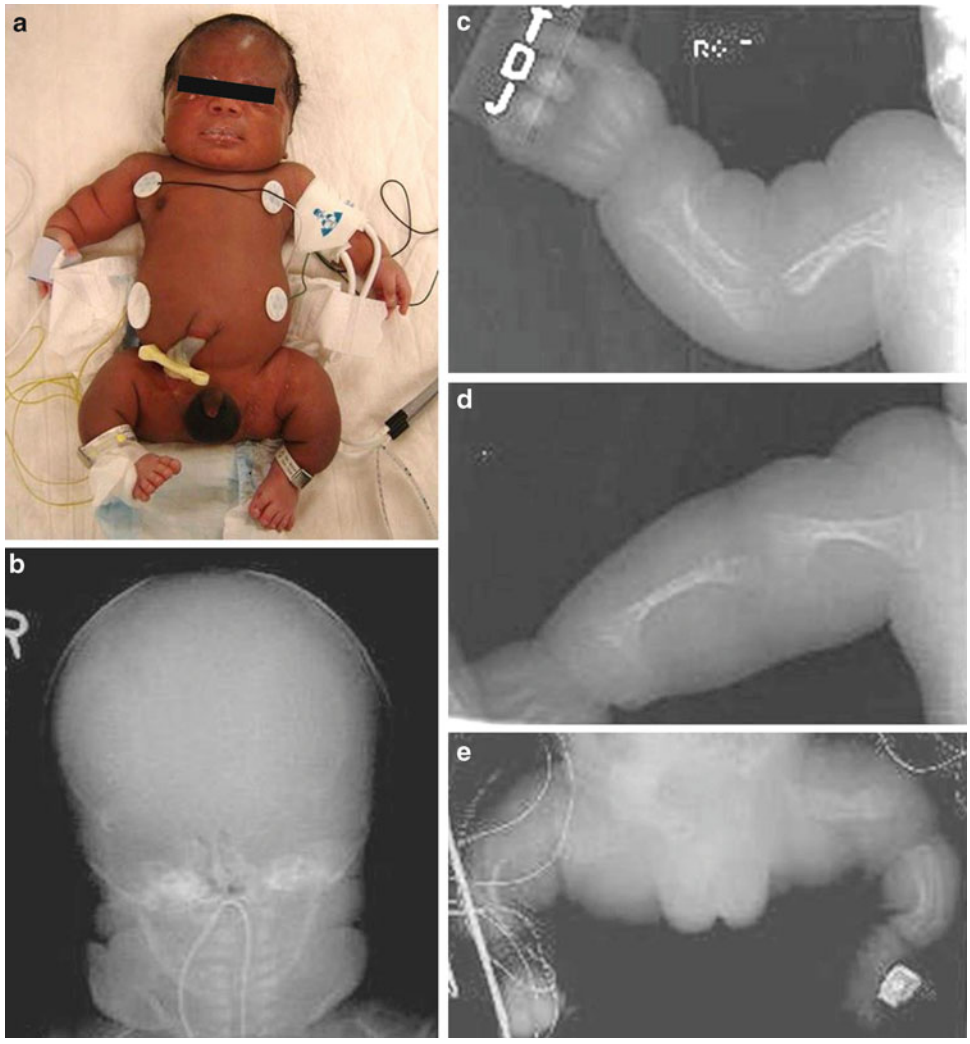

Fig. 7 (**a**–**e**) A neonate with osteogenesis type III showing short-limbed dwarfism, large head, short neck, short thigh, and curbed lower legs. Radiographs showed generalized osteopenia; poor mineralization of the skull; thin ribs with sixth, seventh, and eighth rib fractures with callus formation; short limbs; and bowed femurs with multiple fractures with callus formation. Molecular study showed heterozygous mutation of COL1A2 gene (del of three base pairs [GTT] at cDNA position c.763–765). This mutation has been reported in patients with osteogenesis imperfecta type III

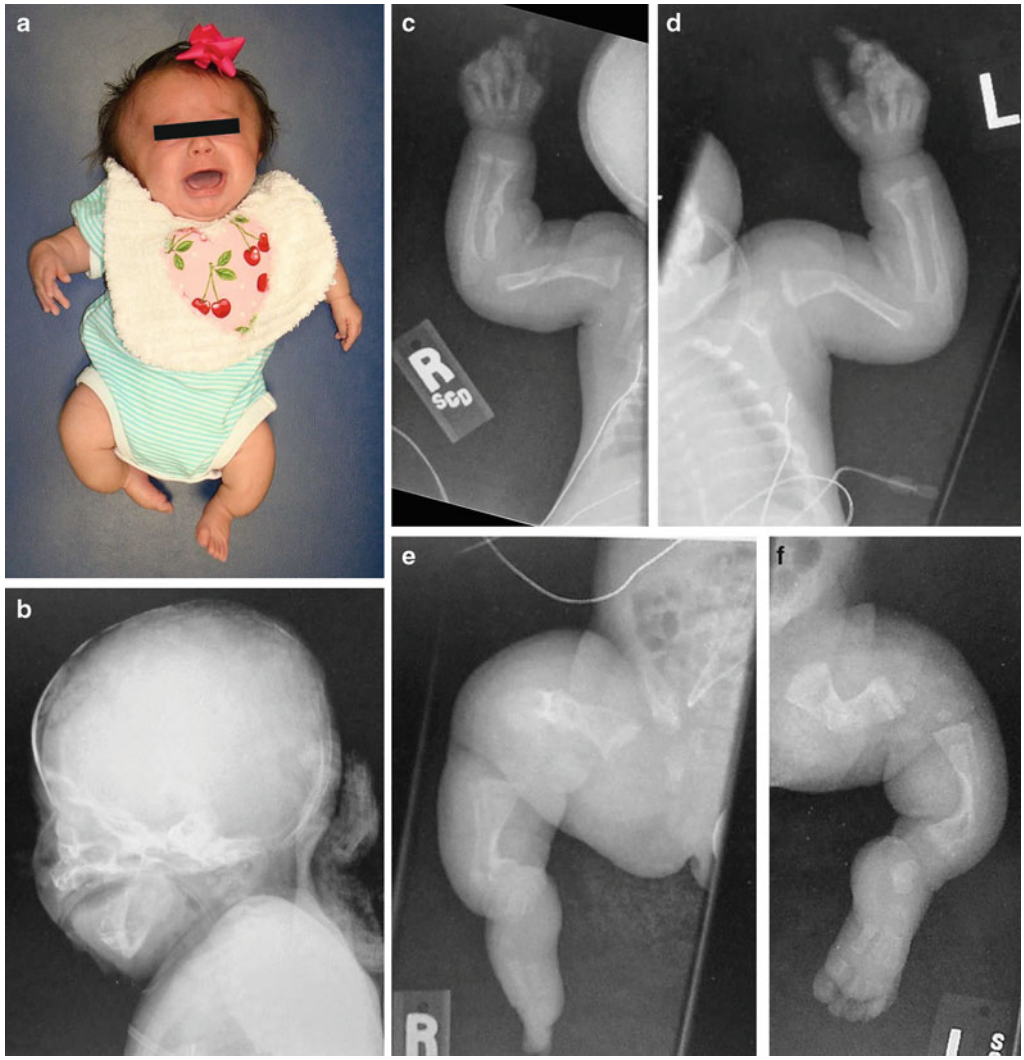

Fig. 8 (**a**–**f**) A neonate with osteogenesis type III showing short-limbed dwarfism, large head, short neck, and short and curbed upper and lower extremities. Radiographs showed generalized osteopenia, poor mineralization of the skull, and short and bowed limbs with multiple fractures with callus formation. Molecular study by sequence analysis indicated a variation in the fragment containing exon 21 and the flanking sequences of the *COL1A2* gene. Sequencing revealed a nucleotide G to A substitution that converted a codon for glycine-289 (GGA) to a codon for glutamic acid (GAA) at cDNA position c.866. The patient thus showed a heterozygous mutation of *COL1A2* gene (Gly289Glu). This mutation has not been reported previously

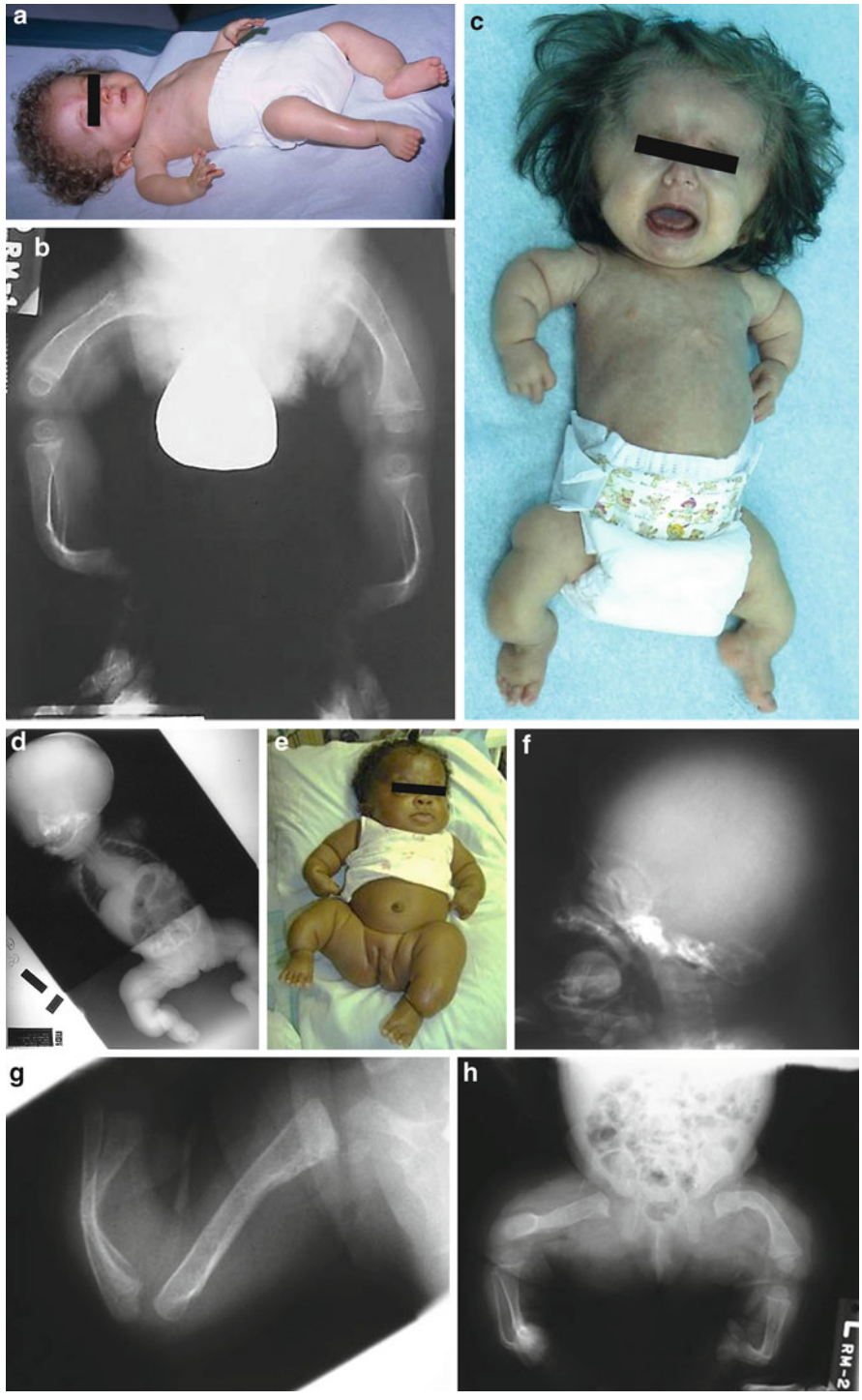

Fig. 9 (**a**–**h**) Three other infants with osteogenesis imperfecta type III showing dwarfism, moderate deformities resulting from in utero fractures, and typical triangular face with relatively large cranium. Radiographs showed undermineralized calvarium with a large fontanel and marked angulation or bowing of long bones, especially tibias and femurs

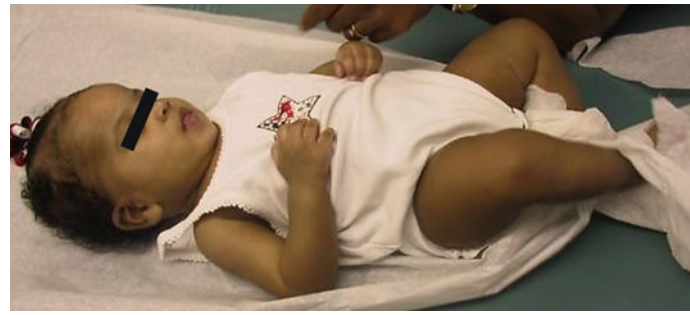

Fig. 10 An infant girl with osteogenesis imperfecta type IV

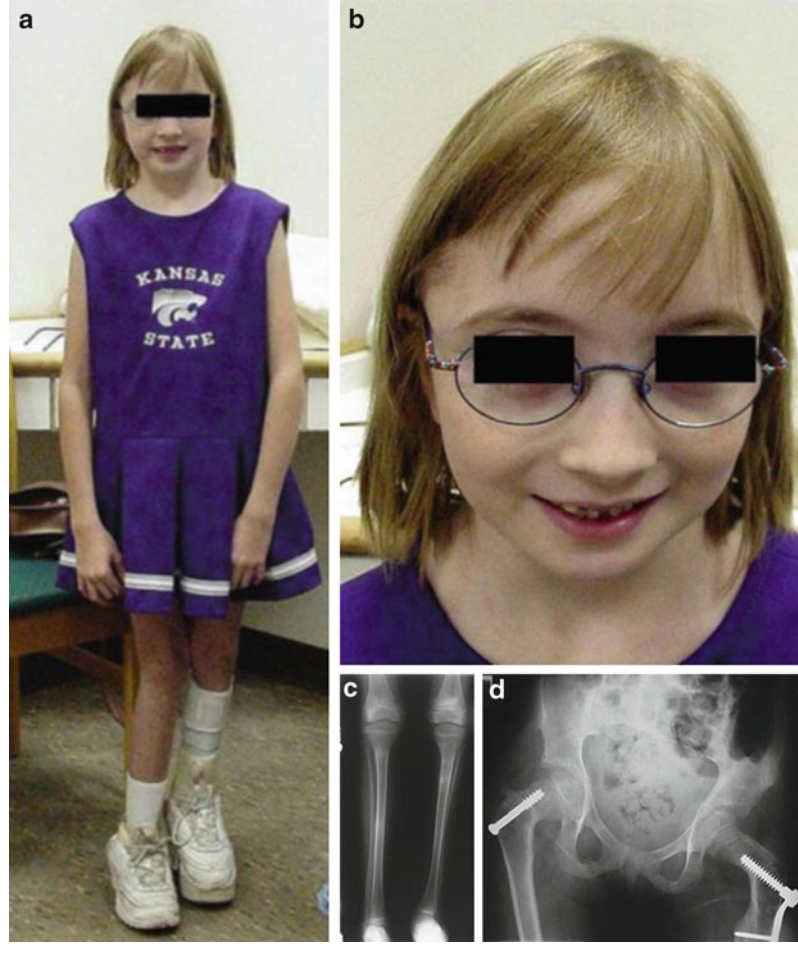

Fig. 11 (**a**–**d**) A girl with Cole-Carpenter syndrome showing ocular proptosis, craniosynostosis, and bone fragility with fractures

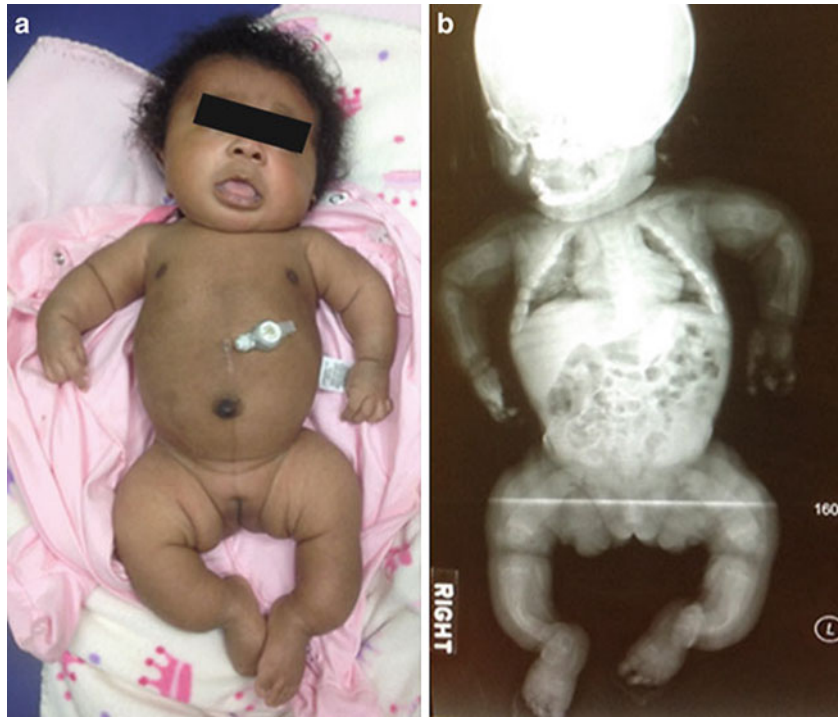

Fig. 12 (**a**, **b**) This 7-month-old female infant (**a**) was evaluated for osteogenesis imperfecta. Prenatal ultrasound showed short fetal bones. Chromosome microarray and chromosome analyses from amniotic fluid were normal. At birth, she was noted to have severe dwarfism, blue sclera, short neck and thorax, and short and deformed limbs. Radiograph (**b**) showed general osteoporosis, short-limb dwarfism, short neck and thorax, beaded and short ribs, "telescoped" humeri and femurs, and angulated tibiae. The *COL1A1/COL1A2* gene analysis showed no deletion or duplication. Individuals with OI type V, VI, VII, or VIII have mutations genes other than COL1A1 or COL1A2 (Byers and Pyott 2012; Shapiro et al. 2013). Apparent homozygosity for a mutation (c.1080 + 1G > T, or IVS5 + 1G > T) in *LEPRE1*, the gene that encodes prolyl 3-hydroxylase 1 (P3H1), was identified in this patient, confirming the diagnosis of type VIII osteogenesis imperfecta (Collaboration with Dr. Susanne Ursin)

Osteogenesis Imperfecta/Ehlers-Danlos Syndrome Overlap Syndrome

Contents

Helical mutations near the amino (N)-proteinase cleavage site have been suggested to result in a mixed osteogenesis imperfecta (OI)/Ehlers-Danlos syndrome (EDS) phenotype (Malfait et al. 2013).

Synonyms and Related Disorders

Ehlers-Danlos syndrome; Mixed OI/EDS phenotype; Osteogenesis imperfecta

Genetics/Basic Defects

1. Most of the patients studied harbored a *COL1A1*/*COL1A2* mutation residing within the most N-terminal part of the type I collagen helix (Nicholls et al. 1992; Feshchenko et al. 1998; Raff et al. 2000; Cabral et al. 2005) (Malfait et al. 2013).
2. These mutations affect the rate of type I collagen N-propeptide cleavage and disturb normal collagen fibrillogenesis.

Clinical Features

1. Mainly present as EDS signs (Malfait et al. 2013)
    1. Severe joint hyperlaxity
    2. Soft and hyperextensible/translucent skin
    3. Abnormal wound healing
    4. Easy bruising
    5. Mild abnormal scarring
    6. Sometimes signs of arterial fragility
2. Show only subtle signs of OI
    1. Blue sclera
    2. Osteopenia
    3. Fractures
    4. Relatively short stature
3. Hypotonia
4. Clinical overlap with other EDS subtypes, including the classic, hypermobility, vascular, arthrochalasis, and kyphoscoliosis types

Diagnostic Investigations

1. Biochemical collagen analysis: a powerful tool necessary to establish the diagnosis because of clinical overlapping with other EDS subtypes
2. Molecular sequencing of *COL1A1* and *COL1A2*: allows identification of

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_265

heterozygous mutations in the triple helical region close to the procollagen type I N-proteinase cleavage site (Malfait et al. 2013)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: if a parent of the proband is affected, the risk to each sib is 50%.
   2. Patient's offspring: a 50% chance of inheriting the mutation and developing the disorder.
2. Prenatal diagnosis: has not been accomplished.
3. Management: please see the chapters of osteogenesis and Ehlers-Danlos syndrome.

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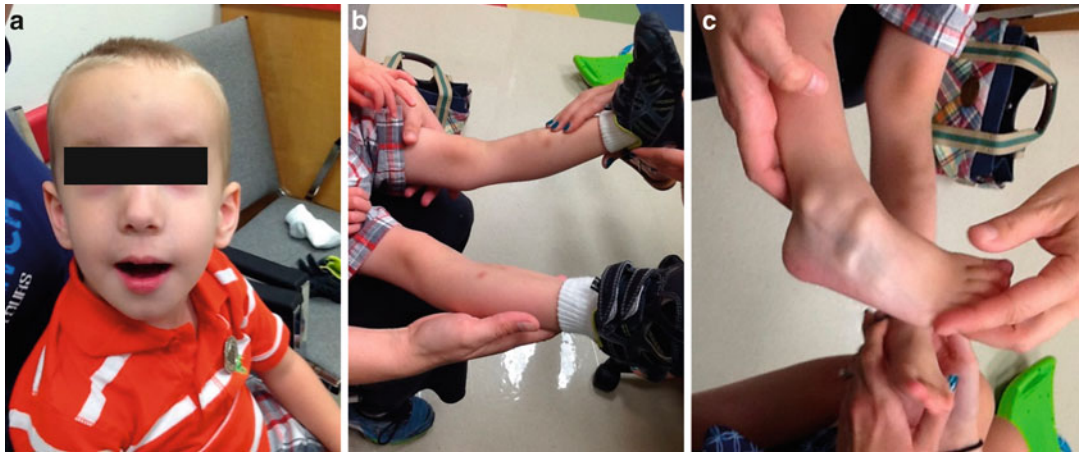

Fig. 1 (**a**–**c**) This 3-year-old Caucasian boy was evaluated for collarbone fractures, blue sclera, hypotonia, and hypermobile joints and to rule out osteogenesis imperfecta. He was noted to have hyperextensible fingers/wrists, knees, and ankles and bruise throughout the body. COL1A2 sequencing identified c.432 + 4_432 + 5insAA in one allele of COL1A2, the gene that encodes the pro-alpha 2 (I) chain of type I procollagen. The reference laboratory was able to characterize the outcome of splicing to have resulted in skipping of exon 9 and a mixed osteogenesis imperfecta and Ehlers-Danlos syndrome phenotype with fractures and joint hypermobility.

Osteopetrosis

Contents

Osteopetrosis is a heterogeneous group of sclerosing bone diseases due to impaired bone and cartilage resorption, resulting from absence or defective function of osteoclasts (Steward 2003). The overall incidence of these conditions is difficult to estimate, but autosomal recessive osteopetrosis has an incidence of 1 in 250,000 births, and autosomal dominant osteopetrosis has an incidence of 1 in 20,000 births (Stark and Savarirayan 2009).

Synonyms and Related Disorders

Autosomal dominant osteopetrosis type I; Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease); Hereditary sclerosing bone dysplasias; Infantile malignant osteopetrosis; Marble bone disease; Osteopathia striata (Voorhoeve disease); Osteoclast-poor osteopetrosis; Osteopetrosis congenita (malignant osteopetrosis) (Carolino et al. 1998); Osteopetrosis tarda (benign adult form of osteopetrosis)

Genetics/Basic Defects

1. Inheritance of recognized subtypes of human osteopetrosis: genetic heterogeneity (Stark and Savarirayan 2009; Kocher and Kasser 2003; Steward 2003, 2010; Coudert et al. 2015)
    1. Chloride channel CLCN7 mutations: responsible for severe recessive, dominant, and intermediate osteopetrosis (Frattini et al. 2003; Sobacchi et al. 2016)
        1. Autosomal recessive osteopetrosis (ARO)
            1. Classic (infantile malignant osteopetrosis) (vacuolar proton pump deficiency (*ATP6i*/*TCIRG1*) (locus 11q13.3-q13.5)): mutations in the gene encoding the a3 subunit of the proton pump are a rather common cause of infantile malignant osteopetrosis (Kornak et al. 2000)
            2. Neuropathic (osteopetrosis and infantile neuroaxonal dystrophy): CLC7 (chloride channel 7) chloride pump deficiency (loss of function *CLCN7* mutations) (locus 16p13.3) (Campos-Xavier et al. 2003) and *OSTM1* mutations cause an extremely severe form of autosomal recessive osteopetrosis with frequent

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CNS involvement (Pangrazio et al. 2006)

3. Autosomal recessive osteopetrosis with renal tubular acidosis (Jacquemin et al. 1998)
   Caused by mutations in *CA2*, the gene encoding carbonic anhydrase II
   Generalized osteosclerosis
   Cerebral calcifications
   Associated with intellectual disability
4. Autosomal recessive osteopetrosis secondary to *PLEKHM1* mutations: mild phenotype and can regress with increasing age (van Wesenbeeck et al. 2007). A relatively malignant form of osteopetrosis was reported to be caused by *PLEKHM1* gene (Bo et al. 2016)

2. More benign osteopetrosis primarily affecting adults: two subtypes based on radiographic features
   1. Autosomal dominant osteopetrosis (ADO) type I (locus 11q12-13) (Van Hul et al. 2002)
   2. Autosomal dominant osteopetrosis (ADO) type II (Albers-Schönberg disease): Genetically homogeneous because of a single gene on chromosome 16p13.3 (Bénichou et al. 2001): caused by *CLCN7* mutations (Waguespack et al. 2003). Because some ARO patients have mutations in both copies of the *CLCN7* gene, ADO II is allelic with a subset of ARO cases (Cleiren et al. 2001). 1p21 is probably a minor locus in ADO II (Bénichou et al. 2000a)
3. Intermediate recessive osteopetrosis (IRO): Children presenting beyond 2 years of age often have a slower progressive disease
   1. An autosomal recessive disease with milder mutations: carbonic anhydrase isoenzyme type II deficiency (CAII) and *CLCN7* mutations (Bénichou et al. 2001)
   2. Early diagnoses of the more severe end of the autosomal dominant spectrum

2. Gene mutated in osteopetrotic patients (Coudert et al. 2015)
   1. *TCIRG1* (loss of function; α3 subunit V-ATPase)
   2. *CLCN7* (loss of function; chloride channel 7)
   3. *OSTM1* (loss of function; osteopetrosis associated transmembrane protein)
   4. *PLEKHM1* (loss of function; pleckstrin homology domain containing family M, member I): ARO
   5. *SNX10* (loss of function; sorting nexin 10): ARO
   6. *TNFSF11* (loss of function; receptor activator for nuclear factor κB ligand): ARO
   7. *TNFRSF11A* (loss of function; receptor activator for nuclear factor κB): ARO
   8. *CAII* (loss of function; carbonic anhydrase II): IRO
   9. *CLCN7* (dominant negative; chloride channel 7): ADO II
3. RANKL deficiency (Askmyr et al. 2008)
   1. Recently discovered in a screen of 40 patients with recessive osteopetrosis with unknown genetic defects (Sobacchi et al. 2007)
   2. Characterized by a decrease in osteoclast numbers
   3. Less severe with a slower progression than the classical malignant forms of osteopetrosis
   4. The gene that is mutated encodes RANKL, one of the osteoclast-promoting cytokines produced by stromal cells in the bone marrow
4. Osteopetrosis associated with ectodermal dysplasia, lymphedema, and immunodeficiency
   1. X-linked (Smahi et al. 2002)
   2. Resulting from a hypomorphic mutation in IKBKG [also known as NEMO (NF-kB essential modulator)]
   3. Most hypomorphic mutations do not cause osteopetrosis but mild ectodermal dysplasia and immunodeficiency in males
5. Osteopetrosis with agenesis of corpus callosum: autosomal recessive

6. Dysosteosclerosis
    1. Autosomal recessive
    2. X-linked also reported
2. Basic defects: Absence or defective function of osteoclasts results in defective remodeling of bone with partial or complete obliteration of marrow cavities, producing bone which is dense but has an increased tendency to fracture
3. Potential clinical consequences of aberrant resorption and remodeling of bones caused by defective osteoclast function (Steward 2010)
    1. Fractures
        1. Undertubulated bones break easily
        2. Common fracture sites (Cheow et al. 2001)
            1. Long bones of the arms and leg
            2. Posterior ribs
            3. Acromial processes
    2. CNS and eye involvements (Abinun et al. 1999; Steward 2003)
        1. Bony overgrowth, or lack of remodeling, results in compression of nerves or blood vessels that pass through bones, especially the optic nerve (resulting in partial or complete visual loss) and, more rarely, the auditory and facial nerves.
        2. Arteries or venous sinuses within the skull can also be constricted, as can the foramen magnum.
        3. Early fusion of bones may result in craniosynostosis.
        4. Some patients have primary neurometabolic (neuronopathic) forms of osteopetrosis and may have abnormal retinal pigmentation and cerebral atrophy.
    3. Cytopenia/pancytopenia (Steward et al. 2005)
        1. Bony encroachment on medullary cavities results in extramedullary hemopoiesis with hepatosplenomegaly and the potential for hypersplenism.
        2. Anemia and thrombocytopenia result and blood films often show a markedly leukoerythroblastic picture, with a high white blood cell count and high numbers of circulating stem cells.
    4. Growth: Most children with osteopetrosis fall below the tenth percentile on growth charts, and some have severe dwarfism (Gerritsen et al. 1994; Driessen et al. 2003).
    5. Hypocalcemia: Defective osteoclast function can disturb calcium homeostasis, which may manifest as symptomatic hypocalcemia in the first few months of life, despite high total body calcium reserves (Gerritsen et al. 1994; Srinivasan et al. 2000).
    6. Respiratory compromise (Wong et al. 1978)
        1. The skull base, choanal bones, and jaw are often severely affected, which produces persistent snuffling, noisy breathing, and upper airway obstruction and may predispose patients to pulmonary arterial hypertension.
        2. Patients often suffer increased ear, nose, and throat infections and respiratory infections.
    7. Dentition (Luzzi et al. 2006)
        1. Tooth eruption often delayed.
        2. Poor tooth quality.
        3. Osteomyelitis of the jaw can occur.
    8. Other organ system involvement: The genes involved may have roles in other organs. For example, a small proportion of children have severe neurometabolic disease, and abnormalities of lymphocytes and immunoglobulin production are now recognized in some variants (Villa et al. 2009; Mazzolari et al. 2009).

Clinical Features

1. Malignant infantile osteopetrosis (Steward 2003)
    1. Usually diagnosed during the first year of life
    2. Signs and symptoms
        1. Presenting signs
            1. Blindness
            2. Failure to thrive
            3. Seizures due to hypocalcemia
            4. Infections

5. Pathologic fractures
2. Neurovascular involvement: The most serious consequences of the osteopetrosis are cranial nerves, blood vessels, and the spinal cord compression by either gradual occlusion or lack of growth of skull foramina.
3. Visual impairment
    1. Optic atrophy: Some degrees of optic atrophy are present in most patients. Blindness is observed in many children with severe forms of autosomal recessive osteopetrosis.
    2. Nystagmus
    3. Strabismus
    4. Proptosis
    5. Limited extraocular movement
4. Compression of facial and trigeminal nerves
    1. Produce paralysis, spasm, or neuralgia.
    2. Involvement of the trigeminal nerve tends to occur in type I autosomal dominant osteopetrosis.
    3. Involvement of the facial nerve is predominant in type II disease.
5. Hearing loss
    1. Poor drainage of the middle ear
    2. Narrowing of the internal acoustic meatus
    3. Osteosclerosis
6. Blood vessel compression
    1. Stenosis of arterial supply (internal carotid artery, vertebral artery)
    2. Stenosis of venous supply
7. Craniofacial features
    1. Macrocephaly
    2. Frontal bossing
    3. Hypertelorism
    4. Exophthalmos
    5. Flat nasal bridge
    6. Chronic rhinitis
    7. Jaw: a frequent site of osteomyelitis
    8. Obligate mouth breathing in most children secondary to obstruction of the upper airway
8. Compromised nutritional state due to difficulty in eating and breathing resulting from limited posterior nasophrynx from bony overgrowth
9. Psychomotor retardation
    1. Secondary to hydrocephalus
    2. Secondary to apnea due to upper airway obstruction
    3. Common in carbonic anhydrase isoenzyme type II deficiency
10. Bone marrow failure
    1. Results from bone marrow encroachment
    2. Leads to extramedullary hematopoiesis and hepatosplenomegaly (abdominal protuberance)
    3. Frequently progresses to hypersplenism and pancytopenia
    4. Signs secondary to thrombocytopenia (petechiae, ecchymoses, epistaxis, melena, gingival bleeding, intracerebral hemorrhages)
    5. Carries a high mortality (early death)

2. Autosomal dominant osteopetrosis type I
    1. Chronic bone pain
    2. Cranial nerve palsies
    3. Hearing loss
    4. Not associated with increased fracture rate (el-Tawil and Stoker 1993)
3. Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease) (Bénichou et al. 2000b)
    1. Originally described by Albers-Schőnberg in 1904
    2. The most common form of osteopetrosis
    3. The prevalence: 5.5 in 100,000
    4. The term “benign osteopetrosis”: a misnomer for autosomal dominant osteopetrosis type II because of the possibility of severe clinical complications
    5. Most prominent symptoms
        1. Bone pain
        2. Multiple fractures: frequent (78%), perhaps due to the reduced elasticity of the brittle bone

3. Cranial nerve palsies
4. Mandibular osteomyelitis

6. Other signs
1. Hip osteoarthritis
2. Thoracic or lumbar scoliosis
3. Hearing loss
4. Visual loss
5. Optic atrophy
6. Multiple dental abscesses
7. Multiple and deep dental decays
8. Bone (except mandibular) joint (hip) sepsis

4. "Intermediate" form of osteopetrosis
1. Usually diagnosed during the first decade and survive into adulthood
2. Short stature
3. Frontal bossing
4. Mild hepatosplenomegaly

5. Carbonic anhydrase isoenzyme type II (CA II) deficiency
1. An autosomal recessive disorder
2. Most cases have been reported from Middle East or the Mediterranean region
3. Osteopetrosis with renal tubular acidosis (usually distal type)
4. Short stature
5. Fractures
6. Psychomotor retardation
7. Cranial nerve compression (>50%)
8. Optic atrophy and visual loss
9. Cerebral calcifications
10. Minor hematological impairment
11. Craniofacial features
1. Micrognathia
2. Narrow prominent nose
3. Poorly developed philtrum
12. Abnormal dentition
1. Peg-shaped carious teeth with malocclusion
2. Delayed eruption of the teeth
3. Retained primary dentition
13. Visual failure
14. Episodic hypokalemic paralysis in some patients

6. Vacuolar proton pump deficiency
1. Visual failure
2. Symptomatic hypocalcemia in the first month (50%)
1. Early or late neonatal convulsions
2. Irritability
3. Jittering episodes
3. Fractures
4. Mild to severe hematological impairment
5. Hepatosplenomegaly
6. Failure to thrive
7. Poor growth
8. Reduced life span

7. CLCN-7 chloride pump deficiency: severe osteopetrosis

8. Neuronopathic osteopetrosis
1. Causing rapid neurodegeneration and death within the first year
2. Widespread axonal spheroids and accumulation of ceroid lipofuscin
3. Often accompanied by severe hematological impairment
4. Gross hepatosplenomegaly
5. Severe anemia/thrombocytopenia
6. High arched palate
7. Gum hypertrophy
8. Hyperreflexia
9. Clonus
10. Opisthotonos
11. Fisting
12. Poor head control
13. Irritability
14. Early death

9. Autosomal recessive osteopetrosis with renal tubular acidosis (Whyte 1993)
1. A milder course
2. Renal tubular acidosis
3. Cerebral calcifications
4. Fractures
5. Short stature
6. Dental abnormalities
7. Cranial nerve compression
8. Developmental delay

10. X-linked osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency (OLEDAID)
1. Common variable immune deficiency in association with a particular subtype of osteoclast-poor autosomal recessive osteopetrosis (Guerrini et al. 2008)
2. Leukocyte adhesion deficiency syndrome (Kilic and Etzioni 2008; Mory et al. 2008)

11. Osteopetrosis with agenesis of corpus callosum: possible variant to neuronopathic osteopetrosis
12. Dysosteosclerosis
    1. Bone fractures
    2. Developmental delay with occasional mental retardation
    3. Cranial nerve impingement
        1. Visual loss (optic atrophy)
        2. Hearing loss
        3. Facial nerve paralysis
    4. Osteomyelitis of the mandible
    5. Macular atrophy of the skin
    6. Flattened fingernails
13. Differential diagnosis (Manusov et al. 1993; Ihde et al. 2011; Sobacchi et al. 2016)
    1. Hyperostosis corticalis generalisata: Endosteal cortical thickening involving the long bones, skull (leading to cranial nerve palsies), and facial bones; mandible enlargement
        1. Van Buchem syndrome
            1. An autosomal recessive disorder
            2. *SOST* (sclerostin)-related sclerosing bone dysplasia
            3. Diffuse/widespread sclerosis of the cortex, usually sparing spine
            4. Facial nerve palsy
            5. Generalized osteosclerosis
            6. Hyperphosphatasemia
        2. Sclerosteosis (Hamersma et al. 2003)
            1. An autosomal recessive disorder
            2. Facial nerve palsies
            3. Syndactyly
            4. Bone overgrowth (tall stature)
            5. Can be lethal as a result of increased intracranial pressure
        3. Worth disease
            1. An autosomal dominant disorder
            2. Caused by *LRP5* (lipoprotein receptor-related protein 5) mutation
            3. No cranial nerve palsy
            4. Torus palatinus
    2. Craniometaphyseal dysplasia (please see the chapter on "► Craniometaphyseal Dysplasia")
        1. Autosomal recessive craniometaphyseal dysplasia (AR-CMD) (OMIM)
            1. Typical features of CMD
               Macrocephaly
               Hearing loss
               Skull hyperostosis with paranasal bossing (metaphyseal widening) but less pronounced calvarial thickening (Iughetti et al. 2000)
            2. Due to diaphyseal osteosclerosis the disorder can occasionally resemble mild forms of osteopetrosis. Pathogenic variants in GJA1 are causative (Hu et al. 2013)
        2. Autosomal dominant craniometaphyseal dysplasia (AD-CMD)
            1. The clinical hallmark of CMD is skull hyperostosis leading to deep-set eyes and paranasal bossing.
            2. Facial nerve palsy is common and occurs more frequently than optic nerve compression (Braun et al. 2001).
            3. The femur shows a modeling defect but no osteosclerosis.
            4. Susceptibility to fractures is not increased.
            5. Pathogenic variants in ANKH are causative (Nürnberg et al. 2001).
    3. Oculo-dento-osseous dysplasia
        1. An autosomal dominant disorder
        2. Enlarged mandible
        3. Focal osteosclerosis in the pelvis
        4. Other findings
            1. Microphthalmia
            2. Large jaw
            3. Hypoplasia of tooth enamel
    4. Osteitis deformans (Paget disease)
        1. Localized osteosclerosis in one or a few regions of the skeleton
        2. Local pain
        3. Bone marrow biopsy finding
    5. Progressive diaphyseal dysplasia (Camurati-Engelmann disease)

1. An autosomal dominant disorder with variable expression
2. Caused by domain-specific mutations of the TGFB gene located on chromosome 19q13 encoding transforming growth factor β-1
3. Associated with progressive sclerosis of the diaphyses of all the long bones due to thickening of the cortices
4. Major clinical features
    1. Leg pain
    2. Muscular weakness
    3. Waddling gait
    4. Failure to thrive
5. Major radiographic features
    1. Fusiform sclerosis of cortical surfaces and subendosteum
    2. Sclerosis of the skull base

6. Pyknodysostosis (de Vernejoul and Bénichou 2001)
    1. An autosomal recessive disorder
    2. Caused by cathepsin K gene mutations, resulting in no immunologically detectable protein (Gelb et al. 1996; Hou et al. 1999)
    3. Hyperostosis of long bones with preserved medullary cavities
    4. Acro-osteolysis
    5. Wormian bones
    6. Dysmorphic features
    7. Generalized osteosclerosis
    8. Frequent fractures
    9. Open fontanel
    10. Associated with mental retardation and dwarfism
7. Dysosteosclerosis
    1. Short stature
    2. Sandwich vertebrae
    3. Platyspondyly
    4. Metaphyseal widening and sclerosis
    5. Often diaphyseal thickening
    6. Campeau et al. (2012) identified biallelic *SLC29A3* variants in two individuals with dysosteosclerosis
8. Osteopoikilosis (please see the chapter on "► Osteopoikilosis")
    1. An autosomal dominant disorder
    2. Caused by *LEMD3* mutation
9. Osteoparthia striata
    1. An X-linked disorder
    2. Dense striations in metadiaphyses of long bones
    3. No other associated abnormalities
10. Progressive diaphyseal dysplasia
    1. An autosomal dominant disorder
    2. Caused by LAP of TGF-β1 mutation
    3. Bilateral/symmetric periosteal and endosteal cortical thickening involving long bones and/or calvaria
    4. Gait disturbances
    5. Pain
    6. Weakness
11. Hereditary multiple diaphyseal sclerosis
    1. An autosomal recessive disorder
    2. Unilateral/asymmetrical cortical thickening, involving long bones only
    3. Milder neuromuscular symptoms than with progressive diaphyseal dysplasia
12. Leukocyte adhesion deficiency type III (LAD-III) (OMIM)
    1. Affected individuals present with recurrent infections and a bleeding diathesis regardless of platelet or leukocyte count.
    2. Pathogenic variants in *FERMT3* (encoding fermitin family homolog 3) are causative.
    3. In some individuals with LAD-III, a high bone density can be found, since fermitin family homolog 3 (also referred to as kindlin-3) signaling is required for osteoclast-mediated bone resorption (Crazzolara et al. 2015).
13. Nonhereditary disorders
    1. Intramedullary osteosclerosis
        1. A more recently described entity associated with increased bone formation within the medullary cavity of the long bones of the lower extremities

2. Typically discovered at radiography performed in a patient with chronic leg pain that increases with physical activity
2. Melorheostosis (Leri disease)
   1. A type of mixed sclerosing bone dysplasia, with disturbances in both endochondral and intramembranous ossification
   2. Sporadic and typically manifests in late childhood or early adulthood
   3. Clinically, may present with pain and stiffness of the involved bones
   4. When the osseous abnormality involves a joint, contractures can occur
3. Heavy metals (lead, bismuth)
   1. Presence of radiodense lines (Harris lines)
   2. Elevated levels of heavy metals
4. Mastocytosis
   1. Poorly demarcated sclerosis in the pelvis, ribs, vertebrae, skull, and proximal long bones
   2. Not uniformly symmetric
   3. Elevated histamine level
5. Renal osteodystrophy
   1. Widespread sclerosis of the skeleton
   2. Increased density less clear
   3. Elevated serum parathyroid hormone
   4. Elevated renal function test
6. Metastatic carcinomas (breast, prostate, lung, kidney, and thyroid)
   1. Dispersed in random fashion
   2. Bone marrow biopsy often diagnostic

Diagnostic Investigations

1. Laboratory work-up for infantile malignant osteopetrosis (Lam et al. 2007)
   1. Anemia
   2. Leukopenia
   3. Thrombocytopenia
   4. Reticulocytosis
   5. Pancytopenia
   6. Hypocalcemia
   7. Inconsistent hypophosphatemia
   8. Defective superoxide generation in peripheral leukocytes
   9. Secondary hyperparathyroidism with elevated serum calcitriol: common (Key et al. 1984; Cournot et al. 1992)
   10. Increased serum acylphosphatase (ACP)
   11. Presence of the brain isoenzyme of creatine kinase (BB-CK) in the serum is a biochemical marker for osteopetrosis
   12. ACP and BB-CK originate from osteoclasts (Whyte et al. 1996)
2. Radiographic features (de Vernejoul and Bénichou 2001)
   1. Pathognomonic radiographic findings of osteopetrosis (Landa et al. 2007)
      1. Generalized sclerosis
      2. Endobone (bone-within-bone) formation
      3. Vertebral end plate thickening
   2. Infantile malignant osteopetrosis (IMO)
      1. Diffuse skeletal densification: increased density of the entire skeleton
      2. Complete absence of the medullary canal in severe cases
      3. Lack of remodeling gives rise to metaphyseal widening or a "club-shaped" appearance of the long bones
      4. "Bone-within-a-bone" phenomena or "endobones" seen especially in the pelvis, vertebrae, hands, and feet
      5. Transverse radiolucent bands within the metaphyseal regions of the long bones: attributed to periodic variations in the ability to resorb bone
      6. Longitudinal striations in the long bones: attributed to periosteal elevation by trauma or microfractures
      7. Increasingly thickened skull with a "hair-on-end" appearance
      8. "Mask sign" (skull)
      9. Common occurrence of fractures
         1. Especially epiphyseal separations and femur fractures
         2. Diaphyseal and metaphyseal fractures: usually transverse or short oblique pattern

10. Some radiological signs are common to all patients with IMO (increased bone density, bone-within-bone appearance, and metaphyseal remodeling), but some genetic defects such as TCIRG1 are associated with the most severe radiological findings (Simanovsky et al. 2016)

3. Various subtypes of osteopetrosis
    1. Vacuolar proton pump deficiency
        1. Generalized increased bone density
        2. Bone-within-bone appearance due to periosteal new bone formation
        3. Modeling deformities
        4. Pseudorickets (widened and irregular metaphyses)
        5. Metaphyseal lucencies in some children
        6. Fractures: common particularly affecting acromial processes, long bones, posterior ribs, and pubic bones
        7. Identified as the primary defect in the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification
        8. A lack of expression of the vacuolar proton pump has been observed in osteoclasts of a patient with craniometaphyseal dysplasia (Felix et al. 1996)
    2. Carbonic anhydrase isoenzyme type II deficiency
        1. Diffuse skeletal densification
        2. Thick sclerotic skull base
        3. Generalized osteopetrosis
        4. Faulty modeling of metaphyses
        5. Transverse striations in metaphyses
        6. Arcuate striations in iliac bones
        7. Bone-within-bone appearance
        8. Sandwich vertebrae
        9. Intracranial calcifications
    3. Neuronopathic osteopetrosis
        1. Typical findings of severe malignant infantile osteopetrosis
        2. Mild to severe cerebral atrophy
    4. Osteopetrosis with agenesis of the corpus callosum
        1. As with neuronopathic osteopetrosis
        2. Absence of the corpus callosum
    5. Dysosteosclerosis
        1. Thickening and sclerosis of cranial vault, base of skull, ribs, and clavicle
        2. Sclerotic long bones with splayed submetaphyseal clear zones
        3. Platyspondyly
        4. Retarded white matter myelination
        5. Intracerebral calcifications
    4. Autosomal dominant osteopetrosis type I
        1. Generalized/diffuse osteosclerosis affects especially the cranial vault
        2. Sclerotic skull base
        3. Vertebral bodies comparatively normal but the vertebral arches appearing dense
    5. Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease)
        1. A spectacular radiological appearance with the segmental distribution of dense bone
        2. Characterized by diffuse osteosclerosis, predominantly involving spine, pelvis, and skull base
            1. Thickened vertebral end plates (“sandwich vertebrae,” Rugger-Jersey spine)
            2. Classic “bone-within-bone” appearance/endobone structures (especially in pelvis)
            3. Thickened (dense) skull base
        3. Common sclerotic bands in the metaphyses
        4. Fractures
            1. Common (78%)
            2. Heal slowly
        5. Mandibular osteomyelitis
        6. Hip osteoarthritis (27%)
        7. Thoracic or lumbar scoliosis (24%)
        8. Cranial nerve encroachment leading to hearing loss, bilateral optic atrophy, and/or facial palsy (16%)
3. Major pathologic features
    1. General features for malignant infantile osteopetrosis
        1. Obliteration of the marrow spaces by unresorbed primary trabecular bone and calcified cartilage

2. The cartilage cores not remodeled despite an increased number of osteoclasts
3. Absent or diminished ruffled border of the osteoclast by electron microscopy

2. Vacuolar proton pump deficiency: increased osteoclasts
3. ClC-7 chloride pump deficiency: normal numbers of osteoclasts (in mice)
4. Neuronopathic osteopetrosis
   1. Autofluorescent neuronal ceroid lipofuscin
   2. Widespread eosinophilic neuroaxonal spheroids
5. Autosomal dominant osteopetrosis type I: normal appearance of trabecular bone remodeling
6. Autosomal dominant osteopetrosis type II (Albers-Schőnberg disease)
   1. Defective trabecular bone remodeling.
   2. Increased number of osteoclasts.
   3. Frequent delayed healing of fractures.
   4. Increased total acid phosphatase probably reflects the increased number of osteoclasts that are unable to resorb bone.
   5. Observation of large multinucleated osteoclasts suggests a defect in osteoclast function rather than differentiation, as in infantile osteopetrosis.
7. Intermediate form
   1. Mild to marked increased bone density of the axial skeleton and long bones
   2. Defects of modeling seen especially at the distal femurs which may have "Erlenmeyer flask" deformity
   3. Frequent coxa vara and pathologic long bone fractures
   4. Problematic dental malocclusion and caries

4. Genetic diagnosis using whole exome analysis in malignant osteopetrosis of infancy (MOI) (Demir et al. 2015; Shamriz et al. 2016)
   1. Until now, homozygous or compound heterozygous mutations in seven genes (*TNFRSF11A*, *TNFSF11*, *TCIRG1*, *CLCN7*, *OSTM1*, *SNX10*, and *PLEKHM1*) have been found in 80% of children with MOI (Sobacchi et al. 2013).
   2. Detection of the exact cause and provision of genetic counseling via individual mutation analysis of all these genes would be expensive and time consuming.
   3. Whole exome sequencing is being increasingly used given that its cost and the time needed for analysis are similar to that of single-gene sequencing (Campeau et al. 2012; Sui et al. 2013).
   4. In addition, whole exome sequencing offers the probability to detect novel causative genes in the remaining 20% of patients with MOI.

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal recessive disorder: 25%
      2. Autosomal dominant disorder: low unless one of the parent is affected or has gonadal mosaicism
      3. X-linked recessive
         1. Carrier mother: 50% of male sibs affected; 50% of female sibs carriers
         2. Noncarrier mother: still with a small risk of having further affected offspring due to gonadal mosaicism
   2. Patient's offspring
      1. Autosomal recessive disorder: low unless the spouse is a carrier
      2. Autosomal dominant disorder: 50%
      3. X-linked recessive
         1. No sons will inherit the mutant allele and therefore will not be affected with osteopetrosis.
         2. All daughters will be carriers for osteopetrosis.
2. Prenatal diagnosis (Sobacchi et al. 2016)
   1. Prenatal radiography (Oğur et al. 1995; Stark and Savarirayan 2009): possible for families with severe autosomal recessive osteopetrosis and unknown mutations
      1. Made at the 25th week of pregnancy at risk for autosomal recessive osteopetrosis

2. Fetal radiographic findings
    1. Marked sclerosis of osteopetrotic bone
    2. Metaphyseal splaying and clubbing of both femurs
2. Prenatal diagnosis available for pregnancies with a 25% risk for fetuses affected with malignant osteopetrosis by amniocentesis or CVS
    1. Using linkage analysis in the region of chromosome 11q12-13 (Kapelushnik et al. 2001; Shalev et al. 2001)
    2. DNA mutation analysis of fetal DNA for the pregnancy at risk for malignant autosomal recessive osteopetrosis by amniocentesis or CVS when the mutation is previously characterized in the family
3. Preimplantation diagnosis is theoretically possible in families, in whom the genetic mutation has been identified
4. If a family decides to continue with an affected pregnancy, hematopoietic stem cell transplantation before the age of 3 months can be planned with the aim of improving neurological outcomes (Stark and Savarirayan 2009)

3. Management (Wilson and Vellodi 2000)
    1. Medical treatment of osteopetrosis is based on efforts to stimulate host osteoclasts or provide an alternative source of osteoclasts. Stimulation of host osteoclasts has been attempted with calcium restriction, calcitrol, steroids, parathyroid hormone, and interferon (Kocher and Kasser 2003).
    2. ARO (Sobacchi et al. 2016)
        1. Calcium supplementation for hypocalcemic convulsions
        2. Management of calcium homeostasis per individual needs
        3. Erythrocyte or platelet transfusions as needed
        4. Antibiotics for leukocytopenia
        5. Immunoglobulins for hypogammaglobulinemia
        6. Surgical decompression of the optic nerve
        7. Treatment of fractures by an experienced orthopedist
        8. Dental care with attention to tooth eruption, ankylosis, abscesses, cysts, and fistulas
    3. ADOII (Sobacchi et al. 2016)
        1. Orthopedic treatment for fractures and arthritis with attention to potential postsurgical complications (delayed union or nonunion of fractures, infection)
        2. Fractures near joints may require total joint arthroplasty
    4. Supportive care
    5. Blood transfusion for anemia secondary to a failure of bone marrow development
    6. Risk of recurrent infections viewed as an indication for bone marrow transplantation
    7. Optical nerve decompression successful only in mildly affected older children
    8. Early insertion of ventilatory “grommet” tube for hearing impairment secondary to a combination of bony compression of the nerve, sclerosis of the middle ear ossicles, and/or chronic middle ear effusion
    9. Nasal gastric feeding for children with chronic anemia and feeding problems caused by bulbar nerve involvement, nasal congestion, and recurrent infections
    10. A high risk of anesthetic morbidity and mortality in patients with malignant osteopetrosis primarily related to airway and respiratory factors
    11. Manage osteomyelitis
        1. Pus drainage
        2. Appropriate antibiotic therapy
        3. Surgical debridement
        4. Reconstruction if indicated
    12. Patient with osteopetrosis with osteomyelitis in both jaws was treated prosthetically, and they fulfilled the requirements of the patient. Prosthetic rehabilitation included the separation of nasal cavity from oral cavity with obturator prosthesis in maxilla and the replacement of missing teeth with removable prosthesis in the mandible (Celakil et al. 2016)

13. Orthopedic cares: complicated by the difficulty of working with extremely hard, brittle, marble bone (Landa et al. 2007)
    1. Fracture fixation
        1. Difficulty inserting pins and screws
        2. Failure of load-bearing plate devices
        3. Increased time to union
    2. Arthroplasty
        1. Iatrogenic fracture during implant placement
        2. Increased risk of osteomyelitis
        3. Obliteration of medullary canal by cortical bone
    3. General considerations
        1. Overheating and breakage of drill bits
        2. Longer surgical time
14. Surgical management of the skeletal problems is reasonable in certain circumstances and is especially indicated for coxa vara and femoral neck fracture (Armstrong et al. 1999)
    1. For most long-bone fractures, nonoperative management works well.
    2. When surgery is required, technical problems due to extreme bone hardness are to be anticipated, and delayed or nonunion is more likely than average.
    3. Patients and surgeons must be aware that the ultimate outcome of surgery may be good, but the postoperative course can be unpredictable and prolonged.
15. Total joint arthroplasty is an effective treatment for painful hip and knee osteoarthritis in patients with osteopetrosis (Xie et al. 2015). Total hip and knee arthroplasty in a patient with osteopetrosis: a case report and review of the literature. *BMC Musculoskeletal Disorders, 16*, 259–263
16. Patients with profound hearing loss caused by osteopetrosis may benefit from cochlear implantation (Szymanski et al. 2015)
17. Corticosteroids and calcitriol (1,25-hydroxyvitamin D) with some short-term initial benefit but with debatable long-term benefit
18. Recombinant human gamma interferon (Eapen et al. 1998)
    1. Enhances bone resorption and leukocyte function (Key et al. 1995)
    2. Effects on morbidity and survival remain unclear
19. Bone marrow or peripheral blood stem cell transplantation
    1. Rational: Osteoclasts are derived from hematopoietic stem cells.
    2. Long-term disease-free survival has been achieved in approximately 70% of infants receiving transplants from matched sibling donors (Cheow et al. 2001).
        1. Repopulating the bones with functioning osteoclasts by successful infusion of donor marrow
        2. Beginning the process of remodeling and restoration of normal calcium homeostasis
        3. Radiographic changes of osteopetrosis expected to gradually returning to normal 4 months to 2 years following bone marrow transfusion
        4. Improvement and resolution of the rachitic changes: the first observation after bone marrow transplantation
        5. Immune recovery
        6. Improved growth
        7. Bone marrow transplant has been used with cure for infantile malignant osteopetrosis (Kocher and Kasser 2003)
20. Improving results with the use of high-dose peripheral blood stem cell grafts for infantile osteopetrosis from alternative donors, including those from parents mismatched for up to one half of their HLA-type (haploidentical)
21. So far, the only cure for children with severe osteopetrosis is allogeneic hematopoietic stem cell transplantation (HSCT), but without a matching donor this form of

therapy is far from optimal (Askmyr et al. 2008)

22. Early diagnosis and timely HSCT is the only curative treatment approach for malignant infantile osteopetrosis, an otherwise fatal disease (Essabar et al. 2014)
23. Patients with OP lacking HLA-matched donors can be successfully treated by transplantation of purified blood progenitor cells from HLA-haploidentical donors (Schulz et al. 2002)
24. Hematopoietic stem cell transplantation in patients with osteopetrosis: associated with disease-specific problems that require careful management, including the potential for life-threatening posttransplant hypercalcemia, a high prevalence of pulmonary arterial hypertension and, in at least one subtype of disease, failure to reverse osteosclerosis despite successful donor cell engraftment (Steward 2010)

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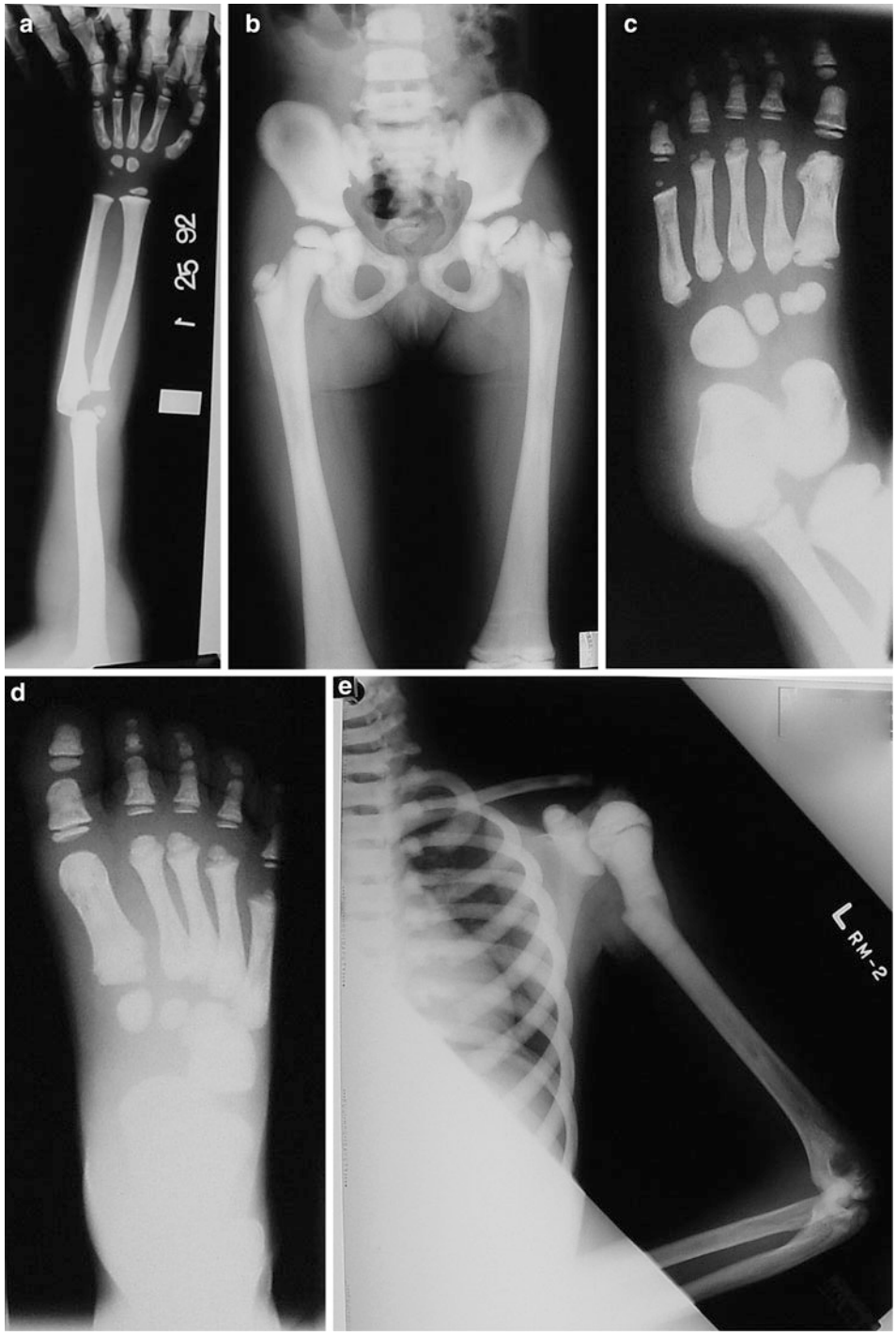

Fig. 1 (**a**–**e**) Radiographs of a girl with Albers-Schőnberg syndrome at 3 years (arm, pelvis, and foot) (**a**, **b**, **c**, **d**) and at 10 years (arm and chest) (**e**) showing sclerotic bones with loss of corticomedullary differentiation, fracture at the left humerus, and endobone appearance of phalanges of the hands and feet

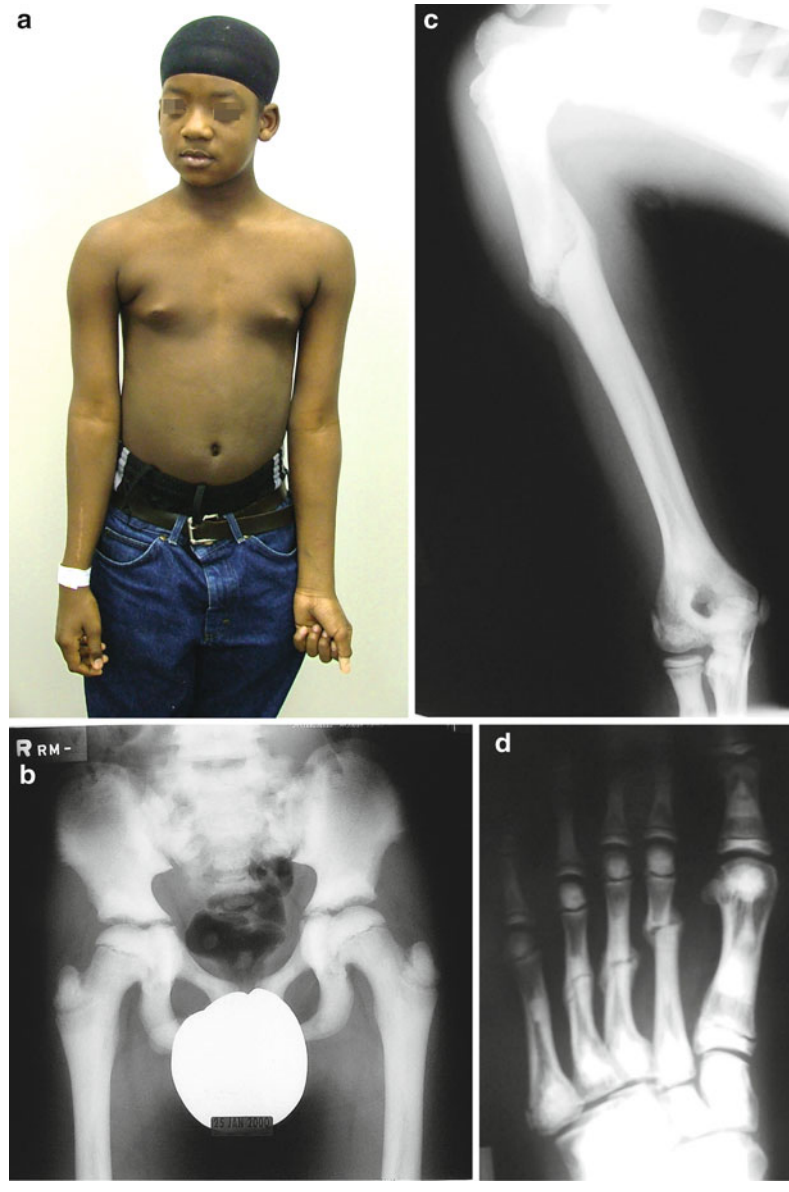

Fig. 2 (**a**–**d**) A 14-year-old boy (**a**) with osteopetrosis showing sclerotic bones with loss of corticomedullary differentiation and multiple fractures, illustrated by a series of radiographs (**b**–**d**)

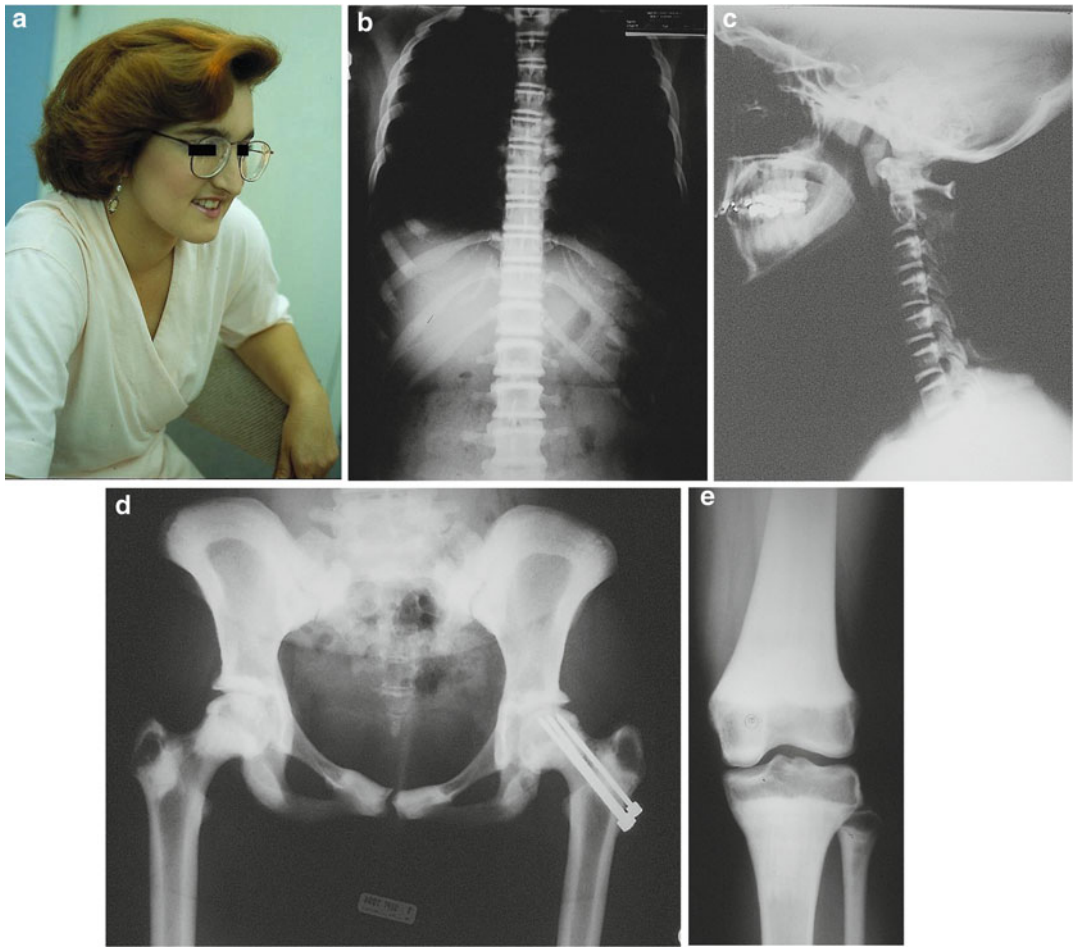

Fig. 3 (**a**–**e**) An adult female (**a**) with osteopetrosis showing generalized sclerotic bones with loss of corticomedullary differentiation including sandwich cervical vertebrae, illustrated by radiographs (**b**–**e**)

Osteopoikilosis

Contents

Osteopoikilosis was first described by Albers-Schönberg in 1915. It is a benign, usually asymptomatic condition diagnosed radiographically by the presence of multiple symmetrical circular/ovoid sclerotic opacities of the ischia, pubic bones, and the epimetaphyseal regions of the short tubular bones. The incidence is estimated as 1/50,000 (Cazzola et al. 1989).

Synonyms and Related Disorders

Buschke–Ollendorff syndrome (dermatofibrosis lenticularis disseminata); Melorheostosis; Mixed sclerosing bone dysplasia; Osteopathia condensans disseminata; Osteopathia striata (striped bone disease; Voorhoeve's disease); Osteosclerotic dysplasia; Spotted bone disease

Genetics/Basic Defects

1. Inherited in an autosomal dominant pattern (Korkmaz et al. 2015; Zhang et al. 2016).
2. Caused by loss of function mutation of LEM domain-containing three gene (*LEMD3*).
3. Usually occurs in isolation.
4. Osteopoikilosis in association with elastic or collagen connective tissue nevi of the skin: known as Buschke–Ollendorff syndrome (dermatofibrosis lenticularis disseminata).
5. In some families and individuals, osteopoikilosis can occur with other osteosclerotic skeletal disorders, such as melorheostosis and osteopathia striata.
6. Novel somatic mutation in *LEMD3* splice site results in Buschke–Ollendorff syndrome (BOS) with polyostotic melorheostosis and osteopoikilosis (Gutierrez et al. 2015).
7. The clinical overlap of BOS, osteopoikilosis, and melorheostosis is further supported by the involvement of *LEMD3* mutations in each diagnosis (Kadhim et al. 2015).
    1. *LEMD3* (LEM domain-containing 3) is a protein-coding gene that has been associated with hyperostotic bone disorders (BOS and osteopoikilosis).
    2. Mutations in this gene have been identified in families with osteopoikilosis, including some individuals, whose presentation is more consistent with melorheostosis, strongly suggesting a common genetic

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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cause (Hellemans et al. 2004; Couto et al. 2007; Mumm et al. 2007).
3. In addition, mutation of *LEMD3* gene has also been suspected to play a role in melorheostosis, although significant investigation to date has yet to identify *LEMD3* mutations in isolated melorheostosis. However, it is rare for sporadic individuals with melorheostosis to have mutations identified in the *LEMD3* gene (Hellemans et al. 2006). This is currently believed to likely be a result of somatic mosaic mutations that are present in the affected tissues, and not in blood, in a percentage lower than the current level of molecular detection (Zhang et al. 2009).

Clinical Features

1. Osteopoikilosis
    1. Presence of multiple osteosclerotic lesions in different parts of the skeleton (Lagier et al. 1984; Chigira et al. 1991; Carpintero et al. 2004).
        1. Epiphyses and metaphyses of long tubular bones
        2. Hands and wrists
            1. Phalanges
            2. Carpal bones
            3. Metacarpals
        3. Feet/ankles
            1. Phalanges
            2. Metatarsals
            3. Calcaneus
            4. Navicular bones
        4. Pelvis
        5. Scapulae
    2. An asymptomatic, uncommon osteosclerotic dysplasia: consists of multiple benign bone islands scattered throughout the axial and appendicular skeleton, typically clustered around the larger joints.
    3. A rare cause of bone pain (Mahbouba et al. 2015).
    4. Osteopoikilosis has been recognized as a condition associated with mixed sclerosing bone dysplasia.
        1. Mixed sclerosing bone dysplasia refers to when three relatively rare benign bone disorders occur in the same patient, occasionally all three at once.
        2. The bone disorders include:
            1. Osteopoikilosis
            2. Osteopathia striata (striped bone disease; Voorhoeve's disease)
            3. Melorheostosis (a condition typically involving one extremity with asymmetric marked cortical thickening that looks like dripping candle wax)
    5. Evident at any age (uncommon before the age of 3 years) and persists for life.
    6. Symmetric distribution.
    7. Generally asymptomatic.
    8. Joint inflammation and pain in about 15–20% of cases (Borman et al. 2002).
    9. Osteopoikilosis reported to coexist with other rheumatologic pathologies:
        1. Rheumatoid arthritis (Cazzola et al. 1989; Ureten 2007)
        2. Reactive arthritis (Mesci 2006)
        3. Discoid lupus erythematosus (Bicer et al. 2002)
        4. Familial Mediterranean fever (Kavukcu et al. 2003)
2. Melorheostosis (Butkus et al. 1997)
    1. A sporadic sclerosing bone condition.
    2. Melorheostosis can be present in a family with autosomal dominant osteopoikilosis (Nevin et al. 1999; Debeer et al. 2003).
    3. Manifesting in a sclerotomal distribution.
    4. Frequently affecting one limb.
    5. Usually asymptomatic.
    6. Pain, stiffness, leg-length discrepancy, and deformity in severe case.
    7. Radiographically, presence of cortical hyperostosis with thickening, resembling dripping candle wax.
3. Osteopathia striata
    1. Occurs in isolation or with cranial sclerosis
    2. A key radiographic feature: longitudinal striation of the metaphyses of the long bones
    3. Clinical features ranging from mild skeletal manifestation to multisystem organ involvement, even with the same family

1. Typical features
    1. Macrocephaly
    2. Cleft palate
    3. Hearing loss
2. Additional features
    1. Cardiac malformations
    2. Developmental delay
    3. Cranial nerve palsies
    4. Anal malformations
    5. Cataracts
    6. Nervous system malformations
    7. Cranial sclerosis (Savarirayan et al. 1997)

4. Buschke–Ollendorff syndrome (Pope et al. 2016)
    1. A rare, autosomal dominant disorder with high penetrance
    2. Caused by *LEMD3* gene mutation
    3. Typically a benign disorder that combines osteopoikilosis together with skin lesions consisting of connective tissue nevi (Buschke and Ollendorff 1928), juvenile elastomas (Uitto et al. 1981), or collagenous composition (dermatofibrosis lenticularis disseminata) (Foo and Kumarasinghe 2005)

Diagnostic Investigations

1. Radiographic features (Mclennan 1999).
    1. Often detected incidentally at radiographic examination: "pepper-pot/spotted bone" appearance (Hill and McKee 2015).
    2. Numerous, small, well-defined circular or ovoid sclerotic foci in a symmetric distribution.
        1. Usually seen in (Amezcua-Guerra et al. 2005):
            1. Epiphyses of short tubular bones
            2. Metaphyseal regions of long tubular bones
            3. Carpal bones
            4. Metacarpals
            5. Metatarsals
            6. Tarsal bones
            7. Sacrum
            8. Scapulae
            9. Iliac bones
        2. Rarely involved in (Mesci 2006):
            1. Skull
            2. Spine
            3. Ribs
            4. Clavicles
    3. The sclerotic lesions as described were in keeping with multiple benign bone islands (enostoses). When clustered around the joints and noted throughout the skeleton, the condition is known as osteopoikilosis (spotted bone disease) (Benli et al. 1992; Negi et al. 2013; Dasgupta and Thomas 2015; Perin et al. 2016).
    4. Differential diagnosis (Mclennan 1999).
        1. Sclerotic bone metastasis
            1. Nearly all tumors result in diffuse osteoblastic (sclerotic) bone metastases affect adults older than 40 years.
            2. The most common primary sites: the prostate (men) and breast (women).
            3. Other common primary sites in adults: the lungs, bladder (transitional cell carcinoma), bowel (malignant carcinoid tumor, mucinous adenocarcinoma), pancreas, and lymph system.
        2. Osteoma
            1. An osteoma is a benign localized mass of dense bone that develops in the periosteum of other bones.
            2. Osteomas typically appear as homogeneously dense foci of sclerosis along the outer cortex of both tubular and flat bones.
            3. Osteomas occur predominantly in the skull and facial bones, particularly in the paranasal sinuses.
        3. Hereditary multiple exostoses (also known as diaphyseal aclasis) (please see the chapter on "► Hereditary Multiple Exostoses")
            1. An autosomal dominant disorder resulting in numerous exophytic exostoses (osteochondromas) near the joints.

   2. The exostoses are usually palpable, but painless.
   3. These benign bony lesions develop in the distal diaphysis and metaphysis of long bones near the epiphyseal plate.
   4. They are most common around the knee and frequently occur around the elbow, scapula, pelvis, and ribs.
2. CT scan and MRI: used to support the diagnosis.
3. Whole-body bone scintigraphy.
   1. Typically normal (Tuncel and Caner 2012)
   2. Occasionally abnormal (Appenzeller et al. 2007), especially in younger patients (Borman et al. 2002; An et al. 2004)
4. SPECT (single-photon emission computerized tomography)/CT showed numerous sclerosing lesions devoid of significant Tc-99 m methylene diphosphonate (MDP) avid uptake (Tsai et al. 2016).
5. Bone biopsy: focal condensations of compact lamellar bone within the spongiosa (Benli et al. 1992).
6. In atypical cases of simultaneous occurrence of fibrotic skin lesions and "spotty bone" in the X-ray, genetic screening of the *LEMD3* gene is recommended (Brodbeck et al. 2016). A correct diagnosis of Buschke–Ollendorff syndrome is necessary to spare patients from expensive investigations and to provide reassurance about the benign nature of the disease (Surrenti et al. 2014).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: a low recurrence risk if parents are not affected
   2. Patient's offspring: a 50% of risk of having an affected offspring if the spouse is normal
2. Prenatal diagnosis: has not been reported
3. Management
   1. Usually, no treatment is required for the condition.
   2. Supportive treatment for joint inflammation or joint pain.

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Fig. 1 A 12-year-old boy with osteopoikilosis which was noticed incidentally from pelvic radiographic examination

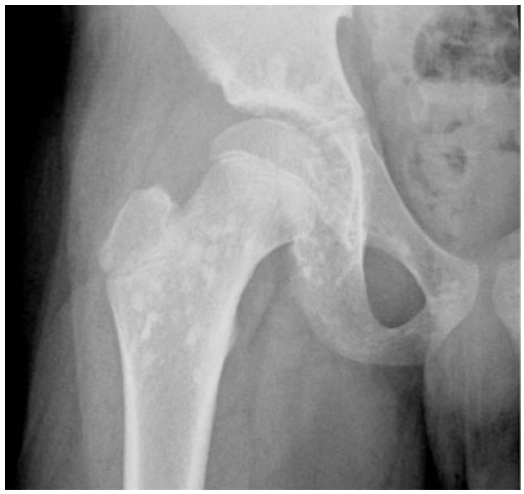

Fig. 2 Pelvic radiograph showed small, oval osteosclerotic bone lesions at the femoral head and neck and around the acetabulum of the pelvis and symphysis pubis

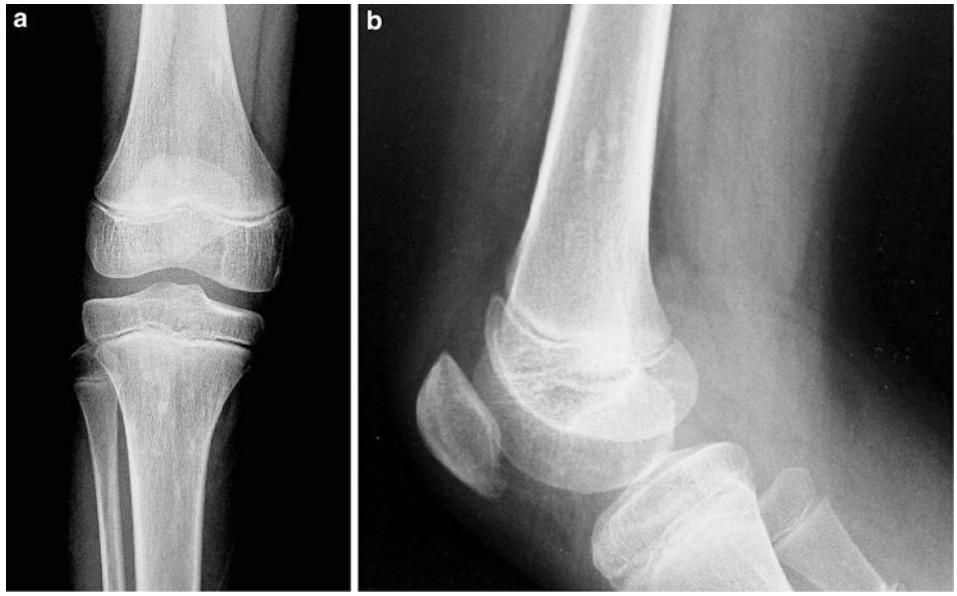

Fig. 3 (**a**, **b**) Oval osteosclerotic bone lesions on the proximal tibia and distal femur

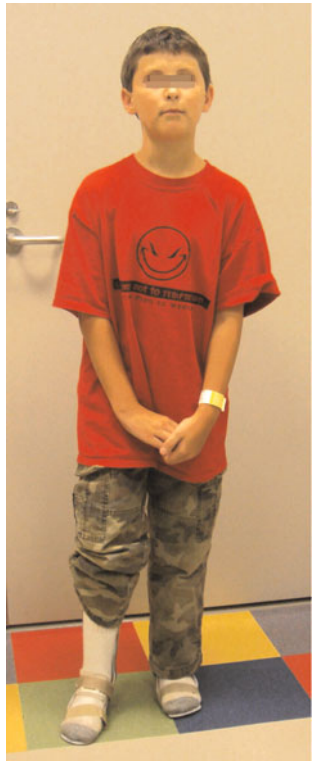

Fig. 4 A 9-year-old boy complained of pain on both ankles and feet. He was diagnosed to have osteopoikilosis from radiographic findings

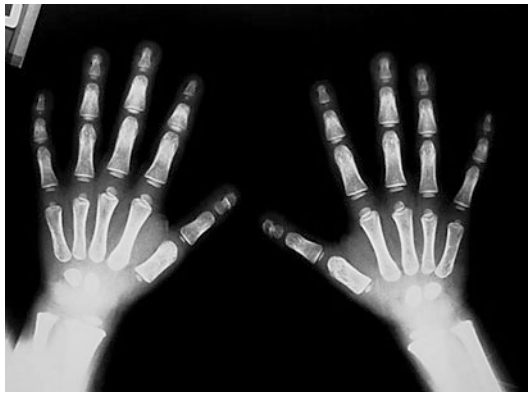

Fig. 5 Hand radiograph at age of 4 years showing multiple sclerotic lesions along the axis of phalanges and metacarpals

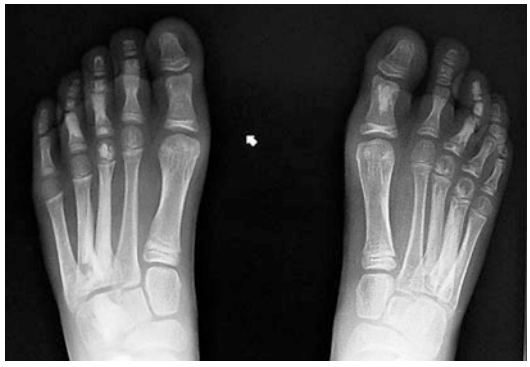

Fig. 6 Feet radiograph at age of 9 years showing multiple sclerotic lesions along the axis of several phalanges

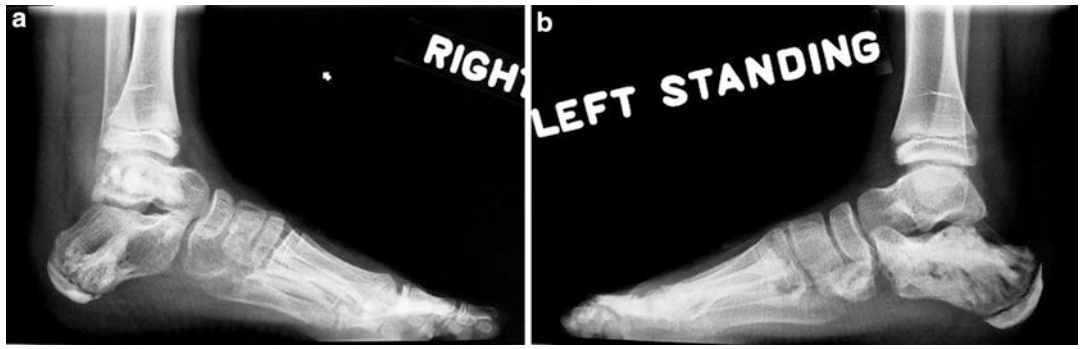

Fig. 7 (**a**, **b**) Lateral view of the feet at age of 9 years showing multiple sclerotic lesions at the calcaneus and talus bones

Otopalatodigital Spectrum Disorders

Contents

Otopalatodigital spectrum disorders, a heterogeneous group of disorders characterized primarily by a skeletal dysplasia of variable severity, include otopalatodigital syndrome type I (OPD I), otopalatodigital syndrome type II (OPD II), frontometaphyseal dysplasia (FMD), and Melnick-Needles syndrome (MNS).

Dudding et al. (1967) in *1967* described three male sibs with conduction deafness, cleft palate, characteristic facies, and a generalized bone dysplasia. In retrospect, the male patient described by Taybi (1962) may have the same condition. The syndrome is now known as OPD I.

Fitch et al. (1976) in *1976* described a familial syndrome of cranial, facial, oral, and limb anomalies in which two male infants have microcephaly, abnormal ears, antimongoloid slant, small mouth, cleft palate, flexed overlapping fingers with syndactyly of the second to the fifth toes, and normal karyotype. The name OPD II was proposed for this syndrome by Fitch et al. (1983).

Gorlin and Cohen (1969) in *1969* described a male patient with extraordinarily marked frontal hyperostosis giving great prominence to the supraciliary ridges, underdeveloped mandible, cryptorchidism, subluxated radial heads, and metaphyseal dysplasia resembling that in Pyle disease (metaphyseal dysplasia).

Melnick and Needles (1966) in *1966* described families having multiple cases in multiple generations of a severe congenital bone disorder characterized by typical facies (exophthalmos, full cheeks, micrognathia, and malalignment of teeth), flaring of the metaphyses of long bones, S-like curvature of bones of legs, irregular constrictions in the ribs, and sclerosis of base of skull.

In *2000*, Verloes et al. (2000) presented clinical evidence for a single entity encompassing FMD, MNS, and OPD I and II. Later, mutations in *FLNA*, a gene encoding the cytoskeletal protein filamin A, were found to be associated with otopalatodigital spectrum disorders.

Filamin A mutations cause periventricular heterotopia with Ehlers-Danlos syndrome (Sheen et al. 2005).

Synonyms and Related Disorders

FG syndrome; Frontometaphyseal dysplasia; Melnick-needles syndrome; Otopalatodigital syndromes type I and type II; Terminal osseous dysplasia; X-linked periventricular nodular heterotopia

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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Genetics/Basic Defects

1. Inherited as X-linked disorders (André et al. 1981; Robertson 2013).
2. Mutations in *FLNA* (Filamin A), a gene encoding the cytoskeletal protein filamin A, mapped on Xq28 (Robertson et al. 2001).
    1. Gain-of-function mutations in FLNA were found to be associated with a group of X-linked dysplasias designed as otopalatodigital (OPD) spectrum disorders (Parrini et al. 2015).
    2. Loss-of-function mutations of the *FLNA* gene cause a neuronal migration disorder defined as X-linked periventricular nodular heterotopia (PNH) (Fox et al. 1998; Robertson et al. 2003; Parrini et al. 2015).
    3. Co-occurring gain-of-function and loss-of-function provide an exceptional model to explain pathogenetic mechanisms leading to otherwise mutually exclusive allelic phenotypes (Robertson 2005; Parrini et al. 2015).
    4. Different mechanisms contribute to the pathogenesis of these conditions based on the contrast in phenotypic consequences between loss-of-function mutation (leading to periventricular nodular heterotopia) and clustered missense mutations (leading to otopalatodigital spectrum disorders).
3. The four otopalatodigital spectrum disorders are likely allelic based on previous clinical observations, despite remarkably diverse phenotypic presentations.
    1. Mild end of the spectrum: Affected males with OPD I have cleft palate and mild skeletal anomalies with conductive deafness caused by ossicular anomalies.
    2. Intermediate end of the spectrum: Affected males with frontometaphyseal dysplasia (FMD) have a propensity to develop stenosis of the subglottic region, ureters, and urethra in addition to skeletal anomalies.
    3. Severe end of the spectrum.
        1. Affected males with OPD II have more marked skeletal anomalies, CNS anomalies, and other congenital malformations.
        2. OPD II: caused by a novel filamin a 629G > T mutation (Mariño-Enríquez et al. 2007; Sankararaman et al. 2013).
    4. Most severe end of the spectrum: Affected males with MNS also have severe skeletal anomalies and other congenital malformations similar to OPD II leading to prenatal and perinatal lethality.
4. Genetically related (allelic) disorders (Moutton et al. 2016).
    1. Frontometaphyseal dysplasia: X-linked inheritance (Gorlin and Winter 1980).
        1. Severe manifestations in males
        2. Extremely variable manifestations in females
    2. Melnick–Needles syndrome (MNS) (Robertson et al. 1997, 2003): report of a family in which a woman and her three daughters exhibited a complex phenotype combining PNH, epilepsy and Melnick–Needles syndrome (MNS), a skeletal disorder assigned to the OPD spectrum (Parrini et al. 2015). All four individuals harbored a novel nonconservative missense mutation in *FLNA* exon 3.
    3. X-linked periventricular nodular heterotopia
        1. Presence of uncalcified nodules of neurons ectopically situated along the surface of the lateral ventricles.
        2. Affected individuals: predominantly heterozygous females; males show early lethality.
        3. Affected females.
            1. Seizures on average at age 14–15 years.
            2. Intelligence ranging from normal to borderline functioning.
            3. Increased risk for stroke and other vascular problems or coagulopathies.
        4. Germline mutations of *FLNA* leading to null alleles are found almost exclusively in females, whereas missense mutations or mosaicism for truncating mutations

can account for affected males or a mild phenotype in females.

4. A variant of X-linked periventricular nodular heterotopia with marked connective tissue dysfunction (skin fragility, vascular dilatation) described in females has been associated with mutations in *FLNA*, predicted to lead to loss of function.
5. Gastrointestinal dysmotility associated with periventricular nodular heterotopia associated with *FLNA* mutations.
6. A dual phenotype of periventricular nodular heterotopia and FMD in a female caused by a mutation variably leading to either a substitution or a small deletion as a result of aberrant splicing.
7. Myxomatous cardiac valvular dystrophy associated with X-linked periventricular nodular heterotopia: caused by *FLNA* mutations.
8. Fronto-otopalatodigital osteodysplasia: clinical evidence for a single entity encompassing Melnick-Needles syndrome, otopalatodigital syndrome types 1 and 2, and frontometaphyseal dysplasia. (Verloes et al. 2000)
9. Other syndromes
    1. Osseous dysplasia with intellectual disability, such as terminal osseous dysplasia (Sun et al. 2010)
        1. An X-linked dominant male-lethal disease caused by a single recurrent mutation in the *FLNA* gene.
        2. Characterized by skeletal dysplasia of the limbs, pigmentary defects of the skin, and recurrent digital fibroma with onset in female infancy.
    2. FG syndrome (Unger et al. 2007)
        1. Originally described as a rare syndromic cause of X-linked mental retardation associated with congenital heart disease, anal atresia, inguinal hernia, cryptorchidism, and other anomalies.
        2. However, recent reports have highlighted the more common milder presentation which has for cardinal features: developmental delay, particularly in speech; neonatal hypotonia; relative macrocephaly; dysmorphic facial features; severe constipation; and few if any congenital malformations.
        3. Filamin A mutation is one cause of FG syndrome.

Clinical Features

1. Periventricular heterotopia (Parrini et al. 2006)
    1. Phenotypic heterogeneity and correlation with Filamin A mutations
    2. Clinical features
        1. Contiguous heterotopic nodules
        2. Mega cisterna magna
        3. Cardiovascular malformations
        4. Epilepsy
2. Males with OPD I
    1. Skeletal anomalies
        1. Digital anomalies
            1. Thumbs: short, often proximally placed
            2. Distal phalanges of other digits: hypoplastic with a squared (or "spatulate") disposition to the finger tips
            3. Characteristic toes: hypoplasia of the great toe, a long second toe, and a prominent sandal gap
    2. Limitation of joint movement (elbow extension, wrist abduction) in almost all affected individuals
    3. Mild limb bowing
    4. Characteristic facial features
        1. Prominent supraorbital ridges
        2. Downslanting palpebral fissures
        3. Ocular hypertelorism
        4. Broad nasal bridge and nasal tip
    5. Deafness: secondary either to ossicular malformation, neurosensory deficit, or a combination of both

6. Cleft palate
7. Oligohypodontia
8. Normal intelligence

3. Females with OPD I (Gorlin et al. 1973)
   1. Exhibit variable expressivity
   2. Some females can be affected to a similar degree as affected, related males.
4. Males with OPD II (Sankararaman et al. 2013)
   1. Skeletal anomalies
      1. Thoracic hypoplasia: thin clavicles and wavy, irregular ribs
      2. Limb bowing
      3. Absent or hypoplastic fibulae
      4. Digital anomalies
         1. Most commonly hypoplasia of the first digit of the hands and feet
         2. Camptodactyly
      5. Restricted joint movements: demonstrated in at least 50% of the cases
      6. Cranium: usually shows a sclerotic base
      7. Delayed closure of the fontanels
   2. Characteristic craniofacial features
      1. Large anterior fontanels, prominent forehead, hypertelorism, downslanting palpebral fissures, stubby nose with flat root, small mouth, micrognathia, cleft palate (Pierre-robin sequence), and malformed or low set ears
      2. More pronounced than those in OPD I
   3. Cardiac septal defects and obstructive lesions to the right ventricular outflow tract in some affected individuals
   4. Associated anomalies
      1. Omphalocele (Young et al. 1993)
      2. Hydronephrosis secondary to ureteric obstruction
      3. Hypospadias
   5. Central nervous system anomalies
      1. Associated with X-linked cerebellar hypoplasia/hydrocephalus (Stratton and Bluestone 1991)
      2. Cerebellar hypoplasia
      3. Rare encephalocele and meningomyelocele
      4. Dandy-Walker malformation, bifid tongue, and corneal clouding (Murphy-Ryan et al. 2011)
   6. Developmental delay: common
   7. Death commonly in the neonatal period secondary to respiratory insufficiency
   8. Survival into the third year of life has been described with intensive medical treatment.
5. Females with OPD II (Gorlin et al. 1973)
   1. Usually present with a subclinical phenotype
   2. Characteristic craniofacial features
      1. Prominent supraorbital ridges and a broad nasal root and tip: most common findings
      2. Occasional conductive hearing loss
   3. Occasional females manifest a phenotype similar in severity to that of males (craniofacial dysmorphism, cleft palate, conductive hearing loss, skeletal and digital anomalies)
6. Males with FMD (Kanemura et al. 1979)
   1. Skeletal anomalies
      1. Digital anomalies
         1. Distal phalangeal hypoplasia
         2. Progressive contractures of the hand over the first two decades resulting in marked limitation of movement at the interphalangeal and metacarpophalangeal joints
      2. Joint limitation at the wrists, elbows, knees, and ankles
      3. Scoliosis
      4. Limb bowing
   2. Characteristic craniofacial features
      1. Pronounced supraorbital hyperostosis
      2. Ocular hypertelorism
      3. Downslanting palpebral fissures
      4. Rare cleft palate
   3. Frequent oligohypodontia
   4. Conductive and sensorineural hearing loss in almost all affected individuals
   5. Common underdevelopment of the musculature, most notably around the shoulder

girdle and in the intrinsic muscles of the hands
6. Extraskeletal anomalies
1. Subglottic stenosis presenting as congenital stridor
2. Hydronephrosis
7. Normal intelligence

7. Females with FMD
1. Characteristic craniofacial features similar to those of affected males.
2. Digital, subglottic, and urologic anomalies observed in males with FMD either do not occur in females or are observed in markedly attenuated form.

8. Males with MNS
1. A lethal multiple congenital malformation syndrome (Donnenfeld et al. 1987)
2. Usually present with a phenotype indistinguishable from, or more severe than, that associated with OPD II
3. Affected male fetuses born to several women with classic MNS have presented with a lethal phenotype reminiscent of a severe form of OPD II.
4. Some mildly affected males have been born to clinically unaffected parents.

9. Females with MNS (Dereymaeker et al. 1986)
1. Skeletal anomalies (osteodysplasty)
1. Short stature
2. Digital anomalies
1. Typically long phalanges of both hands and feet
2. Mild distal phalangeal hypoplasia
3. Thoracic hypoplasia
4. Limb bowing
5. Joint subluxation
6. Scoliosis
2. Characteristic craniofacial features
1. Prominent lateral margins of the supraorbital ridges
2. Exorbitism
3. Micrognathia
3. Frequent oligohypodontia
4. Common sensorineural and conductive deafness
5. Common hydronephrosis secondary to ureteric obstruction
6. Normal intelligence
7. Normal pubertal development

Diagnostic Investigations

1. Diagnosis of the OPD spectrum disorders is made by a combination of clinical examination, radiologic studies, family history consistent with X-linked inheritance, and molecular genetic testing (Robertson 2013).
2. Audiometry for hearing loss.
3. Renal ultrasound for renal tract anomalies.
4. Radiographic studies
1. Males with OPD I
1. Skull
1. Sclerosis of the skull base
2. Thickening of the calvaria
3. Underdevelopment of the frontal sinuses
4. Typically underpneumatized mastoids
5. Increased mandibular angle
2. Spine: Failure of fusion of posterior vertebral or neural arches, particularly in the cervical spine
3. Long bones
1. Mildly bowed upper and lower limbs
2. Common dislocation of the radial heads
4. Hands and feet
1. Characteristic accessory proximal ossification center of the second metacarpal
2. Characteristic short, broad first metacarpal and distal phalangeal hypoplasia most marked in the thumb
3. Presence of accessory carpal bones and fusion of carpal and tarsal bones
5. Pelvis: typically contracted with a lack of normal flaring of the ilia

2. Males with OPD II
    1. Skull: findings similar to those in OPD I but delayed in ossification pattern, manifesting as large fontanels in infancy
    2. Cervical spine
        1. Failure of fusion of the posterior neural or vertebral arches
        2. Segmentation anomalies
    3. Long bones: bowed upper and lower limbs with splaying of the metaphyses
    4. Hands and feet
        1. Abnormal modeling of the metacarpals and phalanges, more prominently on the radial side
        2. Hypoplastic or absent great toe
        3. Broad and poorly modeled phalanges and metatarsals
        4. Pelvis: hypoplastic, with lack of normal flaring of the ilia
3. Females with OPD II
    1. Characteristic sclerosis of the skull base and odontoid process
    2. Flared metaphyses of the long bones
    3. Digital anomalies: either absent or presence of hypoplasia of the first metacarpal or metatarsal
4. Males with FMD
    1. Skull.
        1. Sclerosis of the skull base
        2. Marked thickened calvarium
        3. Craniosynostosis
        4. Underpneumatization of the mastoids
        5. Hypoplasia or aplasia of the paranasal sinuses
        6. A spur arising from the anteroinferior tip of the mandible
    2. Spine.
        1. Fusion of vertebral bodies (especially C2-3-4)
        2. Deficiency of the posterior vertebral arches
    3. Thorax: Ribs can adopt a distorted shape (coat-hanger configuration) even though the thoracic cage is not hypoplastic.
    4. Long bones: undermodeled and frequently mildly bowed.
    5. Hands and feet.
        1. Carpal and tarsal fusions: common
        2. Erosion of the carpal bones: observed in adolescence and adulthood
        3. Metacarpals, metatarsals, and phalanges: elongated and poorly modeled
        4. Distal phalanges of the thumb and great toes: hypoplastic
5. Females with FMD: exhibit the same cranial and long bone features as males, but to a lesser degree
6. Females with MNS
    1. Skull
        1. Sclerotic skull base
        2. Delayed closure of the fontanels
    2. Spine
        1. Vertebral bodies: increased in height, especially in the lumbar region
        2. Scoliosis: common
    3. Thorax
        1. Ribs: irregular in contour and form
        2. Clavicle: similarly wavy and irregular, with some expansion of its proximal end
    4. Long bones: bowed both limbs with marked cortical irregularity
    5. Hands and feet: elongated and undermodeled phalanges, metacarpals, and metatarsals
    6. Pelvis: exhibits a supra-acetabular constriction with flaring of the ilia
5. Molecular genetic testing
    1. *FLNA* is the only gene currently known to be associated with the otopalatodigital (OPD) spectrum disorders.
    2. Sequence analysis of entire coding region and of select exons: available clinically for confirmation of the diagnosis in the proband and carrier testing of the relatives.
    3. Both somatic and germline mosaicism in FLNA leading to periventricular nodular heterotopia (PVNH) have been observed and have been associated with modulation of the severity of the phenotype and survivorship in males (Guerrini et al. 2004; Parrini et al. 2004; Robertson 2007).
        1. Germline mosaicism has been observed in association with OPD I.
        2. Somatic mutation has been shown to have led to MNS, suggesting similar

processes may modulate the expression of OPD spectrum phenotypes (Robertson et al. 2006).

Genetic Counseling

1. Recurrence risk (Robertson 2013)
    1. Sibs of a male proband with OPD I, OPD II, or FMD: Risk depends on the genetic status of the parents.
        1. Mother is a carrier.
            1. A 50% risk to her son to receive the disease gene and express the disease.
            2. A 50% risk to her daughter to receive the disease gene and become a carrier with a range of possible phenotypic expression.
            3. Mother of an affected child, regardless of proven carrier status, has an increased risk of having an affected male fetus due to presence of maternal germinal mosaicism.
        2. Father has an *FLNA* mutation.
            1. All female sibs will inherit the mutation.
            2. Male sibs will not inherit the mutation.
    2. Sibs of a proband with MNS: Risk depends upon the genetic status of the mother.
        1. Mother has the gene mutation.
            1. A 50% chance of transmitting the *FLNA* mutation to each child.
            2. Male sibs who inherit the mutation will be affected and generally dies prenatally or perinatally.
            3. Female sibs who inherit the mutation will have a range of phenotypic expression.
        2. Mother is clinically unaffected: Risk to sibs appears to be low but greater than that of the general population due to possible parental germline mosaicism.
    3. Patient's offspring
        1. Males with OPD II do not reproduce.
        2. Males with OPD I or FMD transmit the disease-causing mutation to all of their daughters and none of their sons.
        3. Females with OPD I, OPD II, or FMD.
            1. A 50% chance of transmitting the disease-causing mutation to each child.
            2. Sons who inherit the mutation will be affected.
            3. Daughters will have a range of possible phenotypic expression.
        4. Males with MNS usually die prenatally or perinatally and do not reproduce.
        5. Females with MNS
            1. A 50% chance of transmitting the disease-causing mutation to each child.
            2. Sons who inherit the mutation will be affected and generally die prenatally.
            3. Daughters will have a range of possible phenotypic expression.
2. Prenatal diagnosis
    1. Prenatal ultrasonography: Prenatal ultrasound diagnoses of OPD II in a fetus of an affected mother and in a fetus of a normal mother (Eccles et al. 1994) have been reported.
    2. A report of a series of 10 fetuses and a neonatally deceased newborn displaying a multiple congenital anomalies syndrome suggestive of otopalatodigital spectrum disorders (OPDSD), in whom *FLNA* analysis was performed (Naudion et al. 2016).
        1. A global mutation rate of 44% was found.
        2. This series allows expanding the clinical and *FLNA* mutational spectrum in OPDSD. However, it was emphasized that difficulties to correctly discriminate OPDSD based on clinical criteria in fetuses are due to the major overlap between these conditions.
        3. Molecular analyses may help pathologists to refine clinical diagnosis according to the type and the location of *FLNA* mutations.
        4. Discriminating the type of OPDSD is of importance in order to improve the

genetic counseling to provide to families.

3. Fetal phenotype in OPDSD (Naudion et al. 2016).
    1. Hypertelorism, flat nose, microretrognathia, first ray hypoplasia, syndactyly, hydronephrosis/oligohydramnios due to urethral obstruction, and cerebellar hypoplasia are the strongest criteria to suggest OPD2 in fetuses.
    2. X-ray findings: uninformative (only splayed metaphyses in a single fetus) as they probably become progressively more obvious during development.
    3. Moreover, one fetus and the previously described fetus with the recurrent MNS mutation (infant 2 from Santos et al. 2010) confirm the neurological anomalies (white matter hemorrhage, leukomalacia, cerebellar neuronal heterotopias, Dandy–Walker malformation); cleft palate and eye anterior segment anomalies may also be observed in MNS.
    4. Sclerocornea has been described in at least two other males with lethal MNS (Santos et al. 2010) and one male patient who died at the age of 9 months (Verloes et al. 2000), while Peters anomaly was identified in a neonatally deceased male (Weh et al. 2014). These ocular anomalies are likely to be part of the phenotypic spectrum of severe OPDSD.
    4. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.
3. Management
    1. Hearing aids for deafness.
    2. Stridor in the neonatal period due to laryngeal stenosis rarely requires surgical intervention and is nonprogressive.
    3. Cosmetic surgery to correct the frontoorbital deformity attempted in some individuals with good results. Regrowth postsurgery does not seem to occur (Kung and Sloan 1998).
    4. Surgery to correct hand and foot malformations and scoliosis.
    5. Chest expansion surgery attempted in several individuals with Melnick-Needles syndrome, with only marginal clinical benefit.
    6. Continuous positive airway pressure (CPAP) for prevention of airway collapse and sleep apnea secondary to micrognathia and tracheobronchomalacia in severely affected individuals. Melnick-Needles syndrome with obstructive sleep apnea successfully treated with nasal continuous positive airway pressure ventilation (Lan et al. 2006).
    7. Anesthetists should be aware of the associated laryngeal stenosis, if intubation and ventilation are required (Leggett 1988; Mehta and Schou 1988).

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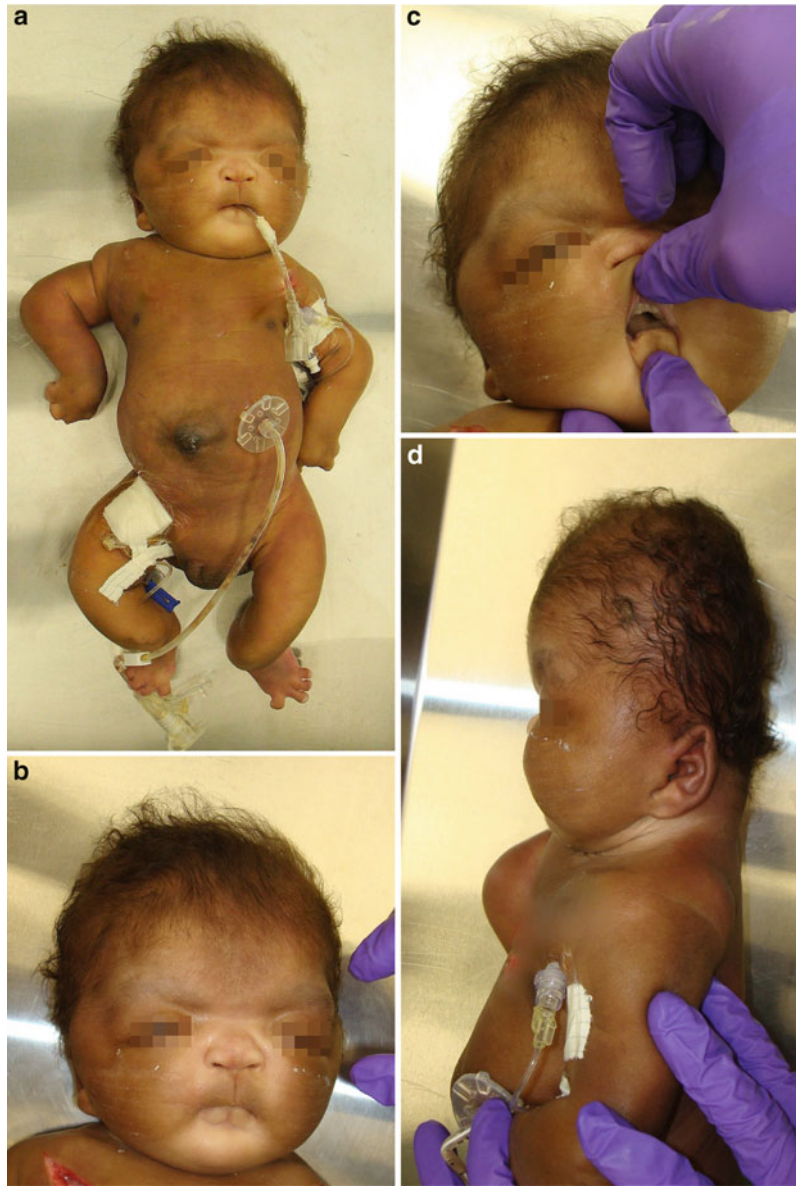

Fig. 1 (**a**–**d**) A 2-month-old premature (33-week gestation) male infant has multiple congenital anomalies (**a**–**d**), consisting of marked brachycephaly (**b**), widely opened anterior fontanel, short neck with redundant nuchal skin, severe downslanting palpebral fissures, arched eyebrows, a small and flat nose, an extremely small mouth with posterior inverted U-shaped cleft palate (**d**), a groove present at philtrum site and lower lip areas (**c**), low-set, posteriorly rotated malformed ears (**b**), a short sternum, a large umbilical hernia, and hypoplastic scrotum with undescended testicles. Marked limb anomalies (**a**) are noted: mildly bowed upper arms and forearms, flexed hands with ulnar deviation and overlapping fingers, and duplicated fifth fingers with clinodactyly, bowing of upper and lower legs, and dorsiflexed feet with four toes each with medially deviated great toes and laterally deviated second through fourth toes. Clinical, postmortem, and radiological findings are consistent with otopalatodigital type II syndrome. DNA testing identified two hemizygous missense mutations: c.613 T > C (p.Cys-205-Arg) and c.5290 G > A (p. Ala-1764-Thr) in the *FLNA* gene (Sankararaman et al. 2013). The first sequence variation is previously reported to be associated with periventricular heterotropia. The significance of the second sequence variant is unknown. *FLNA* mutations with presumed gain of function are previously reported in association with four other disorders: otopalatodigital syndrome type I and II, frontometaphyseal dysplasia, and Melnick-Needles syndrome

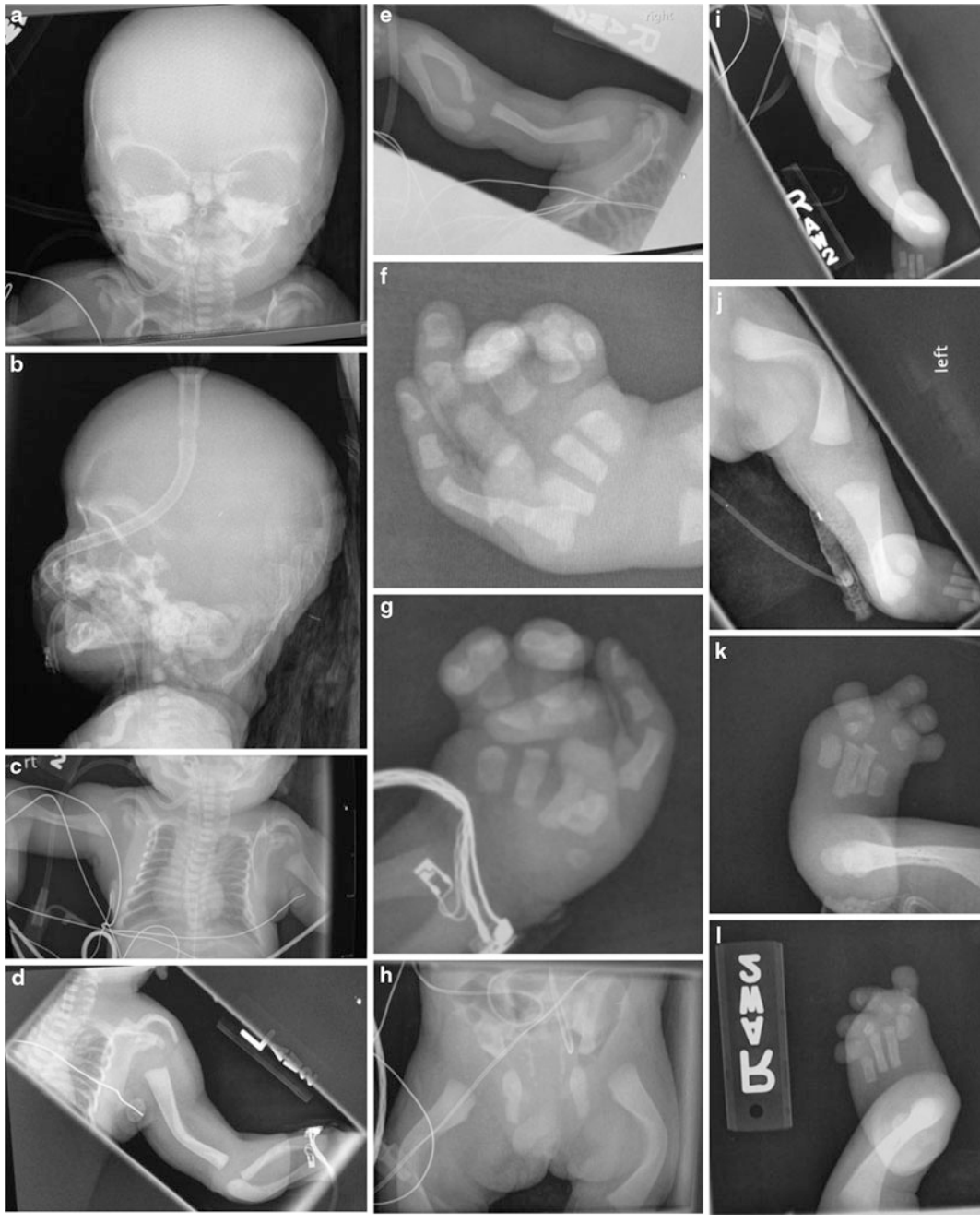

Fig 2 (**a**–**l**) Radiographs show skull (**a**, **b**), hypoplastic scapulae, curved humeri, radii, and ulnae (**c**–**e**), duplicated fourth fingers with four unusually shaped metacarpals and phalanges (**f**, **g**), markedly bent femora (**h**–**j**), bent tibiae, unossified fibulae (**i**, **j**), and four toes in each foot (**k**, **l**) with unusually shaped metatarsals and phalanges

Pachyonychia Congenita

Contents

Pachyonychia congenita (PC) is a group of rare genetically inherited diseases characterized by nail dystrophy and by varying features of ectodermal dysplasias. There are two major clinical subtypes recognized: type I with oral leukokeratosis and type II with multiple pilosebaceous cysts (Çelebi et al. 1999).

Synonyms and Related Disorders

Pachyonychia congenita tarda; PC-1 (Jadassohn-Lewandowsky syndrome); PC-2 (Jackson-Lawler syndrome)

Genetics/Birth Defects

1. Inheritance (Çelebi et al. 1999; Conners et al. 2001):
    1. Type I pachyonychia congenita (Jadassohn-Lewandowsky type):
        1. Autosomal dominant inheritance
        2. Possible autosomal recessive inheritance (Haber and Rose 1986)
    2. Type II pachyonychia congenita (Jackson-Lawler type): autosomal dominant
2. Etiology (McLean et al. 1995; Munro 2001; Terrinoni et al. 2001; Eliason et al. 2012):
    1. Type I – caused by mutations in genes encoding one of the paired keratins of specialized epidermis, KRT6a (Smith et al. 1999a; Forrest et al. 2016) or KRT16 (Smith et al. 1999b), resulting in:
        1. Fragility of specific epithelia.
        2. Phenotypes of pachyonychia congenita I or focal nonepidermolytic palmoplantar keratoderma with insignificant nail changes.
        3. The novel mutation in the KRT6A confirms the role of this gene in causing early severe forms of PC and supports the adoption of a classification system based upon the mutant gene for a disease which may span from mild localized (focal) to extensive mucocutaneous manifestations (Cammarata-Scalisi et al. 2016).
    2. Type II – caused by mutations in genes encoding one of the paired keratins of specialized epidermis, KRT6b (Smith et al. 1998) or KRT17 (Feng et al. 2003):
        1. Linkage analysis mapped pachyonychia congenita type II phenotype within the

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type I keratin gene cluster on chromosome 17q12-21 (Munro et al. 1994).
    2. A germline mutation has been identified in keratin 17 gene (K17).
    3. Colocalization of K17 with keratin 6b.
3. Genotype-phenotype correlation:
    1. Differences in type I and type II phenotypes: largely explainable by the difference in expression patterns between the K6a/K16 and K6b/K17 expression pairs
    2. K6b/K17 expresses at higher levels in the pilosebaceous unit than K6a/K16: responsible for the pilosebaceous cysts in type II
    3. Conversely, K6a/K16 more widely expressed in oral epithelia: responsible for the greater predominance of oral leukokeratosis in type I

Clinical Features

1. Presence of intra- and interfamilial phenotypic variation (Feinstein et al. 1988).
2. Pachyonychia congenita type I (56.2% of cases):
    1. The most common subtype
    2. Onset in infancy
    3. Severe nail dystrophy affecting all the nails symmetrically (Dogra et al. 2002):
        1. The best hallmark of the disease.
        2. Thickened wedge-shaped nails.
        3. Proximal portions of the nails: smooth and normally attached to the lateral nail folds.
        4. Distal portions of the nails: may increase to many times the normal thickness, producing a subungual keratinous mass that pushes the nail plate upward, arching it transversally, folding it longitudinally, and elevating it distally.
        5. Nails commonly shed and regrow with similar but more severe changes.
        6. Projections from the nail beds make the nails susceptible to trauma with consequent chronic paronychial infections.
    4. With or without following associated anomalies (Munro 2001):
        1. Focal nonepidermolytic palmoplantar keratoderma (predominantly a feature of type I)
        2. Follicular keratoses observed on:
            1. Temple
            2. Eyebrows
            3. Extensor aspect of the proximal parts of the extremities
        3. Hyperkeratosis of palms, soles, knees, and elbows
        4. Localized foot blistering
        5. Oral leukokeratosis: a prominent sign
        6. Neonatal teeth
        7. Blister formation on palms and soles
        8. Hoarse voice due to laryngeal involvement (leukokeratosis)
        9. Palmar and plantar hyperhidrosis
3. Pachyonychia congenita type II (24.9% of cases) (Munro 2001):
    1. Nail dystrophy
    2. Less pronounced or absent palmoplantar keratoderma and oral changes
    3. Follicular keratoses
    4. Oral leukokeratosis
    5. Multiple pilosebaceous cysts (most useful distinguishing feature for type II but usually occurring at puberty):
        1. Epidermoid or infundibular cysts (arising from the hair follicle infundibulum)
        2. Eruptive vellus hair cysts and multiple steatocystomas (characteristic of type II) (arising from the sebaceous duct epithelium) (Moon et al. 1994; Smith et al. 1997)
    6. Bullae of palms and soles
    7. Palmar and plantar hyperhidrosis
    8. Natal or neonatal teeth
    9. Pili torti in children
    10. Bushy eyebrows
    11. Hidradenitis suppurativa
4. Pachyonychia congenita type III (Schafer-Brunauer type) (11.7%):
    1. Features of type I and type II
    2. Angular cheilosis
    3. Leukokeratosis of the cornea
    4. Cataracts
5. Pachyonychia congenita tarda (type IV) (7.2%) (Lucker and Steijlen 1995; Mouaci-

Midoun et al. 1996; Hannaford and Stapleton 2000):
   1. A rare form of pachyonychia congenita
   2. Features of type I, type II, and type III
   3. Laryngeal lesions
   4. Hoarseness
   5. Mental retardation
   6. Hair anomalies
   7. Alopecia
   8. Nail changes occurring in the second or third decade
   9. Abnormal painful nails
   10. Palmoplantar keratoderma
6. Pachyonychia congenita with early-onset nail changes in the absence of other associated features.
7. Among patients with a detectable mutation, PC manifests with nail thickening and plantar keratoderma before school age in more than three-quarters of affected children, allowing early diagnosis. The highly visible nail changes and painful plantar thickening exert a psychosocial effect on most affected adolescents (Shah et al. 2014).
8. Differential diagnosis (Smith et al. 2014):
   1. Onychomycosis:
      1. Although the hyperkeratotic nail thickening seen in pachyonychia congenita may be mistaken for onychomycosis, dermatophytic infections do not affect all finger and toenails particularly at an early age.
      2. In the rare conditions of autoimmune endocrinopathy-candidiasis-ectodermal dystrophy and systemic mucocutaneous candidosis, all nails may be affected.
   2. Oral leukokeratosis together with nail dystrophy: often an indication of pachyonychia congenita and may be mistaken for *Candida albicans* (thrush), white sponge nevus, and/or leukoplakia.
   3. Epidermolysis bullosa simplex (please see the chapter "► Epidermolysis Bullosa") or other palmoplantar keratodermas can result in a similar pattern of plantar blister formation or hyperkeratosis, respectively; however, they do not share the characteristic nail changes of PC.
   4. Clouston syndrome, caused by mutation of *GJB6*, the gene encoding the gap junction protein connexin 30, can also mimic PC. Alopecia does not typically occur in PC but is a relatively common feature of Clouston syndrome.
   5. Nonsyndromic congenital nail disorder 10 without the associated palmoplantar keratoderma or other features of PC can be confused with PC. This is an autosomal recessive disorder caused by biallelic pathogenic variants in *FZD6*, encoding frizzled 6 (Wilson et al. 2013).
   6. Familial onychogryphosis without the associated palmoplantar keratoderma or other features of PC can be confused with PC. Individuals who have nail findings only are unlikely to demonstrate mutation in one of the PC keratins.
   7. Twenty-nail dystrophy may occur without keratoderma or other associated changes. Autosomal dominant inheritance has been described.
   8. Dyskeratosis congenita manifests with features overlapping with PC including nail dystrophy, palmoplantar keratoderma (PPK), hyperhidrosis, and oral leukoplakia. Distinctive features include reticulate hyperpigmentation, skin tumors, and hematologic manifestation.
   9. Palmoplantar keratoderma striata (PPKS1), caused by pathogenic variants in *DSG1*, can be confused with focal nonepidermolytic palmoplantar keratoderma (FNEPPK). However, pain is typically either absent or less significant in PPKS1 than in FNEPPK or PC.
   10. Punctate PPK type I, caused by pathogenic variants in *AAGAB*, can be painful and focal (due to coalescence of lesions) (Pohler et al. 2012).
   11. Olmsted syndrome is characterized by painful palmoplantar keratoderma that may occur with additional features including periorificial keratotic plaques and sometimes constricting digital bands on hands and feet that result in spontaneous amputation, mutilating PPK, alopecia, nail

dystrophy, and itching of lesions. It is caused by pathogenic variants in *TRPV3* (Lin et al. 2012).

9. Genodermatoses with nail involvement (Lawry and Ralph 2005; Tosti et al. 2006; Irvine and Mellerio 2010; Inamadar and Palit 2012):
    1. Genodermatoses with characteristic nail changes:
        1. Pachyonychia congenita:
            1. Thick, yellowish-brown-colored nails present at birth or developed during neonatal period with or without natal teeth are pointers to the diagnosis of PC.
            2. Dystrophy of all the twenty nails is a feature common to all the three variants of PC, but other features may be variable.
            3. Upward angulation of the distal free edge of the thickened nail plate (progressive distal thickening) is a distinct feature and helps to differentiate it from other disorders with thick nails.
            4. Recurrent painful paronychia may be associated.
        2. Nail-patella syndrome (please see the chapter "► Nail-Patella Syndrome"):
            1. Anonychia or nonprogressive micronychia (mostly involving thumb and index fingers) present since birth and triangular lunula with distal apex in the midline are highly predictive of nail-patella syndrome.
            2. Nail hypoplasia is more marked on the ulnar sides of the involved fingers.
        3. Yellow nail syndrome: Upper and lower respiratory tract illnesses (sinusitis/bronchitis/recurrent bilateral pleural effusion/bronchiectasis) and primary lymphedema (80%) (Hawsawi and Pope 2010) in combination with thickened, yellow nails are the clues for clinical diagnosis of yellow nail syndrome.
        4. Porphyrias (congenital erythropoietic porphyria, erythropoietic protoporphyria, porphyria cutanea tarda): Photo-onycholysis and marked koilonychia are the characteristic features of various hereditary porphyrias.
    5. Neurocutaneous syndromes:
        1. Tuberous sclerosis complex (please see the chapter "► Tuberous Sclerosis"): Garlic-clove fibromas (Koenen tumor) are multiple, elongated, pink- or flesh-colored tumors with hyperkeratotic tips, arising from beneath the proximal and lateral nail folds (periungual) producing longitudinal midline depression on nail plate. Such lesions appearing at puberty, along with facial angiofibromas and hypopigmented ash-leaf macules, are characteristic of tuberous sclerosis complex.
        2. Osler-Weber-Rendu syndrome: Telangiectasia of nail bed, visible as blanchable, punctate red dots, should prompt the clinician to screen the patient for Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia). These may bleed to give rise to splinter hemorrhage.
        3. Ataxia telangiectasia (please see the chapter "► Ataxia-Telangiectasia").
    6. Disorder of keratinization (Darier's disease): "V"-shaped notch on the free edge of the nail plate and alternate longitudinal red (erythronychia) and white (leukonychia) bands are the distinct features of Darier's disease. Splinter hemorrhages may be associated.
2. Genodermatoses with significant nail changes:
    1. Disorder of keratinization:
        1. Trichothiodystrophy: brittle nails, ridging and splitting of nail plate, nail dystrophy, yellow discoloration, onychogryphosis, and koilonychia. Diffuse alopecia, dental caries, and ichthyosis are the main clinical features.
        2. Bazex's syndrome: Psoriasiform nail changes (thickening and discoloration of nail plate, subungual hyperkeratosis, splinter hemorrhage) are

seen in all types of palmoplantar keratoderma and Bazex's syndrome but are not diagnostic of these disorders.
3. Marked nail changes are seen in transgradient keratodermas like Mal de Meleda, scleroatrophy of Huriez, and Olmsted syndrome.

2. Mechanobullous disorders:
1. Nail changes are milder in EB simplex, like nail dystrophy and onychomadesis. Onychogryphosis of great toenails may be a feature of EB (epidermolysis bullosa) simplex, Ogna variant (Tosti and Piraccini 2005).
2. Severe nail changes like onychodystrophy and anonychia are seen in junctional and dystrophic EB.

3. Poikilodermatous disorders:
1. Kindler syndrome: Gross nail dystrophy and pseudosyndactyly may be observed in patients with Kindler syndrome.
2. Dyskeratosis congenita: Nail dystrophy may be the initial presenting feature (evident by 5–13 years of age) of patients with dyskeratosis congenita.

4. Congenital immunodeficiency: Markedly dystrophic nail plate and recurrent tender paronychia in a child with associated oral thrush warrant screening for chronic mucocutaneous candidiasis.
5. Disorder of pigmentation (incontinentia pigmenti) (please see the chapter "► Incontinentia Pigmenti"): Periungual warty lesions with underlying osteolysis may appear in patients with incontinentia pigmenti during adolescence.

3. Genodermatoses with nonspecific nail changes:
1. Ectodermal dysplasia: Various hypoplastic nail changes (onychodystrophy, micronychia/anonychia) with variable combinations of hypotrichosis or alopecia, hypohidrosis, palmoplantar keratoderma, and dental anomalies are seen in patients with ectodermal dysplasia (Irvine and Mellerio 2010).
2. Disorders of pigmentation:
1. Cronkhite-Canada syndrome: characteristic nail dystrophy due to formation of ventral nail in the absence of normal nail production by the nail matrix
2. Peutz-Jeghers syndrome: punctate brown spots or longitudinal pigmented bands on nails
3. Laugier-Hunziker syndrome: longitudinal brownish bands on nails with adult-onset macular pigmentation of lips and buccal mucosa
4. LEOPARD syndrome (please see the chapter "► LEOPARD Syndrome"): koiloleukonychia

3. Poikilodermatous disorder (Rothmund-Thomson syndrome): Nails may be small and dystrophic.
4. Disorder of keratinization (KID syndrome): onychodystrophy.
5. Neurocutaneous disorders (neurofibromatosis type I) (please see the chapter "Neurofibromatosis Type 1"): "pterygium inversus unguium"-like changes.
6. Metabolic disorders:
1. Fucosidosis: onychogryphosis
2. Fabry disease: "turtle back configuration" of nails

7. Disorder with premature aging (progeria): onychodystrophy.

Diagnostic Investigations

1. Histology and ultrastructure of cutaneous and oral lesions: suggest a keratin disorder (Munro 2001)
2. Molecular analyses of mutations in KRT6A, KRT6B, KRT6C, KRT16, or KRT17 (Wilson et al. 2014): confirmed, at the molecular level, the clinical diagnosis of PC (Wilson et al. 2014)
3. Whole exome sequencing to establish the correct diagnosis (Almutawa et al. 2015)

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib:
      1. Autosomal dominant inheritance: not increased unless a parent is affected
      2. Autosomal recessive inheritance: 25%
   2. Patient's offspring:
      1. Autosomal dominant inheritance: 50%
      2. Autosomal recessive inheritance: not increased unless the spouse is a carrier
   3. Counseling of unaffected parents with a first child diagnosed as having PC should entail a discussion of the possibility of germ cell mosaicism contributing to an increased risk of having subsequent affected children (Pho et al. 2011).
   4. Homozygous or compound heterozygous mutations should be especially sought in PC patients who present with alopecia (Irvine 2012). As four keratin genes are involved in dominant PC, bigenic inheritance is also a possibility (Wilson et al. 2012).
2. Prenatal diagnosis: genomic mutation detection possible in prenatal diagnosis of pachyonychia congenita type I (KRT6a/KRT16) or type II (KRT6b/KRT17) by CVS or amniocentesis.
3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified.
4. Management (Dahl et al. 1995):
   1. No ideal treatment for the thickened nail plate available.
   2. Topical lubricants and keratolytics (Su et al. 1990): indicated to areas of palmar and plantar hyperkeratosis but usually produces only transient benefit. Squamous cell carcinoma developed in one of the patients over the site of chronic plantar ulcerations. Areas of chronic bullous formation or ulceration should be observed for possible skin malignancy.
   3. Antiseptic wet dressings for secondarily infected areas.
   4. Systemic treatment with acitretin producing variable and inconsistent results with caution of side effects (teratogenicity and hyperostosis).
   5. Two patients with genetically confirmed PC type I were treated with plantar injections of botulinum toxin type A. Both patients showed a marked improvement in pain and blistering with an average response time of 1 week, a 6-month mean duration of effectiveness, and a lack of any side effects or tachyphylaxis (González-Ramos et al. 2015).
   6. Gabapentin and plantar injections of botulinum toxin combined with psychological counseling, cognitive behavioral therapy, and physical therapy were all useful in alleviating chronic foot pain in a pediatric patient (Tariq et al. 2016).
   7. Custom-fitted footwear for protective support of painful fissures and blisters on the soles.
   8. Simple avulsion of the distorted nails is inadequate because the dystrophic nail regrows.
   9. Curettage and electrofulguration or surgical excision of the nail matrix and bed can improve function and appearance.
   10. Surgical excision of focal, hyperplastic epithelial mass results in improvement of hoarseness due to laryngeal obstruction by laryngeal lesions. Additional microsurgery may be necessary for the recurrence of the laryngeal lesions.
   11. Therapeutic small interfering RNAs (siRNAs) for pachyonychia congenita (Leachman et al. 2008):
      1. A new siRNA entering clinical trials in PC patients with the *KRT6A* N171K mutation, with a gene-specific *KRT6A* siRNA study possibly to follow.
      2. This is the first-in-man siRNA therapeutic trial for a skin indication and the first siRNA to target a gene mutation.

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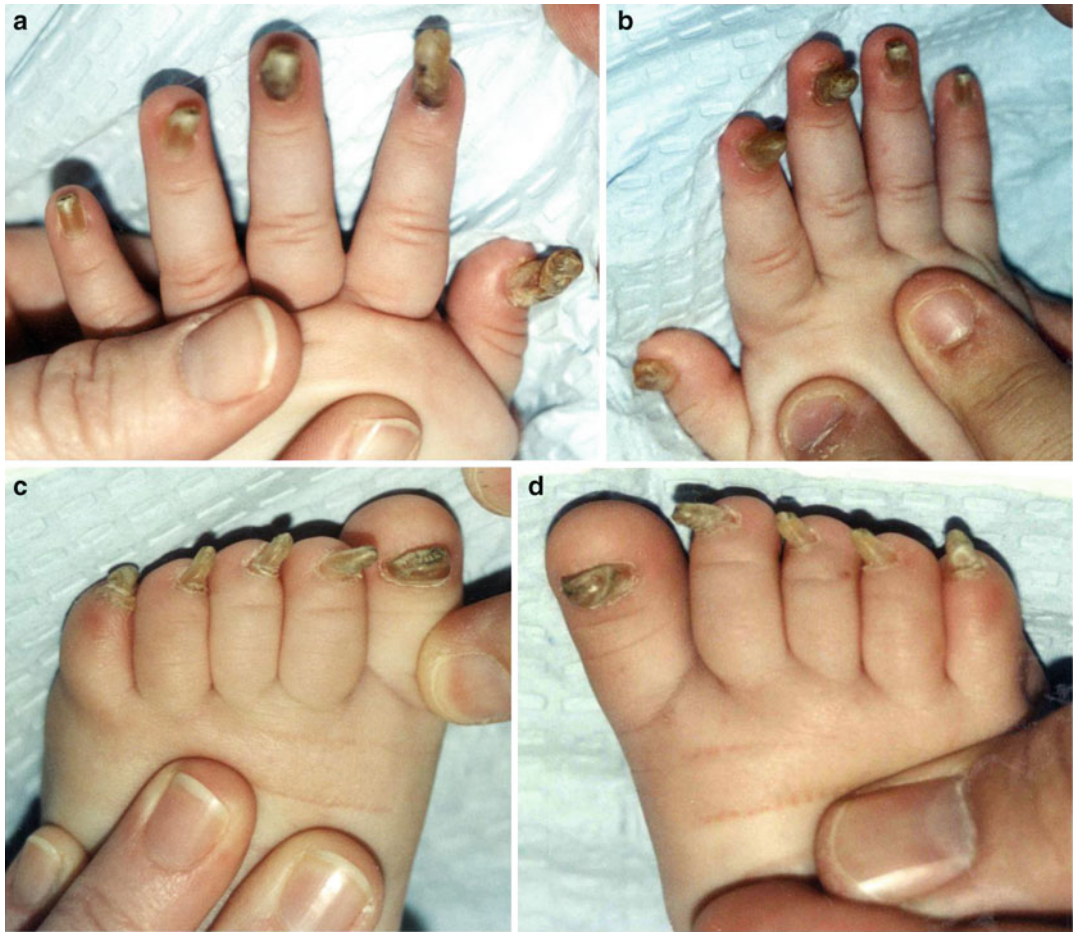

Fig. 1 (**a**–**d**) Characteristic nail changes in an 8-month-old girl with pachyonychia congenita type I showing smooth proximal ends and thick distal ends of the nails, producing a subungual keratinous mass that pushes the nail bed upward, arching it transversally, folding it longitudinally, and elevating it distally. The patient also has oral leukokeratosis

Pallister–Killian Syndrome

Contents

Pallister–Killian syndrome is a rare sporadic cytogenetic abnormality, caused by a tissue-specific mosaic distribution of an additional isochromosome 12p, first described in three adults by Pallister et al. in 1977 (Pallister et al. 1977) and followed by a report of a child by Teschler-Nicola and Killian in 1981 (Teschler-Nicola and Killian 1981). The syndrome is also known as Teschler-Nicola/Killian syndrome, Pallister mosaic aneuploidy syndrome, and isochromosome 12p mosaicism or mosaic tetrasomy 12p (Buyse and Korf 1983). It is the most frequent autosomal tetrasomy in humans (Bresson et al. 1991).

Synonyms and Related Disorders

Isochromosome 12p syndrome; Killian syndrome; Mosaic tetrasomy 12p syndrome; Pallister mosaic syndrome; Pallister–Killian mosaic aneuploidy syndrome

Genetics/Basic Defects

1. Genetics:
   1. Sporadic in mature (Srinivasan and Wright 2014)
   2. Appears to be associated with increased maternal age
2. Basic cytogenetic defect (Bresson et al. 1991; Yeung et al. 2009):
   1. Caused by tetrasomy 12p.
   2. Generally a mosaic.
   3. Frequently undetectable by standard cytogenetic analysis of peripheral blood.
   4. In the great majority of patients, the i(12p) is maternal in origin (maternal meiosis II nondisjunction), with the underlying mechanism thought to involve a combination of centromere misdivision and nondisjunction at meiosis. Although more rarely, paternal nondisjunction has also been reported (Izumi and Krantz 2014).
   5. As a result, the i(12p) is present at conception, and mosaicism results from postzygotic mitotic loss (Peltomaki et al. 1987).
   6. Chromosomally normal cell line in Pallister syndrome arises post-conception from a zygote already aneuploid consequent to meiotic nondisjunction (Wenger et al. 1988).
   7. There is no apparent correlation between the proportion of tetrasomic cells and the severity of clinical presentation (Schinzel 1991).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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Clinical Features

1. Wide spectrum of clinical manifestations (Genevieve et al. 2003; Wilkens et al. 2012).
2. Normal or large birth weight (Mathieu et al. 1997).
3. Craniofacial dysmorphism (Reynolds et al. 1987):
    1. Hypotonia
    2. Coarse face
    3. Brachycephaly
    4. High and broad forehead with frontal bossing
    5. Temporal alopecia
    6. Sparse eyebrows and eyelashes
    7. Hypertelorism
    8. Short nose with anteverted nares
    9. A thick philtrum
    10. A large mouth with down-slanting corners
    11. Full cheeks
    12. Cleft lip/palate
    13. High-arched palate
    14. Micrognathia
    15. Macroglossia
    16. Oral frenula
    17. Delayed dental eruption
    18. Dental anomalies
    19. Low-set and posteriorly rotated ears
    20. Hypertrophy of anthelix crux
    21. Thick earlobes
4. Oro-dental features (Bagattoni et al. 2016).
    1. Twelve probands (57%) showed an atypical dental pattern, with multiple missing teeth (primarily the first permanent molars) and two (10%) double teeth.
    2. The severity of gingivitis and dental caries increased with age, and gingival overgrowth was a common finding.
    3. A characteristic occlusive phenotype was found: a high-arched palate with mandibular prognathism associated with an anterior open bite and crossbite and with posterior crossbite (unilateral or bilateral).
    4. The prevalence of oral habits (nonnutritive sucking, mouth breathing, bruxism) was high, even in older probands.
5. Short neck.
6. Diaphragmatic hernia with or without lung hypoplasia.
7. Imperforate anus.
8. CNS/neurologic abnormalities:
    1. Severe hypotonia
    2. Mental retardation
    3. Dilated ventricles
    4. Bifrontal cortical atrophy
    5. Absent speech
    6. Poor vision
    7. Epilepsy
9. Developmental and behavioral characteristics (Kostanecka et al. 2012):
    1. Wide neurocognitive spectrum of PKS.
    2. Further studies are needed to investigate whether children with PKS are at increased risk for autism and to investigate the prevalence of neurosensory deficits, tactile defensiveness, and lethargy, especially as they may relate to developmental impairments in children with PKS.
10. Cardiac manifestations (Tilton et al. 2014):
    1. Atrial or ventricular septal defects: the most commonly seen congenital heart differences
    2. Occasional occurrence
        1. Bicuspid aortic valve
        2. Aortic dilatation
        3. Cardiac hypertrophy/cardiomyopathy
11. Limb defects:
    1. Talipes
    2. Broad and short hands and fingers
    3. Hypoplastic nails
    4. Abnormal palmar creases
    5. Lymphedema
12. Skin anomalies:
    1. Loose/excess skin
    2. Pigmentary dysplasia
    3. Mild hyperkeratosis
    4. Dry skin
    5. Sweating abnormalities
13. Occasional internal organ malformations:
    1. Umbilical hernia
    2. Malrotation of the gut
    3. Omphalocele

4. Abnormalities of urogenital tract including cystic or dysplastic kidneys
5. Genital anomalies in males
    1. Cryptorchidism
    2. Small scrotum
6. Occasional genital anomalies in females
    1. Ambiguous external genitalia
    2. Hypoplasia of the labia majora
    3. Absence of the upper vagina and uterus

14. Anhydrosis/hypohidrosis and episodic hyperventilation, suggesting involvement of the autonomic system (Blyth et al. 2015).
15. Lethal presentation of mosaic tetrasomy 12p (Pallister–Killian) syndrome in neonatal period: a consistent phenotype characterized by dysmorphic facies and large diaphragmatic hernia (Young et al. 1989).
16. Majority of patients die prenatally, perinatally, or early postnatally and may die even after 10 or 15 years.
17. Phenotype in older children and adults (Quarrell et al. 1988): marked phenotypic changes occurring during childhood and adolescence (Horneff et al. 1993):
    1. Coarse and flat facies
    2. Macroglossia
    3. Prognathia
    4. Everted lower lip
    5. Muscular hypertonia
    6. Contractures
    7. Severe psychomotor retardation

Diagnostic Investigations

1. Cytogenetic studies:
    1. Presence of an extra metacentric chromosome i(12p) mainly in skin fibroblasts (tissue-specific mosaic distribution of an additional isochromosome 12p) (Hunter et al. 1985; Genevieve et al. 2003), but rarely also in cultured peripheral blood lymphocytes (Wenger et al. 1988).
    2. Demonstration of a supernumerary isochromosome of 12p.
    3. Mosaic tetrasomy 21 is mosaic tetrasomy 12p some of the time (Hall 1985).
    4. Confirmation of the chromosomal origin of the supernumerary chromosome (mosaic tetrasomy 12p) in one of the original Pallister–Killian mosaic syndrome cases (Warburton et al. 1988).
    5. Confirmation of 12p tetrasomy by FISH techniques (Speleman et al. 1991; Butler and Dev 1995):
        1. Using centromere probe on chromosome 12
        2. Using whole chromosome 12 painting probe
    6. Cytogenetic studies of several tissues because of mosaicism (Mathieu et al. 1997): the mosaicism is usually detected in cultured skin fibroblasts or amniotic cells and rarely in phytohemagglutinin-stimulated lymphocytes, which suggests stimulation of T lymphocytes may distort the percentage of abnormal cells:
        1. Circulating lymphocytes: mosaicism as low as 1–3%.
        2. Amniocytes, chorionic cells, and skin fibroblasts: mosaicism ranging from 6% to 100%.
        3. Multiplex ligation-dependent probe amplification (MLPA) on buccal smears is a good and noninvasive method to detect extra copies of 12p and should be considered as the first exam, before a skin biopsy for a fibroblast karyotype is performed (Costa et al. 2015). A limitation of MLPA is that mosaicism in low level may not be detected, so a normal MLPA result cannot rule out PKS diagnosis (Van Opstal et al. 2011).
2. Demonstration of the utility of SNP (single nucleotide polymorphism) arrays in conjunction with traditional cytogenetic techniques for the evaluation of PKS. Given that the percentage of mosaic tetrasomic cells in peripheral blood decreases as the individual with PKS ages, SNP arrays should be performed as early as possible to avoid the

need for skin biopsy when possible (Conlin et al. 2012).
3. Array comparative genomic hybridization (aCGH) can detect partial tetrasomy of 12p in blood without invasive skin biopsy (Theisen et al. 2009). However, aCGH on unstimulated blood does not detect all cases of Pallister–Killian syndrome. A skin biopsy should remain the diagnostic gold standard (Hodge et al. 2012). Array CGH only suggested the diagnosis in 15.8%, but buccal FISH could have made the diagnosis in 75.0% (Blyth et al. 2015).
4. Droplet digital PCR (polymerase chain reaction) should be considered as an effective tool for both clinical and research analytics to precisely quantify mosaic genomic copy number alterations or mosaic mutations (Fujiki et al. 2016).
5. Radiography (Jamuar et al. 2012):
    1. A recurrent pattern:
        1. Delayed ossification of the vertebral bodies, pubic bones, triradiate cartilage, and sacroiliac junction, flaring of the anterior ends of the ribs, and metaphyseal broadening of the long bones.
        2. The absence of pubic ossification is particularly easy to recognize and thus may be a useful diagnostic marker.
        3. The delay of the endochondral ossification is apparently related to the feature of short limbs often reported in PKS. Moreover this slow endochondral bone formation is most evident in the axial skeleton.
    2. Additional dysostotic anomalies previously described (Schinzel 1991):
        1. Atlantooccipital fusion
        2. Absence of 12th ribs
        3. Radioulnar synostosis
        4. Absent thumbs
        5. Absence of the talus
        6. Duplication of halluces
6. Echocardiography for congenital heart defect.
7. EEG for seizure activities.
8. MRI of the brain (Saito et al. 2006):
    1. Normal MRI findings
    2. Abnormal MRI findings:
        1. Cortical atrophy with frontal predominance
        2. Ventricular dilatation
        3. Hydrocephalus
        4. Reduced white matter
        5. Thickened cortex
        6. Micropolygyria
        7. Heterotopic neurons
        8. Agenesis of corpus callosum
        9. Pineal gland tumor
        10. Multiple T2-high lesions
        11. T2 elongation in the white matter
9. Postmortem pathologic examinations (Mathieu et al. 1997):
    1. Malpositioned feet
    2. Diaphragmatic defect
    3. Hypoplastic nails
    4. Genital malformation
    5. Imperforate or anteriorly placed anus
    6. Supernumerary spleen
    7. Heart valvular dysplasia
    8. Hypoplasia of the fibula

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: low recurrence risk (all cases are sporadic with only one preliminary case report of recurrence.) (Mathieu et al. 1997)
    2. Patient's offspring: not surviving to reproductive age or severely handicapped by profound mental retardation
2. Prenatal diagnosis (Doray et al. 2002; Srinivasan and Wright 2014):
    1. Ultrasound anomalies (Liberati et al. 2008):
        1. Hydramnios (84%)
        2. Diaphragmatic hernia (16%)
        3. Short limbs, predominantly rhizomelic type of micromelia (10%)
        4. Hydrops fetalis (6%)
        5. Cystic hygroma (3%)
        6. Increased nuchal translucency (3%)
        7. Fetal overgrowth (3%)
        8. Flat fetal facial profile with a small nose and protruding lips (Liberati et al. 2008)
        9. Ventriculomegaly (3%)
        10. Dilatation of cavum pellucidum (3%)

11. Absence of visualization of the stomach (3%)
12. Presence of a sacral appendix (3%)
13. Cardiac malformation
14. Hypertelorism
15. Short neck
16. Other congenital anomalies

2. Cytogenetic studies on amniocytes (Shivashankar et al. 1988; Soukup and Neidich 1990), cells from CVS (Bernert et al. 1992), or fetal blood cells from cordocentesis (Chiesa et al. 1998):
    1. Conventional karyotyping
    2. FISH using chromosome 12 centromeric and whole chromosome painting probes:
        1. Interphase cells
        2. Metaphase cells

3. Management:
    1. Supportive treatment
    2. Surgical repair of diaphragmatic hernia or other congenital anomalies in nonlethal cases

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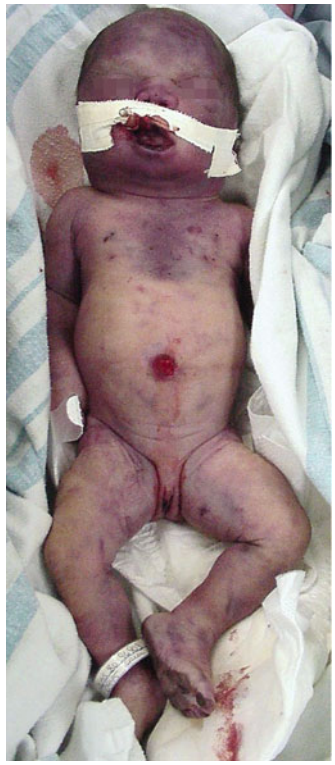

Fig. 1 Postmortem picture of a neonate with prenatally diagnosed mosaic i(12p). Amniocentesis was performed because of ultrasonographic finding of diaphragmatic hernia

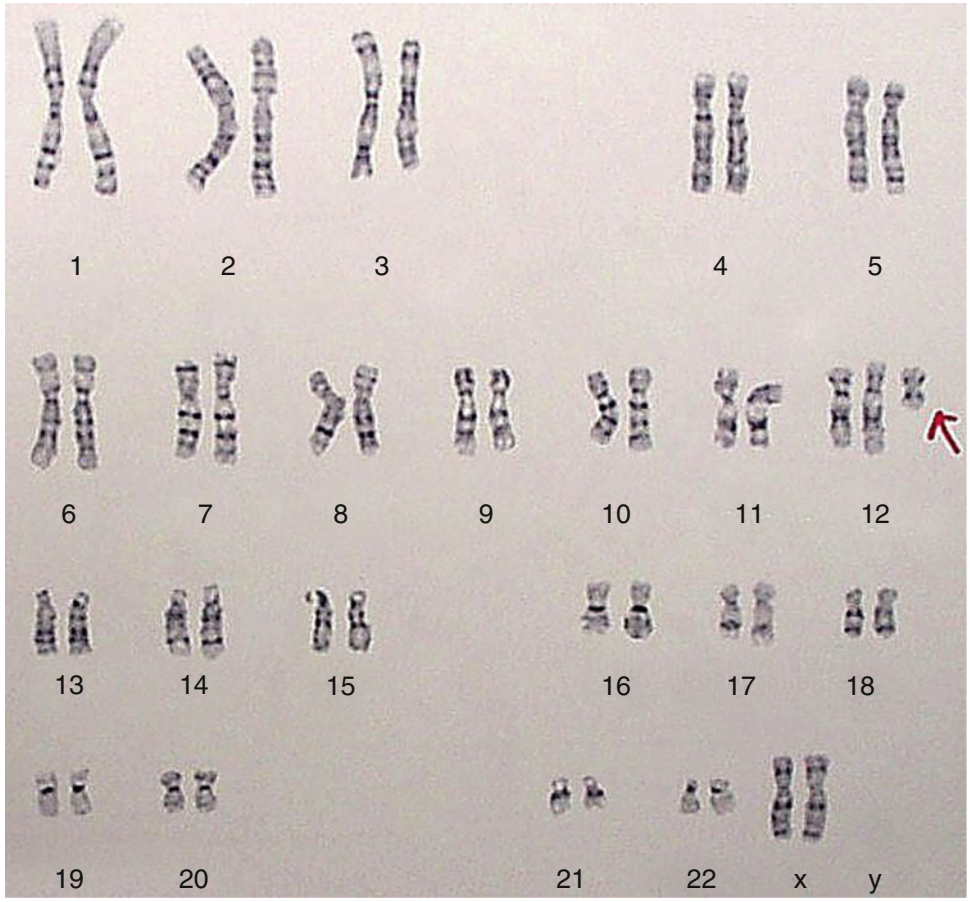

Fig. 2 A G-banded karyotype showing a supernumerary i(12p) (*arrow*)

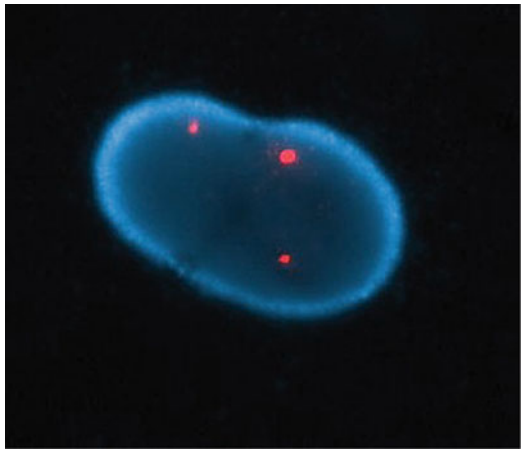

Fig. 3 FISH of an interphase cell with centromere-specific probe for chromosome 12 showing three signals

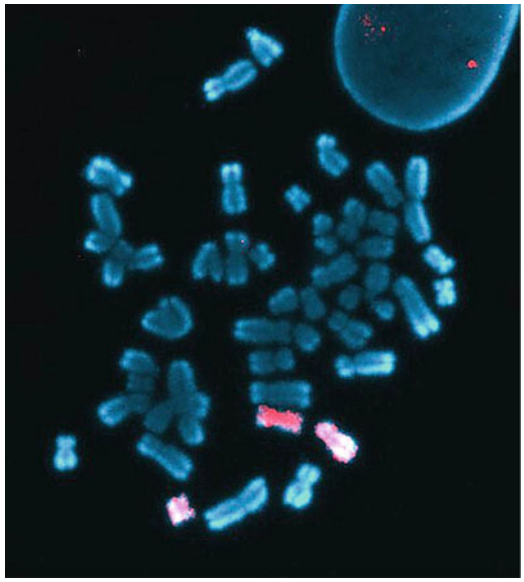

Fig. 4 FISH of a metaphase chromosome spread with a whole chromosome probe specific for chromosome 12 showing two chromosome 12 s and the i(12p) (*arrow*)

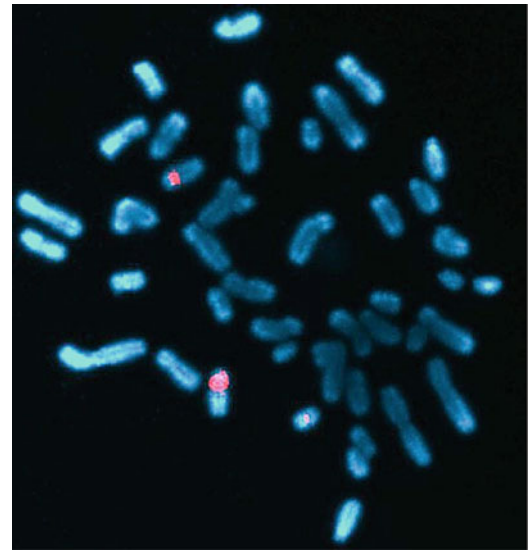

Fig. 5 FISH of a metaphase chromosome spread with a centromere probe specific for chromosome 12 showing two chromosome 12 s and the i(12p) (*arrow*)

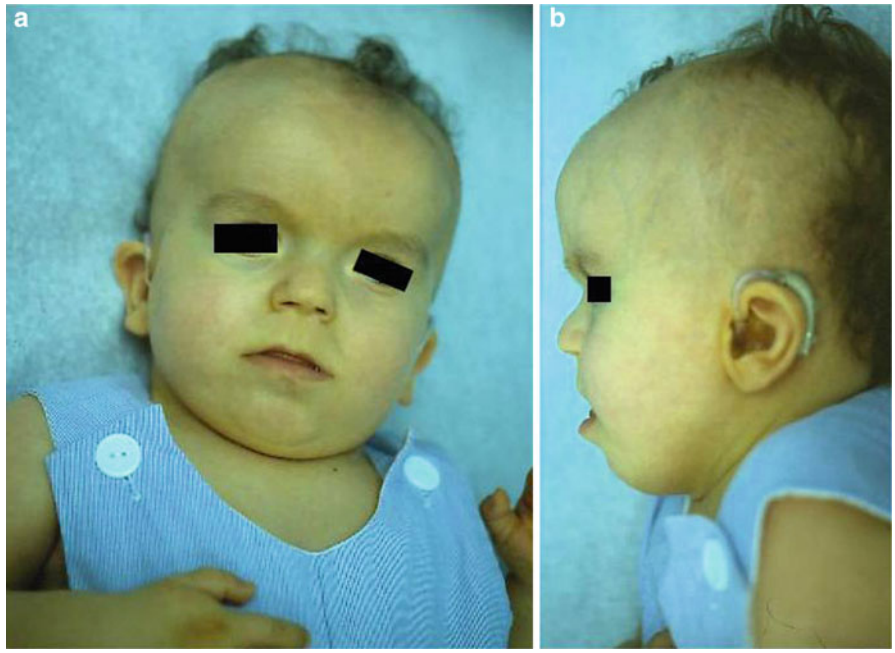

Fig. 6 (**a**, **b**) Another child with Pallister–Killian syndrome confirmed by cytogenetic studies showing prominent forehead, flat nasal bridge, sparse eyebrows, bitemporal alopecia, and everted lower lip

Patellar Instability

Contents

Patellar or patellofemoral instability is a complex problem that is highly prevalent in the population (Gillespie 2012). It is a common cause of knee pain and disability (Minkowitz et al. 2007). Recurrent patellar instability can result from osseous abnormalities, such as patella alta, a distance of >20 mm between the tibial tubercle and the trochlear groove, and trochlear dysplasia, or it can result from soft tissue abnormalities, such as a torn medial patellofemoral ligament or a weakened vastus medialis obliquus (Colvin and West 2008).

Synonyms and Related Disorders

Patella alta; Patellar dislocation; Patellar subluxation; Patellofemoral instability; Slipping or recurrent patella dislocation

Genetics/Basic Defects

1. Definition of patellar instability (Grelsamer 1997; Minkowitz et al. 2007)
    1. A clinical entity or diagnosis of a traumatic dislocation
    2. A sign on physical examination, signifying the ability of the patella to be translated out of the trochlear groove of the femur in a passive manner
    3. A symptom, typically if the knee "gives away" as a result of the patella slipping out of the trochlear groove
2. Acute patellar dislocation
    1. Annual incidence of acute patellar dislocations in Finnish children <16 years of age: 43 per 100,000 children (Nietosvaara et al. 1994)
    2. Mechanisms of acute lateral patellar dislocations (Boden et al. 1997)
        1. An indirect injury
        2. A direct blow
3. Risk factors of recurrent patellofemoral instability (Boden et al. 1997)
    1. Typically an adolescent female
    2. Ligamentous laxity
    3. Multiple developmental anomalies
        1. Trochlear dysplasia
        2. Patella alta (high-standing patella)
        3. Rotational and angular bony alignment
4. Etiology of patellar instability: multifactorial (Redziniak et al. 2009)
    1. Patella alta

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2. Trochlear dysplasia
3. Dysplasia of lateral trochlear margin
4. Shallow trochlear groove
5. Vastus medialis obliquus insufficiency
6. Joint laxity
7. Trauma
8. Previous surgery
9. Tight lateral structures (e.g., lateral retinaculum and iliotibial band)

Clinical Features

1. Acute patellar dislocation (Minkowitz et al. 2007).
    1. Rapid swelling associated with acute injury.
    2. A significant hemarthrosis frequently develops, especially if there is an associated osteochondral fracture.
    3. Loose chondral or bony fragments may be palpable in the joint.
    4. Attached osteochondral fragments may be felt in the medial parapatellar retinaculum.
    5. Focal areas of maximum tenderness suggest soft tissue injury.
    6. Tenderness at the medial femoral condyle may suggest an injury to the medial collateral ligament (MCL) of the knee.
    7. A palpable defect at the vastus medialis obliquus (VMO) distal insertion and a visible change in its symmetry suggest occurrence of significant disruption of the VMO insertion.
    8. A positive apprehension test at 30° of flexion: a classically described examination finding.
    9. Increased medial retinacular laxity not symmetrical with the contralateral knee with or without apprehension (DeLee et al. 2003).
2. Recurrent patellofemoral instability (Minkowitz et al. 2007)
    1. History
        1. A history of general ligamentous laxity or dislocation in the patient or family (Fig. 1) (Koh and Stewart 2014)
        2. Diffuse pain about the knee that is aggravated by going up and down the stairs or climbing hills
    2. Physical examination
        1. Patellar crepitation and swelling of the knee: common
        2. Patellofemoral crepitus: may be palpable
        3. Effusion: may be present
        4. The patellar grind test
            1. Done by applying pressure to the patella and manually displacing it medially, laterally, superiorly, and inferiorly in the trochlear groove.
            2. This test reproduces anterior knee pain when a patellofemoral pathological condition is present.
        5. Apprehension test
            1. The examiner holds the relaxed knee in 20–30° of flexion and manually subluxes the patella laterally.
            2. When the test is positive, the patient suddenly complains of pain and resists any further lateral motion of the patella.
        6. Patellar tilt test
            1. Done with the knee in extension.
            2. The examiner's fingers are placed along the medial side of the patella and the thumb on the lateral aspect.
            3. Inability to raise the lateral facet to the horizontal plane or slightly past indicates excessive lateral retinacular tightness.
        7. Dynamic patellar tracking
            1. Evaluated with the examiner standing in front of the seated patient while the patient slowly extends the knee.
            2. *A positive J sign*, lateral subluxation of the patella as the knee approaches full extension, indicates some degree of maltracking.
        8. Active patellar tracking
            1. Examined with the knee in the extended relaxed position.
            2. The quadriceps is tightened and motion of the patella is examined.
            3. Normally, the patella should move more superiorly than laterally.
        9. Tender patellar: indicates a pathological condition of the articular cartilage

3. Differential diagnosis: ► "Ehlers-Danlos Syndrome" (please see the chapter)

Diagnostic Investigations

1. Radiographic features associated with recurrent patellar instability (Colvin and West 2008; Gillespie 2012)
    1. Patella alta
    2. Patellar tilt
    3. Patellar subluxation
    4. Abnormally elevated distance between the tibial tubercle and trochlear groove (TT-TG distance)
    5. Trochlear dysplasia
        1. Crossing sign
        2. Supratrochlear spur
        3. Double contour (a hypoplastic medial facet)
2. Cross-sectional imaging with transverse computed tomography slices at different positions along the lower limb
    1. Provides a three-dimensional view of the patellofemoral joint and can be used to assess the lateral offset of the tibial tuberosity from the deepest point in the trochlear groove.
    2. A distance between the tibial tuberosity and the trochlear groove exceeding 20 mm is nearly always associated with patellar instability (Dejour et al. 1994).
3. Magnetic resonance imaging (Fig. 2) is better for assessing the integrity of the articular cartilage and soft tissue structures and has become the acceptable method to diagnose the medial patellofemoral ligament (MPFL) (Jain et al. 2011).
    1. Detects disruption of the MPFL (Sanders et al. 2001)
    2. Detects typical injuries seen after a patellar dislocation
        1. Cartilage damage or bone bruising of the medial patellar facet and the lateral femoral condyle (Kirsch et al. 1993)
        2. Injury to the vastus medialis obliquus: frequently presents as edema, hemorrhage, and/or elevation of the muscle away from the medial femoral condyle (Elias et al. 2002)
    3. Repair or reconstruction of the MPFL and distal realignment procedures: currently the most common surgical treatment options
4. Bone scan: can provide valuable functional information about the metabolic activity of the bone (Dye and chew 1994; Koh and Stewart 2014)
    1. A diffuse uptake pattern: seen in patients with patellofemoral pain
    2. A more localized pattern : seen in patients with specific areas of overload or a symptomatic chondral defect causing increased activity in the underlying bone

Genetic Counseling

1. Recurrence risk
    1. Risk to patient's sib: not increased unless in an autosomal dominant inheritance
    2. Patient's offspring: 50% in an autosomal dominant inheritance
2. Management (Colvin and West 2008; Gillespie 2012)
    1. Nonoperative treatment: generally recommended for primary patella dislocations
        1. Immobilization
        2. Physical therapy: mainstay therapy focusing on establishing optimal lower extremity balance, strength, and function
        3. Patellar taping or bracing
    2. Arthroscopic and minimally invasive techniques: typically limited to those patients with minimal amounts of bony malalignment or trochlear dysplasia or as an adjunct to provide additional soft tissue balancing in patients who undergo bony procedures (Koh and Stewart 2014)
        1. Arthroscopic medial plication techniques
        2. Miniopen medial reefing techniques
    3. Operative treatment
        1. For presence of osteochondral fracture fragment or retinacular injury

2. Reconstruction of the medial patellofemoral ligament with autograft or allograft in a patient with recurrent instability, with or without trochlear dysplasia, who has a normal tibial tubercle-trochlear groove distance and a normal patellar height
3. Distal realignment procedures
    1. Used in patients who have an increased tibial tubercle-trochlear groove distance or patella alta
    2. Contraindicated in patients with associated medial or proximal patellar chondrosis because of the potential to overload tissues that have already undergone degeneration
4. Tibial tubercle osteotomy
    1. Able to directly address some of the underlying biomechanical factors that predispose to patella instability with an increased anterior TT-TG distance or with patella alta.
    2. Anteromedial transfer can unload damaged articular cartilage (Fulkerson 2007).
5. Trochleoplasty for treatment of severe trochlear dysplasia in patients with instability

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Fig. 1 (**a**–**d**) This 8-year-old Caucasian boy (**a**) was with his older brother and mother for evaluation of familial patellar instability leading to recurrent patellar subluxations and/or dislocations, shown by radiograph (**c**). Since 7 years of age, he repeatedly dislocated both patellae on normal walking or running. He could move the dislocated patellae back into normal places by his hands. His older brother and mother also have history of recurrent patellar dislocations. Patella operations were performed on both knees of the patient (**b**) and the *right* knee of the mother (**d**)

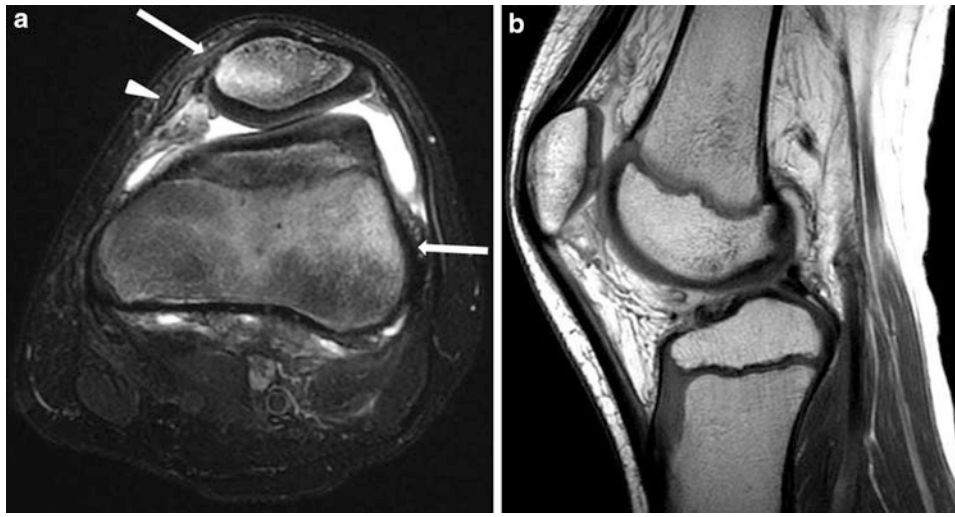

Fig. 2 (**a**, **b**) A 12-year-old boy with history of right transient patellar dislocation 2 years ago presented with *left* knee pain after an injury 4 weeks ago. MRI image (**a**) showed classic findings of transient patellar dislocation. There is subchondral marrow edema in the medial patella and lateral femoral condyle (*white arrows*). The medial patellofemoral ligament is torn (*white arrowhead*). A high riding patella, consistent with patella alta (**b**), is commonly associated with recurrent patellar instability (Courtesy of Dr. Grace Guo)

Peutz-Jeghers Syndrome

Contents

Peutz-Jeghers syndrome (PJS) was first described in 1921 by Peutz (Peutz 1921) and subsequently elaborated upon by Jeghers in 1949 (Jeghers et al. 1949) (Dong and Li 2004). The syndrome is characterized by gastrointestinal hamartomatous polyps and mucocutaneous hyperpigmentation of the lips, buccal mucosa, and digits. Incidence is estimated to be 1 in 50,000 to 1 in 200,000 live births (Giardiello and Trimbath 2006).

Synonyms and Related Disorders

Hamartomatous intestinal polyposis; Periorificial lentiginosis; Polyps-and-spots syndrome

Genetics/Basic Defects

1. An autosomal dominant disorder.
2. Mutations in the serine-threonine kinase 11 (*STK11*, also known as *LKB1*) gene on chromosome 19p13.3, are considered the major cause of PJS (Jenne et al. 1998).
3. Germline mutations of *STK11* are documented in up to 70–80% of patients with PJS and up to 15% of cases have deletions of all or part of *STK11* (Hemminki et al. 1998).
4. Loss of heterozygosity at 19p13.3 seen in PJP polyps and malignancy suggests that STK11 acts as a tumor suppressor gene
5. Sporadic cases (up to 25% of documented cases): felt to be due to de novo mutations in *STK11* or low-penetrance variants (Giardiello et al. 2000).

Clinical Features

1. Hyperpigmentation (Schreibman et al. 2005; Giardiello and Trimbath 2006; Beggs et al. 2010).
    1. Melanotic pigmented macules
        1. Seen in around 95% of patients
        2. May be the first clue to an individual having PJS
        3. Dark brown or blue-brown in color (1–5 mm in size)
        4. Locations
            1. Vermilion border of the lips (94%)
            2. Buccal mucosal (66%)
            3. Hands/fingers (74%)
            4. Feet/toes (62%)
            5. Nostrils
            6. Perianal area

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Usually occurring in infancy and fading in late adolescence but tend to persist in the buccal mucosa
3. Often precede the gastrointestinal manifestations

2. Gastrointestinal manifestations.
   1. Hamartomatous polyposis (Giardiello 1995)
      1. Occur most numerously in the small intestine but frequently in the colon and stomach.
      2. The polyps usually number between 1 and 20 per segment of the intestinal tract and vary in size from 0.1 to 5 cm in diameter.
      3. Polyps are seen at the following locations and frequency: small intestine (64%), colon (64%), stomach (49%), and rectum (32%) (Utsunomiya et al. 1975).
      4. They can also occur elsewhere (Sommerhaug and Mason 1970; Murday and Slack 1989; Vogel et al. 2000).
         1. Renal pelvis
         2. Urinary bladder/ureter
         3. Lungs/bronchi
         4. Gallbladder
         5. Nares
   2. Intussusception: most frequent complication in young age
      1. Occurring in 47% of patients
      2. Primarily in the small intestine (95% of cases)
   3. Chronic bleeding, anemia, and abdominal pain due to intussusception, obstruction, or infarction
3. Cancer risk (Su et al. 1999; Giardiello et al. 2000; Hearle et al. 2006).
   1. An increased risk of many cancers in PJS based on epidemiological and molecular genetic studies
   2. The most common cancers: luminal gastrointestinal cancers (colorectal cancer, most common; upper GI, less common) and breast cancer, followed by pancreatic cancer
   3. Other rare neoplasms (Harned et al. 1995)
      1. Adenoma malignum (a uterine cancer)
      2. Benign testicular neoplasms
      3. Malignant and benign neoplasms of the thyroid, gallbladder, ureter, and urinary bladder
   4. The risk increased rapidly after age of 50
4. Three diagnostic criteria for Peutz-Jeghers syndrome (Riegert-Johnson et al. 2011; Chae and Jeon 2014).
   1. Mayo clinic (2010)
      1. Without a family history of PJS: either of the following are present:
         1. Characteristic melanotic macules and one or more intestinal polyps with PJS-type histology
         2. Two intestinal polyps with PJS-type histology
      2. With family history of PJS in a sibling or child: if any of the following are present:
         1. Characteristic melanotic macules
         2. One or more intestinal polyps with PJS-type histology
         3. An *LKB1* mutation
   2. World Health Organization (2000)
      1. Without a family history of PJS – a diagnosis of PJS is made if there are:
         1. Three or more histologically confirmed PJS polyps
         2. Any number of PJS polyps and characteristic, prominent, PJS mucocutaneous pigmentation
      2. With family history of PJS in a sibling or child – if there are:
         1. Any number of PJS polyps
         2. Characteristic, prominent, PJS mucocutaneous pigmentation
   3. Tomlinson and Houlston (1997) – a diagnosis of PJS can be made if there are:
      1. Two or more intestinal polyps with PJS-type histology
      2. One intestinal polyp with PJS-type histology with either typical melanotic macules or a family history of PJS and characteristic melanotic macules
5. Correlation of *STK11* mutation detection rates with diagnostic criteria: over 95% of patients who meet the criteria for PJP had a mutation detected (64% point mutation, 30% deletions) (Aretz et al. 2005).

6. Differential diagnosis (Higham et al. 2010).
    1. Differential diagnosis of polyposis
        1. Familial juvenile polyposis (Zbuk and Eng 2007)
            1. Multiple juvenile polyps primarily in the colorectum
            2. Often symptomatic prior to age 20
            3. No mucocutaneous pigmentation
            4. Malignant predisposition: adenocarcinoma (colorectal, gastric, pancreas)
            5. Caused by *SMAD4* and *BMPR1A* gene mutations (van Hattem et al. 2008)
        2. Hereditary mixed polyposis syndrome: characterized by mixed hyperplastic, adenomatous, and juvenile polyps, associated with *BMPR1A* gene (Cao et al. 2006)
        3. Cronkhite-Canada syndrome (Daniel et al. 1982)
            1. Not familial: unlike most of the other polyposis syndromes
            2. Occurs in older adults
            3. Gastrointestinal polyps
            4. Abdominal pain, severe protein-losing diarrhea, weight loss, and anorexia: common
            5. Brown macules on the palmar and plantar skin surfaces of the hands and feet
            6. Nail loss secondary to dystrophic changes
            7. Rare gastric and colon adenocarcinomas
        4. Familial adenomatous polyposis (Gardner syndrome): please see the chapter of "Familial Adenomatous Polyposis"
        5. Bannayan-Ruvalcaba-Riley syndrome: please see the chapter of "Bannayan-Riley-Ruvalcaba Syndrome"
        6. Basal cell nevus syndrome (Gorlin syndrome): please see the chapter of "Gorlin Syndrome"
    2. Differential diagnosis of mucocutaneous pigmented lesions (Harned et al. 1995)
        1. Carney complex (McCarthy et al. 1986).
            1. Spotty skin pigmentation
            2. Lentigines
            3. Most commonly on the face, especially on the lips (freckling), eyelids, conjunctiva, and oral mucosa
        2. Cowden syndrome (multiple hamartoma syndrome).
            1. An autosomal dominant trait
            2. Primarily occurs in whites
            3. Characterized by hamartomas and neoplasms of ectodermal, mesodermal, and endodermal origin affecting multiple organ systems: thyroid goiters, adenomas, and follicular adenocarcinomas; female breast carcinoma; genitourinary lesions including uterine and cervical carcinomas and transitional cell carcinoma of the renal pelvis and urinary bladder; a variety of skeletal abnormalities and nervous system and solid visceral tumors
            4. Mucocutaneous lesions – present in all patients – the hallmark of the disease
            5. Facial papules, oral mucosal papillomatoses, acral keratosis, and multiple sclerotic fibromas: the most characteristic lesions
        3. Laugier-Hunziker syndrome: a rare acquired disorder characterized by diffuse macular hyperpigmentation of the oral mucosa and, at times, longitudinal melanonychia (Rangwala et al. 2010).
        4. LEOPARD syndrome: please see the chapter.

Diagnostic Investigations

1. Histology.
    1. Pigmented macules: increased melanin in basal cells, possibly due to an inflammatory block to melanin migration from melanocyte to keratinocyte (Beggs et al. 2010)
    2. Polyps: frond-like elongated epithelial component and cystic gland dilatation extending into the submucosa or muscularis propria, and arborizing smooth muscle extending into polyp fronds

2. Radiology: examine entire GI tract to document the location, size, and number of polyps (Godard et al. 1971).
    1. Abdominal plain films
        1. Most common abnormalities
            1. Reflect partial or complete intestinal obstruction
            2. Small bowel dilatation
            3. Multiple air-fluid levels
        2. Intussusception: occasionally seen as a soft tissue density
    2. Barium swallow required to demonstrate GI polyps
    3. Barium enema
    4. Pneumocolon examination
    5. Multidetector computed tomography: allows for the depiction of small bowel polyps and their complications (e.g., intussusceptions) (Tomas et al. 2014)
    6. MR enterography (Gupta et al. 2010)
        1. A promising alternative to capsule endoscopy for small bowel surveillance in adults with PJS
        2. Less prone to missing large polyps
        3. May be more reliable in polyp size assessment
    7. Molecular genetic analysis of *STK11* (www.ncbi.nlm.nih.gov/books/NBK1266/)
        1. Sequence analysis/mutation scanning to detect sequence variants
        2. Deletion/duplication analysis to detect (multi)exonic and whole-gene deletions

Genetic Counseling

1. Recurrence risk according to autosomal dominant inheritance
    1. Patient's sib
        1. A 50% risk if one parent is affected.
        2. A low risk if both parents are clinically unaffected.
        3. Two possible explanations (germline mosaicism in a parent or a den novo mutation in the proband) exist (Hernan et al. 2004). However, no instances of germline mosaicism have yet been reported.
    2. Patient's offspring: a 50% risk to the offspring of an affected individual with a positive family history and/or a pathogenic *STK11* mutation
2. Prenatal diagnosis: available through chorionic villus sampling and amniocentesis if a pathogenic mutation is confirmed
3. Management (Beggs et al. 2010)
    1. General
        1. Annual full blood count
        2. Liver function testing
        3. Annual clinical examination
    2. Gastrointestinal
        1. Baseline colonoscopy and upper gastrointestinal endoscopy at age 8
            1. Polyps detected: continue every 3 years until age 50
            2. No polyps detected: repeat age 18 years, then every 3 years until age 50
        2. Intraoperative enteroscopy and double-balloon enteroscopy (Kopacova et al. 2009)
        3. Colonoscopy: 1–2 yearly after age 50
        4. Video capsule endoscopy: every 3 years from age 8
    3. Breast
        1. Monthly self-examination from age 18
        2. Annual breast MRI from age 25–50
        3. Annual mammography thereafter
    4. Genital tract
        1. Annual examination and testicular examination from birth until age 20
        2. Testicular ultrasound if abnormalities detected at examination
        3. Cervical smear with liquid-based cytology: every 3 years from age 8

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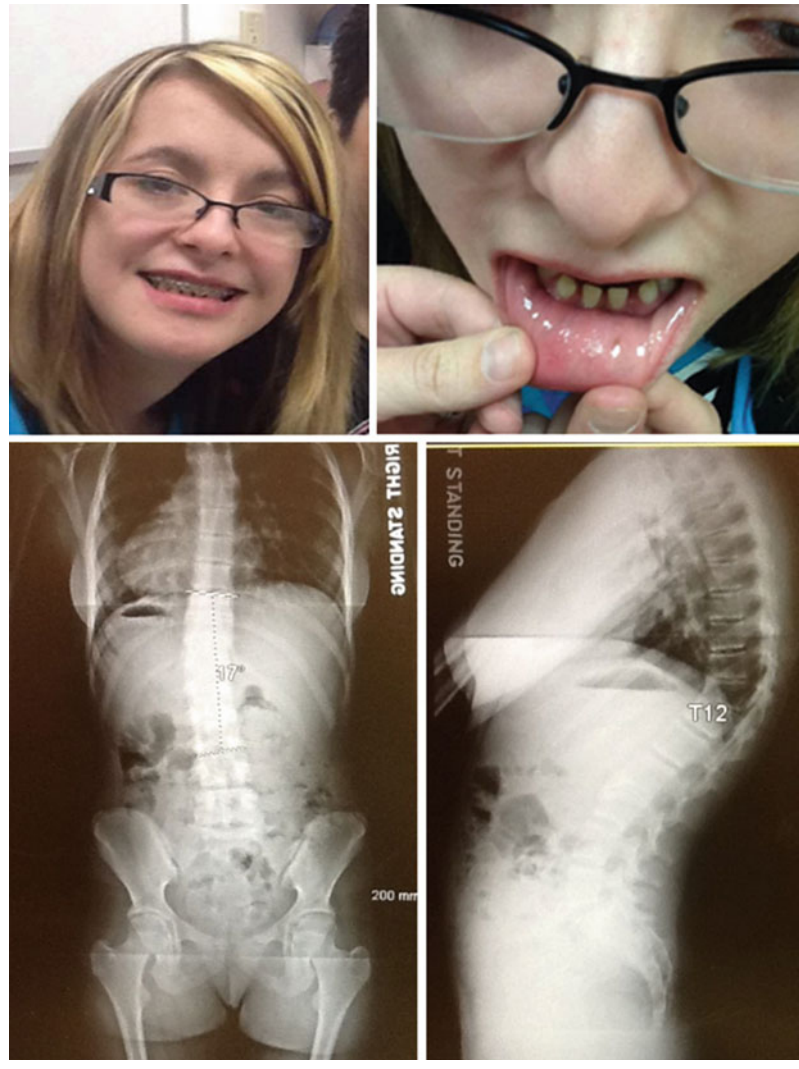

Fig. 1 (**a**, **b**) This 16-year-old Caucasian female (**a**) was seen initially for developmental delay with hearing and visual impairments, tetralogy of Fallot, and congenital spinal fusions (T11–T12 and L2–L3) contributing to accentuated kyphosis at this level (**c**, **d**). Chromosome analysis showed terminal deletion of 19pter-p13.2. Chromosome microarray analysis showed 1.261 MB terminal deletion of 19pter-p13.2 [arr 19p13.3 (41,981–1,136) × 1]. Because of the presence of hyperpigmented lesions on the oral mucosa (**b**), Peutz-Jeghers syndrome was suspected. DNA mutation study of *STK11* was positive. Recently, she had recurrent abdominal pains and was diagnosed to have intussusception twice. A large polyp was noted in the small intestine

Phenylketonuria

Contents

Classical phenylketonuria (PKU) is a rare metabolic disorder, resulting from a deficiency of a liver enzyme, phenylalanine hydroxylase. The deficiency of the enzyme leads to elevated phenylalanine (Phe) levels in the blood and various tissues including the brain. The incidence in Caucasians is approximately one in 10,000, giving a heterozygote frequency of one in 50 to one in 70. About one in 15,000 infants is born with PKU in the United States.

Synonyms and Related Disorders

Hyperphenylalaninemia; Maternal PKU; Phenylalanine hydroxylase deficiency; PKU

Genetics/Basic Defects

1. Inheritance
    1. Autosomal recessive
    2. Parents: obligatory carriers
2. Basic defect
    1. Deficient activity of the enzyme phenylalanine hydroxylase (PAH), resulting in hyperphenylalaninemia (HPA) (Scriver and Kaufman 2001). PAH, a liver-specific enzyme, catalyzes the conversion of phenylalanine to tyrosine, using tetrahydrobiopterin as a cofactor (Dyer 1999). Chromosomal locus of the *PAH* gene is on 12q24.1.
    2. Subclassification of PKU (Matalon and Michals 1991): defective activity of phenylalanine hydroxylase leads to a spectrum of clinical presentations.
        1. Classical PKU: blood phenylalanine greater than 1200 mumol/L usually indicates severe deficiency of phenylalanine hydroxylase.
        2. Atypical PKU: blood phenylalanine levels between 600 and 1200 mumol/L.
        3. Benign hyperphenylalaninemia: blood phenylalanine remains between 120 and 480 mumol/L on a normal diet.
        4. Malignant PKU: A deficiency of the cofactor tetrahydrobiopterin (BH4), which is required for phenylalanine hydroxylase activity, leads to hyperphenylalaninemia. This cofactor is also required for the enzymatic hydroxylation of tyrosine and tryptophan. Cofactor defects account for only 1–3% of hyperphenylalaninemia, which has been termed “malignant PKU,” but they must

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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be identified so that appropriate treatment can be established.

3. Tetrahydrobiopterin (BH4) deficiency (Al Hafid and Christodoulou 2015).
    1. In the 1970s it became apparent that there was a subset of patients with hyperphenylalaninemia who developed neurological complications despite prompt adherence to dietary therapy (Rey et al. 1976).
    2. This subgroup of patients (known to have atypical PKU) turned out to have mutations that cause defects in BH4 synthesis or recycling (Kaufman et al. 1978).
4. Identification of more than 400 different mutations in the *PAH* gene (National Institutes of Health Consensus Development Conference Statement 2001; Mitchell et al. 2011).
    1. Missense (62%)
    2. Deletion (mainly small) (13%)
    3. Splice (11%)
    4. Silent (6%)
    5. Nonsense (5%)
    6. Insertion (2%)
    7. Deletion or duplication of exon(s) or whole gene (<1%)
5. Compound heterozygotes in most PKU patients, contributing to the clinical heterogeneity and biochemical heterogeneity.
6. Strong correlations between PAH genotype and biochemical and clinical phenotypes in the heterogeneous American sample population, extending previous findings from relatively homogeneous European populations. These correlations further demonstrate the clinical utility of genotype analysis in the treatment of patients with PKU and HPA (Eisensmith et al. 1996).
7. Consequences of accumulation of phenylalanine (Phe) and other amino acids in the CNS.
    1. Irreversible brain damage from the first few weeks of life
    2. Severe learning disabilities and associated behavioral and psychological problems
3. Phenylketonuria pathophysiology (Schuck et al. 2015): Metabolic alterations include:
    1. Bioenergetic deficit
    2. Oxidative stress
    3. Impairment of lipid and protein metabolism
    4. Disruption of calcium homeostasis and neurotransmitter synthesis in the brain
    5. These metabolic disturbances might collaborate to the cognitive dysfunction and brain pathology of PKU.

Clinical Features

1. Treated patients
    1. Symptom-free on strict metabolic control using a low-phenylalanine diet for the infants detected by newborn screenings
    2. Normal development with a normal life span when diagnosed early in the newborn period and treated effectively with lifelong dietary control
2. Untreated patients
    1. Profound mental retardation
    2. Psychomotor handicaps
    3. Microcephaly
    4. Delayed speech
    5. Seizures
    6. Light hair and eyes and fair skin secondary to decreased formation of melanin pigment because of compromised tyrosine formation
    7. Musty body or urine odor secondary to excretion of phenylacetic acid into the sweat and the urine
    8. Vomiting
    9. Irritability
    10. Eczema
    11. Subtle neurologic findings, sometimes noted even in treated individuals
        1. Hypertonic reflexes
        2. Intention tremor
    12. Behavior problems
        1. Autistic-like behaviors
        2. Hyperactivity
        3. Agitation

4. Aggression

3. Maternal PKU: a metabolic teratogen (Levy and Ghavami 1996)
   1. Background information
      1. Loss of dietary compliance frequently starting during mid-childhood
      2. Noncompliance on special diet by many affected adolescent females, capable of reproduction, with blood phenylalanine levels above the current recommended therapeutic range
      3. Loss of follow-up of such females despite effort to identify them
      4. Teratogenic effect of elevated phenylalanine levels during pregnancy
      5. Fetal anomalies preventable by dietary therapy starting before conception and throughout pregnancy on women with PKU
   2. Abnormalities in the children of women with uncontrolled PKU during pregnancy (Rouse et al. 1997, 2000).
      1. Psychomotor retardation (92%)
      2. Intrauterine growth retardation (40%)
      3. Microcephaly
      4. Congenital heart defects (10%)
      5. Postnatal growth retardation
      6. Neurologic deficits
      7. Mild craniofacial dysmorphic features
      8. The frequency of abnormalities directly related to the degree of elevation of maternal phenylalanine levels during pregnancy
      9. Abnormalities more likely to occur if maternal phenylalanine levels are not controlled during critical periods of embryogenesis and organogenesis early in pregnancy
   3. Currently, the control of phenylalanine levels during pregnancy is recommended at 2–6 mg/dL or 1–4 mg/dL: at least as strict, if not more strict, as that currently recommended for PKU treatment during early childhood. Although tight control can improve pregnancy outcomes greatly, it is important to avoid phenylalanine deficiency because this can result in muscle breakdown, leading to paradoxic hyperphenylalaninemia, hypoglycemia, seizures, and death (Clarke 2003).
   4. Women with mild forms of PKU having relatively mild elevations of the phenylalanine are at risk of adversely affecting the fetuses if the mothers are unmonitored and untreated during pregnancies. Because placental gradient favors the fetus, the levels of Phe are higher in the fetus than in the mother.
   5. Effects of uncontrolled maternal PKU occur regardless of the genetic PKU status of the fetus.

Diagnostic Investigations

1. Universal newborn screening from a heel-stick blood spot for PKU (since the 1960s) for early detection and treatment of the disorder (Dougherty and Levy 1999; Hellekson 2001; Howell et al. 2001; Koch 1999; National Institutes of Health Consensus Development Conference Statement 2001; Mitchell 2013).
   1. Guthrie bacterial inhibition assay.
      1. Inexpensive
      2. Simple
      3. Reliable
   2. Fluorometric analysis.
      1. Quantitative and automated test
      2. Fewer false positive
   3. Tandem mass spectrometry: newborn screening for PAH deficiency in the United States is now primarily performed by tandem mass spectrometry (Vockley et al. 2014).
      1. Quantitative and automated test
      2. Fewer false positive
      3. Measurements of tyrosine
      4. Identification of other metabolic disorders on a single sample
2. Phenylketonuria screening: effect of early newborn discharge (Sinai et al. 1995).
   1. Twenty-four percent of term newborns in the United States are discharged by 24 h of life.
   2. Most hospitals screen all infants for PKU before discharge regardless of age.
   3. The majority of states do not mandate rescreening; rescreening policies among

pediatricians and institutions in those states vary widely.
4. A significant number of infants do not receive repeated screening and are therefore at risk for delayed or missed diagnosis of PKU because of insensitive initial screens.

3. About one percent of all babies tested from newborn screening prove to be "false positives" (Mabry 1990). Two-thirds of those with persistent hyperphenylalaninemia prove to have classical PKU. Nonclassical PKU with less intense, persistent hyperphenylalaninemia is due to different alterations in the enzyme, phenylalanine hydroxylase. Additionally, about one percent of the confirmed positive patients are due to either a defect in the synthesis or regeneration of the cofactor, tetrahydrobiopterin; these latter forms are not amenable to treatment with the low-phenylalanine diet. Screening programs have developed directives regarding the timing and conditions for obtaining the specimens for testing. Specific confirmatory tests of those with positive results must be performed. Even so, about one in 70 affected babies is "missed," resulting in mental retardation, seizures, and neurologic deficits.
4. Plasma quantitative amino acid analysis especially phenylalanine and tyrosine levels (National Institutes of Health Consensus Development Conference Statement 2001).
   1. Phe concentrations persistently >2 mg/dL in the untreated state
   2. Recommended blood Phe levels in US clinics
      1. 2–6 mg/dL for age <12 years
      2. 2–10 mg/dL for age >12 years
   3. Frequent monitoring of blood Phe levels
      1. During the first year: once a week to once a month
      2. After the first year: once a month to once every 3 months
   4. Recommended blood Phe levels in pregnant maternal PKU
      1. <6 mg/dL achieved at least 3 months before conception
      2. 2–6 mg/dL during pregnancy
5. MRI of the brain (Levy et al. 1996a).
   1. Hypoplasia of the corpus callosum: a marker for adverse brain development in maternal PKU
   2. Areas of demyelination
6. Molecular genetic testing.
   1. Primary purpose
      1. Confirmatory diagnostic testing.
      2. Determine carrier status of at-risk relatives.
      3. For prenatal diagnosis.
   2. Methodology (Mitchell et al. 2011)
      1. Targeted mutation analysis: 1–15 common mutations (alleles may be population related) (30–50%)
      2. Mutation scanning: common and private sequence variants (99%)
      3. Sequence analysis: common and private sequence variants (99%)
      4. Duplication/deletion analysis: exonic or whole-gene deletions/duplications (rare)
      5. Linkage analysis

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Twenty-five percent affected
      2. Fifty percent carrier
      3. Twenty-five percent normal
   2. Patient's offspring
      1. Not increased unless the spouse is also a carrier in which case there will be a 50% risk of having an affected offspring and a 50% of having a carrier offspring
      2. All offspring of PKU mothers
         1. Carry at least one abnormal gene at the PAH locus inherited from their homozygous-affected mothers (obligatory heterozygotes).
         2. Approximately, one in 120 (1/4 × 1/30) offspring will be affected by inheriting two abnormal *PAH* genes from both parents depending on the PKU carrier status of the father.

2. Prenatal diagnosis (Mitchell 2013)
    1. Fetal ultrasonography in noncompliant maternal PKU (Levy et al. 1996b)
        1. Intrauterine growth retardation
        2. Microcephaly
        3. Congenital heart disease
    2. DNA mutation analysis on fetal cells by amniocentesis or CVS
        1. Provided the disease-causing mutations in the *PAH* gene identified in an affected family member. Prenatal diagnosis for PAH deficiency is only available using DNA-based methodologies (Vockley et al. 2014).
        2. Informative markers available for linkage analysis.
    3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member.
3. Management
    1. Maternal diet influences offspring outcome – before, during, and after pregnancy (Waisbren et al. 2015).
    2. Management during pregnancy (Singh et al. 2014; Vockley et al. 2014).
        1. Fetal development is optimal when maternal PHE levels are <360 μmol/l prior to conception.
        2. There is a linear relationship between maternal PHE levels >360 μmol/l throughout gestation and lower IQ of the developing fetus.
        3. Elevated blood PHE levels in the first 8–10 weeks of gestation are associated with an increased risk of CHD and poor fetal growth.
        4. Achievement of maternal PHE levels between 120 and 360 μmol/l prior to conception is recommended.
        5. Monitor dietary intake of pregnant women with PAH deficiency.
        6. Ensure nutrient adequacy.
        7. Consider sapropterin use on a case-by-case basis for pregnant women who have difficulty adhering to the diet.
        8. Large neutral amino acids (LNAAs) should not be used during pregnancy, as they do not consistently alter maternal blood PHE levels.
        9. Mothers with PAH deficiency may safely breastfeed.
    3. Dietary phenylalanine restriction: the only known strategy of preventing neurological impairment and mental retardation in patients with PKU.
        1. Natural history of the disease modified by a low-phenylalanine diet.
        2. Early strict restriction of phenylalanine intake resulting in normal intelligence.
        3. Phenylalanine-restricted diet for patients with PAH deficiency (Camp et al. 2014; Vockley et al. 2014).
            1. Treatment for PAH deficiency should be lifelong for patients with untreated PHE levels >360 μmol/l.
            2. Maintaining a treated PHE level of 120–360 μmol/l is recommended for all patients of all ages.
        4. Special medical foods devoid of or low in phenylalanine supplemented with tyrosine
        5. Tyrosine supplementation in the diet for PKU produces marked but nonsustained increases in plasma tyrosine levels, with calculated brain influx that often remains suboptimal. This could explain the lack of consistent neuropsychologic benefit with tyrosine supplementation (Kalsner et al. 2001).
        6. Restricted diet worth trying in most individuals with previously untreated PKU with possible benefits (Yannicelli and Ryan 1995) in the areas of concentration, alertness, mood, irritability, and adaptive behavior (Fitzgerald et al. 2000).
    4. Late-treated PKU: although the severe cognitive impairment associated with untreated PKU can in many cases be partially reversed with dietary treatment, prompt initiation of treatment following newborn metabolic screening is essential for optimal development and the prevention of disability (Grosse 2010).
    5. Adult complications in PKU (Hoeks et al. 2009): consisting of two

components, namely, high Phe levels (e.g., neurological and neuropsychological problems) and complications occur as a cause of dietary protein restriction (e.g., vitamin deficiencies and osteoporosis).

1. Adults with PKU who were treated from early infancy have normal intelligence, but their neuropsychological test scores are somewhat lower than those of the general population, their parents, and their unaffected siblings (Weglage et al. 1993).
2. Adults with PKU who were continuously treated but relaxed the diet have displayed white matter abnormalities on structural magnetic resonance imaging (Cleary et al. 1994; Sener 2003), which are considered to be indicative of a reduction in myelin (Dyer et al. 1996; Joseph and Dyer 2003). These abnormalities disappear after reintroducing a strict diet.
3. Neurological investigations in early-treated adults with PKU who discontinued the diet reveal a higher incidence of minor neurological signs including tremor, brisk deep tendon reflexes, or clumsy motor coordination (Thompson et al. 1990; Pietz et al. 1998). In rare cases, severe neurological deterioration may occur after cessation of dietary treatment.
4. Severe behavior and psychiatric problems are seen in profoundly retarded (untreated) adults with PKU in the third and fourth decade of life (Paine 1957). With introduction of a Phe-restricted diet, these symptoms are sometimes reversible (Baumeister and Baumeister 1998).
5. The risk for neurocognitive or psychological symptoms in PAH deficiency is related to age of onset of therapy, lifelong PHE levels, and adherence to treatment. Age-specific neuropsychiatric and cognitive testing is necessary to adequately assess clinical needs. Appropriate intellectual and mental health assessments are an important component of care for individuals affected with PKU (Vockley et al. 2014).
6. Vitamin B12 deficiency.
    1. Vitamin B12 is only found in animal protein, the sources being meat, fish, and poultry. Since the PKU diet is restricted in protein, vitamin B12 must be provided either combined with the amino acid supplement or from a separate supplement.
    2. Vitamin B12 deficiency can occur when PKU patients relax their diet in adolescence (Robinson et al. 2002). They tend to choose products that are low in animal protein, and amino acid supplements are not taken properly (Hvas et al. 2006).
7. Osteoporosis: possibly due to long-standing dietary deficiency in protein, calcium, vitamin D, or trace elements or a primary defect in bone turnover inherent to the disease itself (Modan-Moses et al. 2007).

6. Nutritional management of PKU (Feillet and Agostoni 2010).
    1. Becomes more complex with the multitude of amino acid substitutes available and with the different nutritional issues, such as polyunsaturated fatty acids, micronutrient deficiencies, bone disease, and antioxidant status, that have arisen.
    2. Long-term dietary guidance and monitoring of the nutritional status of patients with PKU should be part of a follow-up program that continues for life.
7. Sapropterin (Vockley et al. 2014).
    1. Currently, the only FDA-approved medication for the treatment of PAH deficiency and may be useful in reducing PHE levels in responsive patients.
    2. Reduction of blood PHE, increase in dietary PHE tolerance, or improvement

in clinical symptoms are all valid indications for continuation of therapy.

8. Tetrahydrobiopterin (BH4) therapy (Al Hafid and Christodoulou 2015).
    1. Synthetic biopterin compounds were made available in the late 1970s (Schircks et al. 1976), and the benefit of administering this preparation in patients with atypical PKU was first demonstrated by Schaub et al. (1978).
    2. These patients also require neurotransmitter precursors (L-dopa/carbidopa and 5-hydroxytryptophan) as part of their treatment and for dihydropteridine reductase deficiency, folinic acid supplementation (reviewed in Blau et al. (2011)).
9. Large neutral amino acids (LNAAs) (Al Hafid and Christodoulou 2015).
    1. The LNAAs, Phe, tyrosine, tryptophan, and the branched chain amino acids share the same amino acid transport system across the blood–brain barrier. Therefore, at high concentrations, phenylalanine in the blood will compete with other LNAAs for transport across the blood–brain barrier (Pietz et al. 1999).
    2. Large neutral amino acid supplementation has been shown to reduce cerebral Phe concentrations despite the observed increase in plasma Phe levels (Pietz et al. 1999). However, others have shown decreased blood Phe levels in PKU patients with LNAA supplementation (Sanjurjo et al. 2003; Schindeler et al. 2007; Matalon et al. 2006, 2007), suggesting that LNAAs not only compete with Phe for transport across the blood–brain barrier (Pietz et al. 1999) but may also exert its effect by competing with Phe for active transport across the intestinal mucosa (Koch et al. 2003b; Matalon et al. 2006, 2007).
10. Glycomacropeptides (GMP) (Al Hafid and Christodoulou 2015).
    1. GMP is a protein derived from cheese whey that is naturally low in Phe and is rich in valine, isoleucine, and threonine (Etzel 2004).
    2. GMP, manufactured to sufficient purity and supplemented with the essential amino acids tyrosine, tryptophan, arginine, cysteine, and histidine, can be a useful adjunct to the Phe-restricted diet (Ney et al. 2009; van Calcar et al. 2009).
    3. GMP may be used to replace 50% of the protein intake to improve the nutritive value and palatability of diet and to provide a more satisfactory diet (Zaki et al. 2016). No toxicity or side effects were reported in patients on that regimen.
    4. GMP-MFs (traditional amino acid medical foods) provide a safe and acceptable option for the nutritional management of phenylketonuria (Ney et al. 2016).
11. Alternative treatments (Al Hafid and Christodoulou 2015).
    1. Gene therapy.
        1. The use of self-complementary AAV vectors resulted in normalization of hyperphenylalaninemia for up to 80 weeks in both males and females (Yagi et al. 2011).
        2. The transfer of foreign genes using nonviral vectors into tissues or organs by direct injection of naked plasmid DNA has been achieved leading to transgene expression and therapeutic responses (Lechardeur and Lukacs 2002; Niidome and Huang 2002).
    2. Phenylalanine ammonia-lyase (PAL) (Strisciuglio and Concolino 2014).
        1. Enzyme therapy can be done either by enzyme replacement with PAH or by enzyme substitution with phenylalanine ammonia-lyase (Sarkissian et al. 1999).

2. The metabolism of Phe takes place for the most part in the liver, and orthotropic liver transplantation corrects the metabolic phenotype (Vajro et al. 1993).
3. Liver transplantation is not a treatment option except for unusual PKU patients who need a liver transplant for another disease such as cirrhosis, because of the burden of daily therapy in transplanted patients. In mice, enzyme replacement with PAH-fusion proteins is a promising approach (Eavri and Lorberboum-Galski 2007).
4. Enzyme substitution therapy with phenylalanine ammonia-lyase (PAL) appears more promising. It can act as a surrogate for the deficient PAH and converts the excess systemic Phe to trans-cinnamic acid and ammonia. Both pharmacological and physiological principles of therapy have been demonstrated following the use of PAL given orally or by injection in PKU mouse models (Gámez et al. 2004).

3. Cell-directed therapy (Strisciuglio and Concolino 2014): cell-based therapies using stem cells or more differentiated progenitor cells may represent the future of cell transplantation for treatment of metabolic liver diseases such as PKU.
4. Genetically modified (GM) probiotic for the production and delivery of metabolic enzymes.

4. Counseling for maternal PKU
   1. Genetic and nutritional evaluation and counseling, optimally before contemplating pregnancy.
   2. The achievement of pre- and periconceptional dietary control with a Phe-restricted diet significantly decreased morbidity in the offspring of women with HPA (Koch et al. 2003a).
   3. Benefits of dietary phenylalanine restriction in pregnant women with hyperphenylalaninemia decrease the incidence of following fetal effects (Hanley et al. 1999; Platt et al. 2000).
      1. Mental retardation
      2. Microcephaly
      3. Congenital heart disease
      4. Intrauterine growth retardation
   4. Quality of life and psychologic adjustment in children and adolescents with early-treated phenylketonuria can be normal (Landolt et al. 2002).
   5. The significant relationship among genotype, biochemical phenotype, and cognitive performance observed is of importance for the development of an optimal strategy for future treatment of females with PKU who plan pregnancy (Güttler et al. 1999).
   6. Female individuals with severe PKU should be offered a diet for a lifetime. If good metabolic control is established, then women with PKU will have children with IQ scores that are not influenced by their disease (Güttler et al. 2003).
   7. Long-term compliance with treatment remains a key challenge for the future, especially with respect to adolescents and young adults, those trying to become pregnant, and during pregnancy (Blau et al. 2010).
   8. Assistance of women with hyperphenylalaninemia, who are unable or unwilling to maintain blood phenylalanine levels in the range for optimum pregnancy outcome, to obtain adequate means for birth control, including tubal ligation if requested.
   9. Counseling of women with hyperphenylalaninemia who conceive with blood phenylalanine levels greater than 4–6 mg/dL concerning risks to the fetus offers detailed ultrasonography to detect fetal abnormalities such as growth retardation and congenital heart defects.
   10. Close monitoring of serum phenylalanine levels at 2–6 mg/dL during pregnancy of PKU mother and intake of vitamins (folic acid and vitamin B12, in particular) and other nutrients (National Institutes of Health

Consensus Development Conference Statement 2001).

11. Blood testing for hyperphenylalaninemia indicated to children born to women with features of maternal PKU fetal effects without a known cause.

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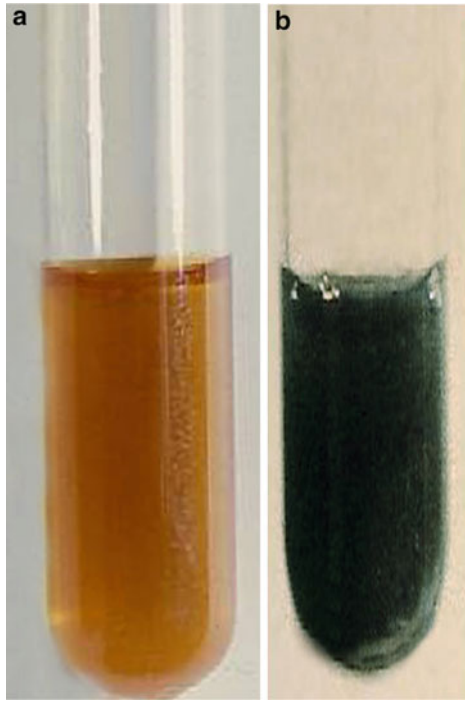

Fig. 1 (**a**, **b**) Normal-colored urine (*left*) (**a**) and deep-green color change after adding ferric chloride due to the presence of phenylpyruvic acid (*right*) (**b**)

Fig. 2 (**a**–**c**) Two successfully treated girls: the first girl at age 3 years and 7 months (**a**), the second girl at age 6 years (**b**) and at age 16 years (**c**)

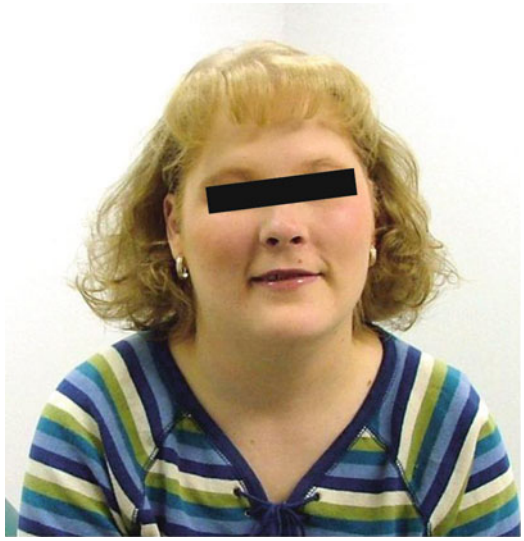

Fig. 3 A successfully treated 25-year-old adult female with PKU

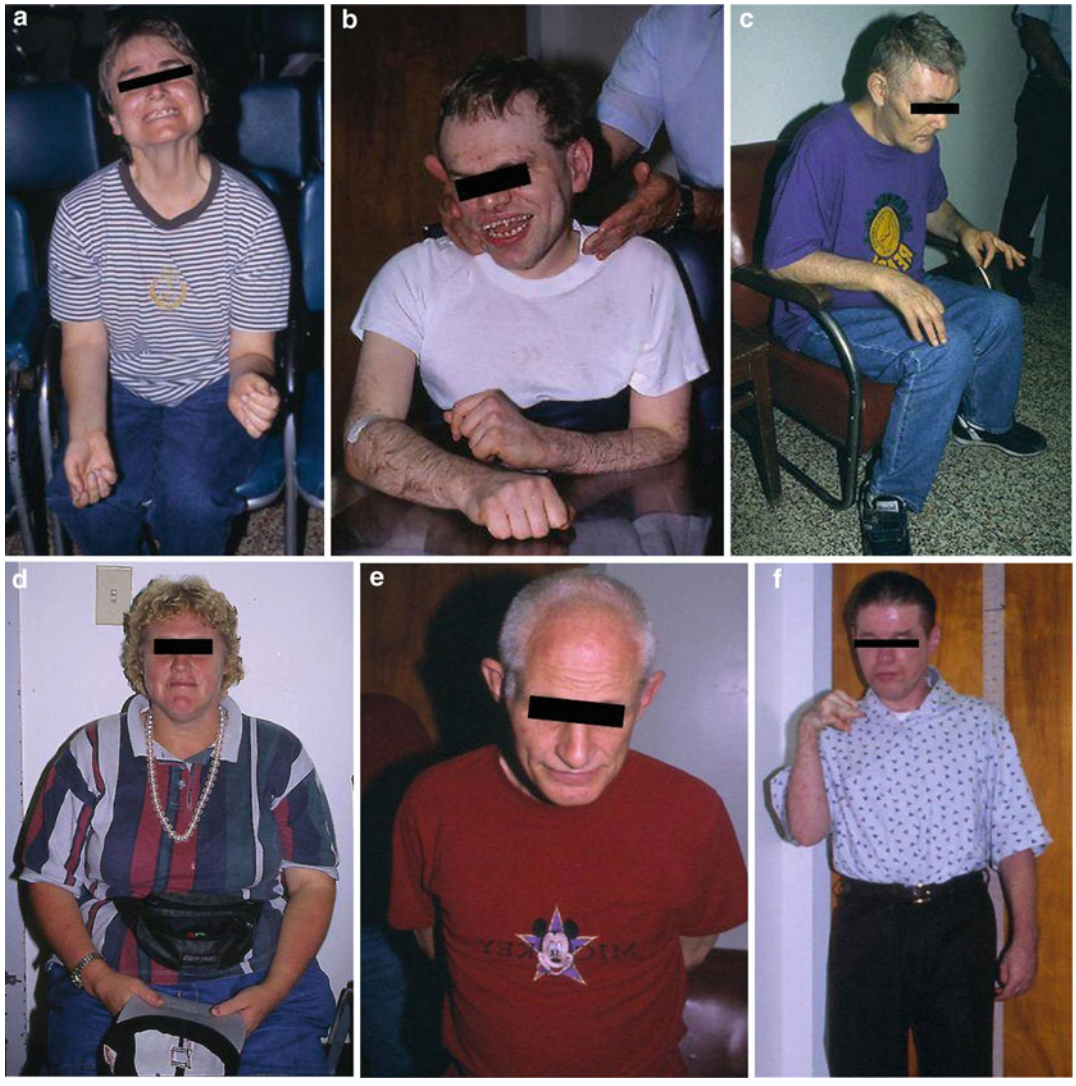

Fig. 4 (**a**–**f**) Six adults with untreated PKU showing varying degrees of mental retardation

Fig. 5 Noncompliant PKU mother and her infant with microcephaly and mental retardation

Pierre Robin Sequence

Contents

Pierre Robin described a group of patients with cleft palate, micrognathia, and glossoptosis in *1923* (Robin 1923). The meticulous documentation of the triad of findings led to the recognition of the sequence that bears his name (Randall et al. 1965). Pierre Robin sequence is estimated to affect approximately 1 in 8,500 births (Bush and Williams 1983).

Synonyms and Related Disorders

Glossoptosis, micrognathia, and cleft palate; Pierre Robin syndrome (PRS); Robin anomalad

Genetics/Basic Defects

1. Inheritance
    1. Sporadic in most instances
    2. Rare occurrence of isolated robin sequence in siblings: rare (da Costa and Matias 2014)
    3. May be familial with autosomal dominant mode of inheritance (Sidhu and Deshmukh 1989)
    4. Robin anomalad: its nonspecificity and associated syndromes (Cohen 1976)
    5. Syndromic form: etiologically heterogeneous (Shprintzen 1988, 1992; Cohen 1999; Holder-Espinasse et al. 2001; Taylor 2001; Evans et al. 2011; Buchanan et al. 2014)
        1. Monogenic
            1. Stickler syndrome (common cause) (Sheffield et al. 1987; van den Elzen et al. 2001): associated with mutations in COL genes (*COL2A1*, *COL9A1*, *COL11A1*, and *COL11A2*) (Acke et al. 2012)
            2. Velocardiofacial syndrome (microdeletion of chromosome 22q11.2)
            3. Beckwith-Wiedemann syndrome
            4. Camptomelic syndrome
            5. Cerebrocostomandibular syndrome
            6. Congenital myotonic dystrophy
            7. Larsen syndrome
            8. Mandibulofacial dysostosis
            9. Miller-Dieker syndrome
            10. Nager syndrome (Rosa et al. 2015)
            11. Otopalatodigital syndrome II
            12. Popliteal pterygium syndrome
            13. Robin-oligodactyly syndrome
            14. Spondyloepiphyseal dysplasia
            15. Treacher Collins syndrome associated with mutations in the *TCOF1*,

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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PLORIC, and *POLRID* genes (Kadakia et al. 2014)
   2. Chromosomal
      1. Del(22q) velocardiofacial syndrome (common cause)
      2. Del(4q32-qter) syndrome
      3. Del(2q24-q22) syndrome
      4. Del(6q) syndrome
      5. Dup(11q21-q23) syndrome
      6. 17q21 deletion/translocation near SOX9
   3. Teratogenic
      1. Fetal alcohol syndrome
      2. Fetal hydantoin syndrome
      3. Fetal trimethadione syndrome
      4. Maternal diabetes
   4. Deformation
      1. Oligohydramnios
      2. Uterine structural anomalies
      3. Amniotic band syndrome
   5. Disruption: amniotic band disruption
   6. Unknown cause:
      1. CHARGE syndrome
      2. Femoral dysgenesis
      3. Moebius sequence
      4. Robin/amelia association
      5. Distal arthrogryposis-Robin syndrome
2. Pathogenetically and phenotypically variable (Robin sequences and complexes) (Carey et al. 1982)
   1. Malformation sequence based on intrinsic mandibular hypoplasia that prevents the normal descent of the tongue interfering with palatal fusion, for example:
      1. Treacher Collins syndrome
      2. Del(22q) syndrome
   2. Deformation sequence based on extrinsic mandibular hypoplasia caused by intrauterine constraint
      1. Oligohydramnios (reduced amniotic fluid results in compression of the chin against the sternum restricting mandibular growth and impacting the tongue between the palatal shelves)
      2. Mandibular catch-up growth expected after birth when intrauterine deforming forces are no longer acting since micrognathia is based upon intrauterine molding
      3. Neurogenic hypotonia leading to lack of mandibular exercise
      4. Connective tissue dysplasia: Stickler dysplasia complex
      5. Spondyloepiphyseal dysplasia congenita complex
3. Genetic basis of the Pierre Robin sequence (Jakobsen et al. 2006)
   1. A comparison among cases in the literature and cases in cytogenetic databases revealed consistency to a certain degree to loci 2q24.1-33.3, 4q32-qter, 11q21-23.1, and 17q21-24.3.
   2. No particular candidate genes can be identified for certain from the present study, but GAD67 on 2q31, PVRL1 on 11q23-q24, and the SOX9 gene on 17q24.3-q25.1 are suggested to be important.

Clinical Features

1. Classic triads
   1. Posterior, U-shaped cleft palate
   2. Micrognathia/retrognathia
   3. Glossoptosis (observed tendency of the tongue to move posteriorly obstructing the oropharynx)
2. Pierre Robin sequence using different criteria
   1. Mandibular deficiency
   2. Cleft palate (U-shaped) (Hanson and Smith 1975)
   3. Upper airway obstruction
3. Respiratory difficulty
   1. Often the first sign causing concern relating to feeding
   2. May not necessarily be present at birth
   3. Upper airway obstruction and apnea
      1. Glossoptosis associated with retrognathia
      2. Upper airway collapse secondary to:
         1. Hypotonic pharynx
         2. Laryngomalacia
         3. Laryngeal cleft
         4. Laryngeal web

4. Complications of continuing airway obstruction
    1. Failure to thrive
    2. Pectus excavatum
    3. Decreased pulmonary function
    4. Sudden death
4. Failure to thrive
5. Developmental delay
    1. Usually not present in isolated Robin sequence
    2. May be present depending on the underlying syndrome
6. Middle ear diseases associated with cleft palate
    1. Otitis media (80%)
    2. Auricular anomalies (75%)
    3. Hearing loss, mostly conductive (60%)
7. Cleft palate-associated problems (Williams et al. 1981)
    1. Speech defects (severe nasal escape of air)
    2. Abnormal articulation
    3. Velopharyngeal insufficiency
8. "Catch-up growth" of the mandible
    1. Normal mandibular growth in patients with Robin sequence secondary to mechanical constraint
    2. Deficient mandibular growth in patients with intrinsic mandibular anomalies
9. Other signs and symptoms and associated anomalies depending on the underlying conditions

Diagnostic Investigations

1. Assess respiratory sounds with stethoscope during feeding and at rest.
2. Monitor developmental milestone achievement.
3. Pulse oximetry monitoring to document drops in oxygen saturation.
4. Flexible fiber optic nasopharyngoscopy.
    1. To identify exact mechanism of upper airway obstruction.
    2. To assess pharyngeal, palatal, lingual, and laryngeal morphology and function during feeding and swallowing
5. Identify the underlying cause of the micrognathia.
6. Orthodontic assessment.
7. Hearing assessment.
8. Polysomnography, polygraphy, and oximetry (Breugem et al. 2016).
    1. Polysomnography or polygraphy can quantify airway obstruction and identify comorbidities, such as central apnea (DeHaan et al. 2015).
    2. Oximetry may be specific for detecting obstructive sleep apnea (OSA), but it is not sensitive for detecting airway obstruction and OSA (Marcus et al. 2012).
9. Cervical spine evaluation to rule out cervical instability, especially those with suspected abnormalities in bone or collagen formation (Barr et al. 2016).
10. Cephalometric radiographs
    1. Deformation sequence
        1. Mandible
            1. Short body
            2. Short ramus
            3. Increased gonial angle
            4. Incomplete catch-up growth
        2. Cranial base angle: decreased
    2. Treacher Collins syndrome
        1. Mandible
            1. Short body
            2. Short ramus
            3. Characteristic shape
            4. Severely affected growth
        2. Cranial base angle: decreased
    3. Del(22q11.2) syndrome
        1. Mandible
            1. Retrognathia
            2. Essentially normal in shape
        2. Cranial base angle: increased
    4. Stickler dysplasia complex
        1. Mandible
            1. Short ramus
            2. Antegonial notching of body
        2. Cranial base angle: decreased
    5. Spondyloepiphyseal dysplasia congenita complex: short body of mandible
11. Chromosome analysis: del(22q11.2) and others.
12. Molecular diagnosis (Cohen 1999).
    1. Treacher Collins syndrome: mutations in *TCOF1*

2. Stickler dysplasia complex
   1. Mutations in *COL2A1*
   2. Mutations in *COL11A1*
3. Spondyloepiphyseal dysplasia congenita complex: mutations in *COL2A1*

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: rare unless Pierre Robin sequence is a part of a syndrome
   2. Patient's offspring: rare unless Pierre Robin sequence is a part of a syndrome
2. Prenatal diagnosis (Hsieh et al. 1999)
   1. Ultrasonography (Pilu et al. 1986)
      1. Polyhydramnios
      2. Micrognathia/retrognathia and cleft palate
      3. Cardiac anomalies
   2. Chromosome analysis: occasional (trisomy 21, 18)
3. Management (Shprintzen 2001; Evans et al. 2011)
   1. Prone positioning of infants (Tewfik et al. 2015) believed to help prevent the tongue and mandible from obstructing the airway, leading to generally improved oxygen saturation
   2. Nasogastric tube placement for early feeding and ensuring adequate relief of the airway obstruction (Heaf et al. 1982)
   3. Occupational therapy directed toward management of the palatal abnormality
   4. Perioperative care of the neonate and infant with PRS (Cladis et al. 2014)
      1. The primary concern is upper airway obstruction with subsequent respiratory distress and feeding difficulty.
      2. The later may manifest as reflux and failure to thrive. PRS comprises a heterogeneous group of patients.
      3. Some may present with an isolated mandibular abnormality, while other patients with PRS have associated anomalies or syndromes.
      4. The patient with mild airway obstruction can be managed conservatively with nasopharyngeal airways, prone positioning, and mechanical feeders.
      5. Moderate or severe obstruction requires more invasive interventions such as gastrostomy tube placement, tongue-lip adhesion, mandibular distraction osteogenesis, and tracheostomy.
   5. Surgical intervention for upper airway obstruction (Bath and Bull 1997; Scott et al. 2012)
      1. Glossopexy/tongue-lip adhesion (Argamaso 1992) to bring tongue forward and attach it to an anterior structure to prevent the tongue from falling back into the airway
      2. Tracheotomy (Myer et al. 1998) needed only in cases where conservative treatments fail
      3. Mandibular distraction osteogenesis (surgical incision of the mandible followed by the application of traction to stimulate new bone growth): reduces cleft palate width and lengthens soft palate, influencing palatoplasty in patients with Pierre Robin sequence (Collares et al. 2016)
      4. Repair of cleft palate
   6. Treat middle ear infections
      1. Antibiotics
      2. Placement of tympanostomy tubes
   7. Speech therapy

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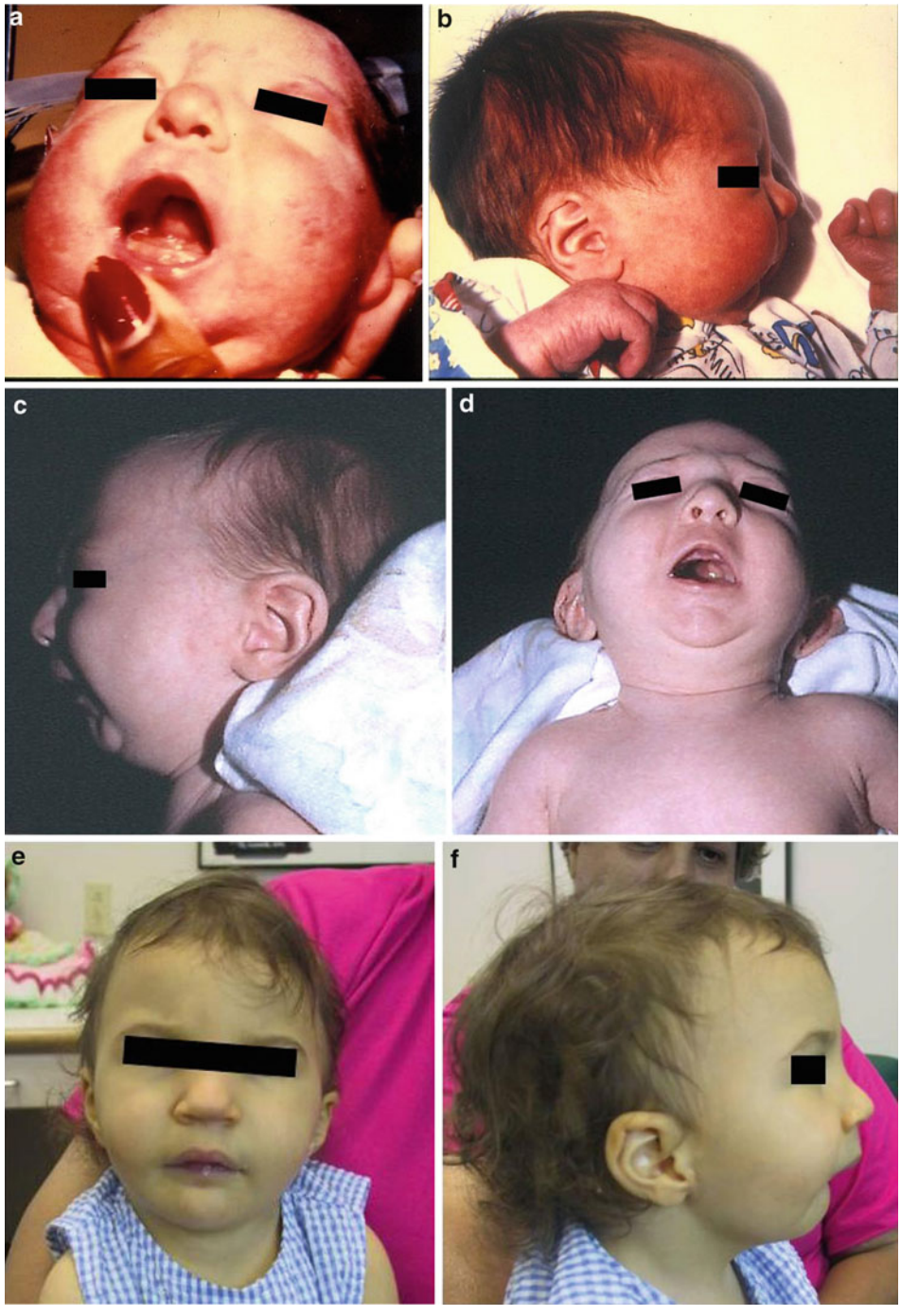

Fig. 1 (**a**–**f**) Three infants (**a**, **b**; **c**, **d**; **e**, **f**) with typical Pierre Robin sequence

Polycystic Kidney Disease: Autosomal Dominant Type

Contents

Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of polycystic kidney disease with an estimated incidence of approximately 1/400–1/1,000 individuals worldwide. It roughly accounts for 10% of patients with chronic renal failure requiring hemodialysis or transplantation (Arnaout 2001).

Synonyms and Related disorders

Adult type; Polycystic kidney disease

Genetics/Basic Defects

1. Inheritance:
   1. Autosomal dominant with almost complete penetrance
   2. Negative family history in 40% of cases
2. Genetically heterogeneous with at least three different genes now known to cause ADPKD. All three types of ADPKD present with an identical profile of extrarenal manifestations (including liver cysts and aneurysms) (Wilson 2004):
   1. Type I (85–90% of cases): caused by mutations in *PKD1* gene, which is:
      1. Mapped on chromosome 16p13.3.
      2. The most severe form with a lower median survival and a higher risk of progressing to end-stage renal disease.
      3. Closely linked to TSC2, a gene responsible for a major form of tuberous sclerosis.
      4. ADPKD1 is an inherited disorder that has led to the discovery of a novel protein, polycystin. Polycystin, a 460 kd protein with a host of domains implicating a potential role in cell-cell and cell-matrix regulation, is encoded by a 52 kb gene with a 14 kb mRNA (Grantham 1996). ADPKD1 is caused by mutated DNA that encodes an abnormal form of polycystin.
      5. Highly variable severity of renal cystic disease (Rossetti et al. 2002a).
   2. Type II (most of the remaining cases): caused by mutations in *PKD2* gene, which is:
      1. Mapped on chromosome 4q13-q23 (Kimberling et al. 1993).
      2. Identified by positional cloning.
      3. Producing milder disease but otherwise phenotypically identical with the *PKD1* disease.

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4. PKD2 protein is also large (110 kd) and is thought to interact with polycystin (Grantham 1996).
5. Although PKD2 is clinically milder than PKD1, it has a deleterious impact on overall life expectancy and cannot be regarded as a benign disorder (Hateboer et al. 1999).

3. In the vast majority of cases, the disease is caused by mutations in *PKD1* or *PKD2* and appears to be recessive at the cellular level. Somatic second hits in the normal allele of cells containing the germline mutation initiate or accelerate formation of cysts. The intrinsically high frequency of somatic second hits in epithelia appears to be sufficient to explain the frequent occurrence of somatic second hits in the disease-causing genes (Arnaout 2001).
4. A small number of familial cases reported to be unlinked to both the *PKD1* and *PKD2* loci, suggesting the existence of at least one more proposed gene (*PKD3*) which has not been identified (Daoust et al. 1995; Ariza et al. 1997).
5. Patients with mutations in both the PKD1 and PKD2 genes (transheterozygotes) (Pei et al. 2001) have a more severe clinical course than those with mutations in only one of the genes.

3. Mechanism of cyst formation: somatic second-hit model (Wilson 2004):
   1. A germline mutation in one PKD allele in all cells in ADPKD
   2. A random somatic mutation (second hit) occurring in the normal allele causing increased cell proliferation, leading to cyst formation
4. Molecular basis of ADPKD (Rossetti et al. 2002b):
   1. Protein products of the disease gene forming a macromolecular signaling structure, the polycystin complex, that regulates fundamental aspects of renal epithelial development and cell biology
   2. Protein products of PKD1 and PKD2 (polycystin-1 and polycystin-2), respectively:
      1. Share sequence homology
      2. May form components of a receptor/channel complex
   3. Polycstin-1:
      1. Predicted to have a receptor-like structure
      2. May be involved in cell-cell/matrix interactions
      3. May have a regulatory role over a polycystin channel
   4. Polycystin-2:
      1. Similar to and functioning as an ion channel subunit
      2. Causes nonselective cation permeability
   5. Basic defect in ADPKD: could be in polycystin-regulated intracellular Ca^{++} levels
5. Molecular basis of other polycystic kidney disease (Wilson 2004):
   1. Autosomal recessive polycystic kidney disease (please see the chapter "▶ Polycystic Kidney Disease: Autosomal Recessive Type"):
      1. Caused by mutation in *PKHD1* loss of functional fibrocystin
      2. Fibrocystin: a receptor-like membrane protein with putative extracellular matrix interaction domains as well as intracellular signaling sites
   2. Juvenile nephronophthisis:
      1. Caused by mutation in *NPH1* loss of functional nephrocystin
      2. Nephrocystin: an intracellular protein that interacts with the focal adhesion complex, the cilium, and tyrosine signaling molecules
6. Disease characteristics:
   1. Principal ductal organs with cyst formation:
      1. Kidneys
      2. Liver
   2. Consequences of cyst enlargement:
      1. Progressive destruction of normal renal tissue
      2. End-stage renal failure in >50% of patients by age 60
   3. Systemic involvement:
      1. Arterial hypertension developing early and observed in >50% of patients

2. Vascular aneurysms
3. Cardiac valve defects
4. Colonic diverticula

Clinical Features

1. Autosomal dominant polycystic kidney disease:
    1. Presenting in the fetus or newborn is rare (Edwards and Baldinger 1989).
    2. First symptoms of the disease occur usually in the third or fourth decade of life (Wolyniec et al. 2008).
2. Intrafamilial and interfamilial variability in the onset, phenotype, and progression of the disease:
    1. Due to genetic heterogeneity:
        1. More common PKD1 (accounting for approximately 85% of cases associated with more severe disease)
        2. Evidence of significant intrafamilial phenotypic variation suggesting modifying factors (such as the angiotensin-converting enzyme insertion/deletion polymorphism) as well as environmental factors that influence the clinical course
        3. Association of the position of the *PKD1* mutation with earlier end-stage renal disease
    2. Age of onset:
        1. Presenting at any age
        2. Generally presenting in the fourth and fifth decades of life
        3. Occasionally presenting in the fetal or neonatal period
3. Onset of disease in the childhood in children who carry *PKD1* gene:
    1. Frequency of children with renal cysts detectable by ultrasound:
        1. Sixty percent by 5 years of age
        2. Seventy-five to eighty percent among children aged 5–18 years
    2. Number of renal cysts at 11 years:
        1. One to ten in 60% of children
        2. More than ten cysts in 40% of children
4. Age at the time of diagnosis and progression of the disease:
    1. Diagnosis in utero or in the first year of life (intrauterine or infantile onset)
        1. Manifesting unusually severe disease
        2. End-stage renal disease during childhood in 18% of cases
    2. Diagnosis after the first year of life:
        1. Increase in the number of cysts over a mean interval of 3.7 years
        2. Systolic hypertension in 9% of cases
        3. None with decreased renal function
5. Renal manifestations (Fick and Gabow 1994; Fick et al. 1994):
    1. Development of bilateral renal cysts:
        1. Primary renal manifestation
        2. Leading to functional changes (impaired renal concentrating capacity, hypertension)
        3. Leading to various clinical manifestations
    2. Flank or back pain (about 60%)
    3. Acute pain:
        1. Infected cyst
        2. Ruptured cyst (associated with gross hematuria)
        3. Nephrolithiasis (20–36%) (Torres et al. 1993)
    4. Urinary tract infection (40–68%)
    5. Hematuria
    6. Mild proteinuria
    7. End-stage renal disease
6. Extrarenal manifestations (Fick and Gabow 1994; Perrone 1997; Luciano and Dahl 2014):
    1. Liver involvement (Chauvear et al. 2000):
        1. Most common extrarenal manifestation
        2. Liver cysts uncommon before 16 years of age
        3. Liver cysts observed in about 75% of patients older than 60 years
        4. No liver symptoms in most patients with ADPKD
        5. Occasionally encountered liver changes:
            1. Congenital hepatic fibrosis
            2. Segmental dilation of the biliary tract

6. Liver cysts responsible for most of the hepatic complications
7. Acute complications (Chauvear et al. 2000):
    1. Cyst infection
    2. Cyst hemorrhage
    3. Cyst rupture
    4. Cyst torsion
8. Chronic complications related to progressive increase of the polycystic liver (Chauvear et al. 2000):
    1. Abdominal mass
    2. Ascites
    3. Hepatic venous outflow obstruction (Budd-Chiari syndrome)
    4. Portal hypertension with variceal bleeding
    5. Inferior vena cava compression
    6. Bile duct compression
    7. Jaundice
9. Intrahepatic biliary cysts:
    1. More common in women
    2. Exacerbated by pregnancy

2. Unrelated to liver cysts (Chauvear et al. 2000):
    1. Congenital hepatic fibrosis or biliary fibroadenomatosis, focal or diffuse
    2. Idiopathic dilation of the intra- or extrahepatic biliary tract (Caroli syndrome)
    3. Cholangiocarcinoma
3. Other rare cystic involvement (Fick et al. 1994):
    1. Pancreatic cysts (10%) (Kim et al. 2016)
    2. Arachnoid cysts (5%)
    3. Ovarian cysts
4. Cardiovascular manifestations not uncommon:
    1. Intracranial berry aneurysms (5–10%)
    2. Dolichoectatic arteries
    3. Aortic root dilatation
    4. Dissections of intracerebral, coronary, thoracic, iliac, aortic, and splenic arteries reported
    5. Cardiac valve defects
5. Other noncystic involvement (Mikolajczyk et al. 2016):
    1. Colonic diverticula (80% of patients with end-stage renal disease)
    2. Hernias (25%)
    3. Large bile duct abnormalities
7. Clinical course in children:
    1. Clinical spectrum ranging from severe neonatal manifestations mimicking autosomal recessive polycystic kidney disease to renal cysts noted on ultrasound in asymptomatic children
    2. Diagnosis made in utero by ultrasound: massively enlarged cystic kidneys
    3. Newborn presenting with Potter phenotype and death from pulmonary hypoplasia
    4. Newborn with large abdominal masses
    5. After neonatal period:
        1. Hypertension
        2. Abdominal pain
        3. Palpable abdominal mass
        4. Hematuria
        5. Renal insufficiency, only rarely
        6. Renal infections
    6. Rare extrarenal manifestations:
        1. Liver cysts
        2. Cerebral vessel aneurysms
    7. Prognosis:
        1. Severe symptoms in neonatal or infantile cases
        2. Milder symptoms in late childhood cases
8. The progression of ADPKD clearly occurs in childhood and manifests as an increase in cyst number and renal size (Fick-Brosnahan et al. 2001).
9. There was a significant relationship between the severity of the renal structural involvement and the frequency of flank and back pain, hypertension, and impaired renal concentrating capacity. There was progression of the disease, reflected by an increase in cyst number and an increase in the frequency of pain and hypertension. However, glomerular filtration rate (GFR) remained stable in all children (Fick et al. 1994).
10. Genotype-phenotype correlation in children with ADPKD (Fencl et al. 2009):

1. PKD1 children have more and larger renal cysts, larger kidneys, and higher ambulatory blood pressure than do PKD2 children.
2. Renal cysts and enlarged kidneys detected prenatally are highly specific for children with PKD1.

11. Reproductive issues for adults with ADPKD (Vora et al. 2008):
    1. Men with ADPKD:
        1. Necrospermia
        2. Immotile sperm
        3. Seminal vesicle cysts
        4. Ejaculatory duct cysts
    2. Female fertility is not affected:
        1. Affected women with ADPKD and normal renal function have a high rate of successful uncomplicated pregnancies.
        2. Pregnant women with ADPKD with compromised kidney function should be monitored carefully for the development of hypertension and preeclampsia.
12. Risk factors precipitating faster progression of the disease:
    1. The *PKD-1* gene
    2. Male gender
    3. Earlier onset of symptoms:
        1. Renal enlargement
        2. Hematuria
        3. Proteinuria
        4. Incipient renal failure
        5. Hypertension
    4. Having >10 renal cysts before age 12 years
    5. Having blood pressures above the 75th percentile for age, height, and gender
    6. Polycystic liver disease:
        1. Frequently associated with autosomal dominant polycystic kidney disease
        2. Develops later than renal cysts
        3. Develops earlier and more severe in women than in men
13. End-stage renal disease:
    1. The most feared renal complication of ADPKD
    2. Occurs in more than half of patients by the seventh decade of life
14. Differential diagnosis (Wolyniec et al. 2008):
    1. Autosomal recessive polycystic kidney disease: manifests advanced renal insufficiency present already in childhood or early youth (see the chapter "► Polycystic Kidney Disease: Autosomal Recessive Type")
    2. "► Tuberous Sclerosis" (see the chapter):
        1. Cysts in the kidneys observed in 20% of patients with tuberous sclerosis complex
        2. Associated with characteristic skin and neurological symptoms
    3. "► Von Hippel-Lindau Disease" (see the chapter)
    4. Medullary cystic kidney disease:
        1. Most commonly occurs as juvenile nephronophthisis
        2. Associated with chronic renal failure in childhood
    5. "► Oral-Facial-Digital Syndrome" (see the chapter)
    6. Multicystic renal dysplasia in adults:
        1. Usually a unilateral disorder
        2. Frequent presence of calcification in the cyst walls and abnormal structure of parenchyma between the cysts visible on ultrasound
    7. Medullary sponge kidney: lithiasis and nephrocalcinosis commonly observed in the course of the disease
    8. Acquired cystic kidney disease
15. Differential features of ARPKD and ADPKD (Verghese and Miyashita 2014):
    1. ARPKD:
        1. Mode of inheritance: autosomal recessive.
        2. Location of cysts: Cysts are dilation of renal collecting ducts.
        3. Gross appearance: reniform shape maintained; multiple minute cystic spaces throughout the capsular surfaces. Cut sections of the kidney show subcapsular extensions of radially oriented cylindrical or fusiform ectatic spaces from the medulla to the cortex.

4. Age of presentation: most often in the neonatal period or childhood.
5. Frequency: 1 in 20,000 live births.
6. Extrarenal features: can occur in neonates; congenital hepatic fibrosis in all patients; manifestations of oligohydramnios, such as pulmonary insufficiency; Potter facies, club foot, and so forth
7. Renal prognosis: Fetuses with severe renal failure, oligohydramnios, and pulmonary hypoplasia often die of pulmonary complications. Patients with less severe renal manifestations who survive the neonatal period have a 50% chance of developing end-stage renal disease (ESRD) by age 10 years.

2. ADPKD:
   1. Mode of inheritance: autosomal dominant
   2. Location of cysts: Cysts develop anywhere along the nephron.
   3. Gross appearance: loss of reniform shape of kidney; numerous, large, round nodules/cysts of varying sizes on the external surface of the kidney and randomly distributed through the entire parenchyma of the kidney.
   4. Age of presentation: Most often initially presents in adults aged 20–40 years, but increasingly there are reports of ADPKD presenting in childhood and even in utero.
   5. Frequency: one case in 400–1000 population.
   6. Extrarenal features: does not occur in neonates. Congenital hepatic fibrosis and portal hypertension are very rare. Manifestations of oligohydramnios are rare. Includes hepatic cysts, pancreatic cysts found exclusively in patients with PKD1, cerebral vessel aneurysms, mitral valve prolapse, endocardial fibroelastosis, increased left ventricular mass with diastolic dysfunction even in normotensive children, ovarian cysts.
   7. Renal prognosis: Chances of ESRD are 2% in those <40 years of age and increase to 50% by the seventh decade of life.

Diagnostic Investigations

1. Urinalysis:
   1. Hematuria
   2. Mild proteinuria
   3. Evidence of infection
2. Sonography:
   1. Prenatal presentation:
      1. Large hyperechogenic kidneys: the most consistent renal ultrasonographic findings in children (Fick et al. 1993)
      2. Variable size
      3. Mixtures of small and large cysts
      4. Exceptionally uncommon oligohydramnios
   2. Postnatal presentation: invariably large cysts
3. Renal ultrasound and IVP:
   1. Enlarged kidneys
   2. Macrocysts and distortion of the collecting system
4. Age at clinical onset and at ultrasonographic detection of adult polycystic kidney disease (Bear et al. 1984): The probability of ultrasonographic detection of asymptomatic APKD is estimated as 0.222, 0.657, and 0.855 at age 5, 15, and 25 years, respectively.
5. CT scan and/or MRI for renal, hepatic (Gupta et al. 1999), pancreatic, and ovarian cysts
6. CT scan and/or MRI angiography for intracranial aneurysm
7. Renal function tests
8. Renal ultrasound to assess carrier status:
   1. A painless and relatively noninvasive procedure
   2. Detection rate in asymptomatic subjects from families with known ADPKD:
      1. Twenty-two percent of cases in the first decade

2. Sixty-six percent of cases by the second decade
3. Eighty-six percent by age 25

9. Molecular diagnosis (Harris and Rossetti 2010):
   1. Diagnosis of ADPKD before the onset of symptoms is usually performed using renal imaging by either ultrasonography, CT, or MRI. In general, these modalities are reliable for the diagnosis of ADPKD in older individuals.
   2. However, molecular testing can be valuable when a definite diagnosis is required in young individuals, in individuals with a negative family history of ADPKD, and to facilitate preimplantation genetic diagnosis.
   3. Although linkage-based diagnostic approaches are feasible in large families, direct mutation screening is generally more applicable.
   4. Identification and characterization of *PKD1* and *PKD2* provided an opportunity for mutation-based molecular diagnostics to be used for ADPKD. Mutations in *PKD1* account for about 85% of cases and cause more severe disease than mutations in *PKD2*.
   5. As ADPKD displays a high level of allelic heterogeneity, complete screening of both genes is required.
   6. Consequently, such screening approaches are expensive. Screening of individuals with ADPKD detects mutations in up to 91% of cases.
   7. However, only about 65% of patients have definite mutations, with about 26% having nondefinite changes that require further evaluation.
   8. Collation of known variants in the ADPKD mutation database and systematic scoring of nondefinite variants is increasing the diagnostic value of molecular screening.
   9. Mutation analysis of the entire PKD1 gene (Rossetti et al. 2001): The majority of changes were predicted to truncate the protein through nonsense mutations (32%), insertions or deletions (29.6%), or splicing changes (6.2%) (Rossetti et al. 2001).
   10. A complete mutation screen of the ADPKD genes by denaturing high-performance liquid chromatography (DHPLC) (Rossetti et al. 2002b).
   11. Diagnosis of autosomal dominant polycystic kidney disease using efficient PKD1 and PKD2 targeted next-generation sequencing (Trujillano et al. 2014).
   12. Prenatal forms of autosomal dominant polycystic kidney disease (ADPKD) are rare but can be recurrent in some families, suggesting a common genetic modifying background. Few patients have been reported carrying, in addition to the familial mutation, variation(s) in polycystic kidney disease 1 (*PKD1*) or *HNF1* homeobox B (*HNF1B*), inherited from the unaffected parent, or biallelic polycystic kidney and hepatic disease 1 (*PKHD1*) mutations (Audrézet et al. 2016).

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib:
      1. Not increased in de novo case
      2. Fifty percent if one of the parent is affected
   2. Patient's offspring:
      1. Fifty percent risk of acquiring the disease
      2. Both sexes of offspring affected equally
2. Carrier testing for family members at risk:
   1. Ultrasound and radiography
   2. Molecular mutation analysis of *PKD1* and *PKD2* genes
3. Prenatal diagnosis:
   1. Prenatal ultrasonography:
      1. Enlarged kidneys (hyperechogenic) with or without cysts: the most common fetal findings.
      2. Absence of urine in the bladder.
      3. May not be evident until the third trimester.

4. Evidence of uteroplacental insufficiency (Vora et al. 2008):
    1. Intrauterine growth restriction
    2. Oligohydramnios
5. Though a highly penetrant disease, due to varied clinical expression and the typical late onset of symptoms, reproductive-aged women may not know their carrier status. Fetal US findings of ADPKD prompted maternal diagnosis of ADPKD (Euser et al. 2015).

2. Molecular mutation analysis of *PKD1* and *PKD2* genes on fetal DNA obtained from amniocentesis or CVS, provided the mutation has been identified in the affected family members or linkage has been established in the family.
3. Preimplantation genetic diagnosis possible, provided the mutation has been identified previously (Harris and Torres 2015). Genetic testing offers the chance of performing prenatal or preimplantation testing of embryos in families with severe cases of the disease (Balcells and Criach 2011).

4. Management (Harris and Torres 2015):
    1. No treatment currently directed at the disease process.
    2. Monitoring of presymptomatic patients with ADPKD:
        1. Monitor blood pressure
        2. Test renal function
        3. Advantages:
            1. Prevent or control hypertension
            2. Prevent or control infection
            3. Identify potential kidney donors from among the family
            4. Offer advice on reproduction
            5. Provide prenatal diagnosis
    3. Identification of alterable factors such as hypertension, number of pregnancies, and recurrent urinary tract infections provides the clinician with the opportunity to modify these factors and improve the management of patients with autosomal dominant polycystic kidney disease (Gabow et al. 1992).
    4. In patients with ADPKD, an effort should be made to keep the arterial blood pressure below 120/80 mmHg. In patients at high risk of progression whose renal function is still intact (eGFR $>$ 60 mL/min), strict blood pressure control ($<$110/75 mmHg) is indicated and possibly V2R blockade with tolvaptan as well (Kühn and Walz 2015).
    5. Treatment of polycystic kidney disease:
        1. Narcotic analgesics for pain
        2. Antibiotics for infection
        3. Treatment of nephrolithiasis:
            1. Potassium citrate for uric acid lithiasis, hypocitric calcium oxalate nephrolithiasis, and distal acidification defects
            2. Extracorporeal shock wave lithotripsy
            3. Percutaneous nephrostolithotomy
        4. Needle aspiration of dominant cysts
        5. Laparoscopic management of renal cystic disease (Hemal 2001): a highly effective, safe, and minimally invasive alternative to open surgery and antegrade or retrograde endoscopic procedures
        6. Open renal cyst decortication
        7. Therapeutic intervention aimed at slowing the progression of renal failure:
            1. Control of hypertension
            2. Control of hyperlipidemia
            3. Dietary protein restriction
            4. Control of acidosis
            5. Prevention of hyperphosphatemia
        8. Renal dialysis
        9. Renal transplantation for end-stage renal disease
    6. Treatment of massive polycystic liver disease (Chauvear et al. 2000):
        1. Aspiration of cyst fluid.
        2. Stenting.
        3. Cyst fenestration.
        4. Liver resection.
        5. Liver transplantation.
        6. Selected patients with severe symptoms benefit from liver resection and extensive fenestration with acceptable morbidity and mortality. Total hepatectomy and orthotopic liver

transplantation may be considered for patients with severe adult polycystic liver disease (Chen 2000).

7. Treatment for nephrolithiasis: extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy (Torres et al. 1993).
8. Treatment of cerebral aneurysms (Pirson et al. 2002):
    1. Asymptomatic aneurysm:
        1. Observation and yearly follow-up
        2. Surgery for enlarging aneurysm
    2. Ruptured or symptomatic aneurysm: surgical clipping at its neck
9. Management of aortic dissection:
    1. Aortic root dilatation:
        1. Yearly follow-up
        2. Strict blood pressure control with β-blockade
    2. Surgery (replacement of the aorta) for aortic root greater than 55–60 mm
10. Multidrug approach in management of patients with ADPKD (Ecder 2016):
    1. A multidrug approach is needed in the management of patients with ADPKD, not only to slow the progression of renal disease but also to decrease the cardiovascular complications, the major cause of morbidity and mortality in these patients (Ecder 2013).
    2. Aggressive blood pressure control with an ACE inhibitor or an angiotensin receptor blocker forms the basis of this therapy.
    3. The addition of tolvaptan (Gansevoort et al. 2016) is expected to provide supplementary benefit in decreasing the decline of renal function in these patients.
    4. Statins would have beneficial effects on slowing the progression of ADPKD.

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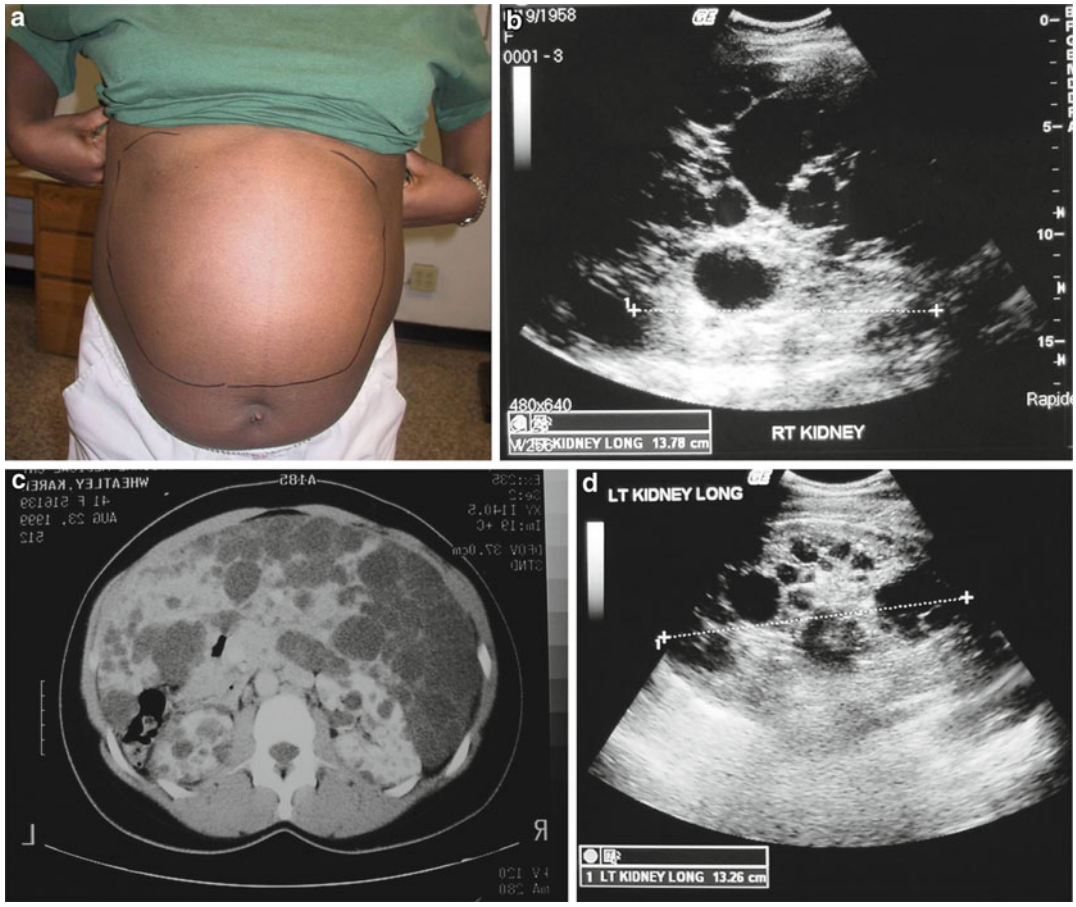

Fig. 1 (**a**–**d**) A lady (**a**) with autosomal dominant polycystic kidney disease and with family history of multiple affected family members. Her liver was markedly enlarged as shown by a *pencil mark* on the patient's photo. The ultrasonography of the kidneys showed numerous cysts with minimal residual normal appearing cortex. The *right* kidney (**b**) measured 11 cm, with the largest cyst measuring 2.9 cm. The *left* kidney measured 13.3 cm in length, with the largest cyst measuring 3.8 cm (image not shown). The abdominal CT scan (**c**) showed marked hepatomegaly which occupies the entire abdomen. Numerous hepatic cysts and renal cysts were evident. Numerous cysts of different sizes were also detected in her brother's enlarged kidneys by ultrasonography (the *left* kidney is shown here on image (**d**))

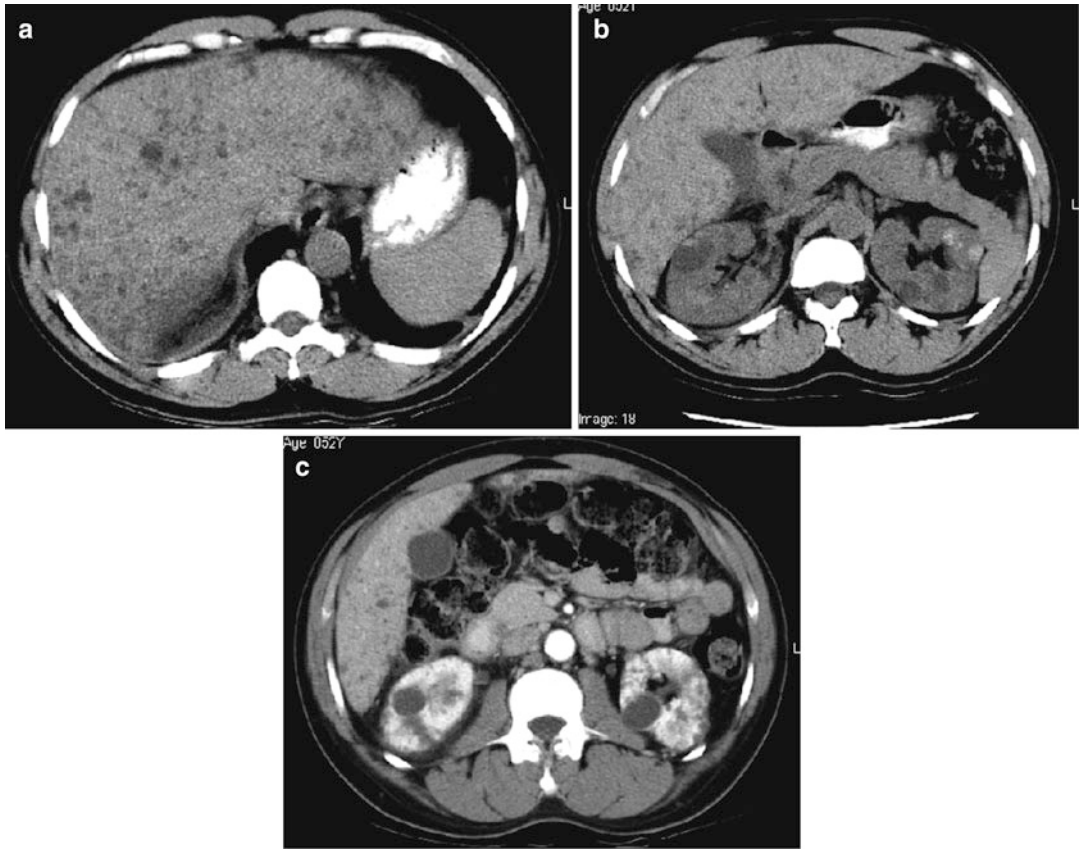

Fig. 2 (**a**–**c**) Three CT scans of an adult patient with polycystic kidney disease with and without contrast showing multiple cysts in the kidneys and liver

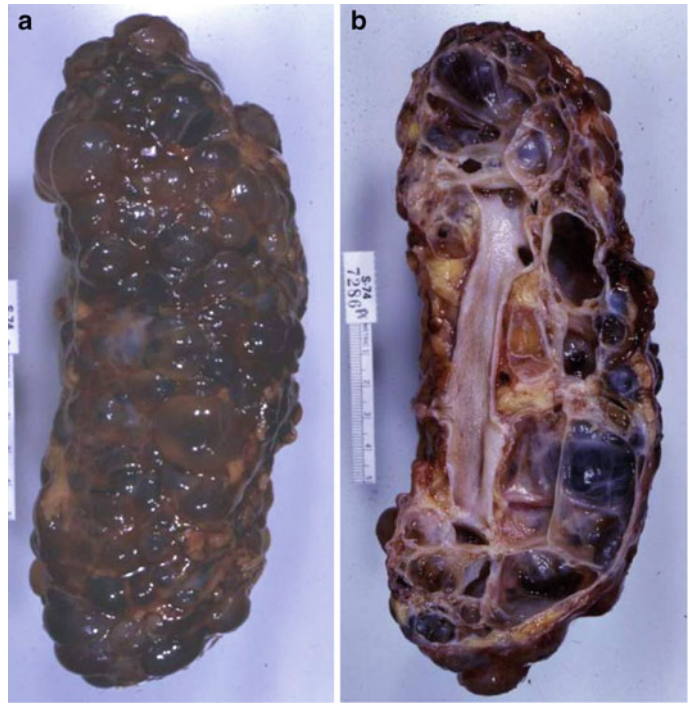

Fig. 3 Appearance of the gross (**a**) and cut section (**b**) of a kidney (745 g) surgically removed from a 43-year-old female with autosomal dominant polycystic kidney disease

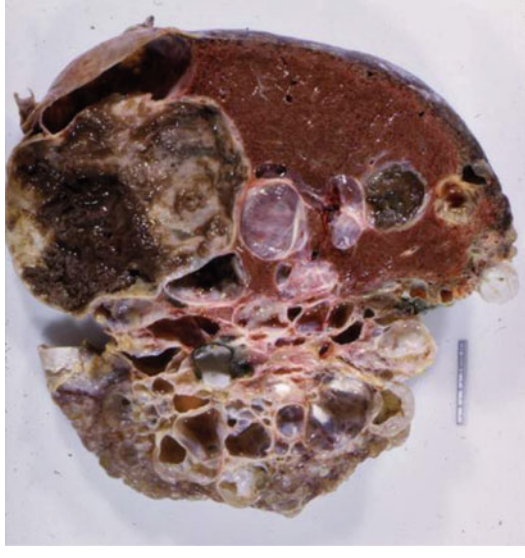

Fig. 4 Multiple hepatic cysts of a patient with autosomal dominant polycystic kidney disease

Polycystic Kidney Disease: Autosomal Recessive Type

Contents

Autosomal recessive polycystic kidney disease (ARPKD) or polycystic kidney and hepatic disease 1 (*PKHD1*) is an often devastating form of polycystic kidney disease. It is also known as infantile polycystic kidney disease. The incidence of ARPKD is estimated to be 1 in 20,000 live births, and the frequency of the heterozygous carrier state is 1 in 70 (Lonergan et al. 2000).

Synonyms and Related Disorders

Congenital hepatic fibrosis (Caroli disease); Infantile polycystic kidney disease; Polycystic kidney and hepatic disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. No clear evidence of genetic heterogeneity.
3. ARPKD: a hepatorenal fibrocystic disorder with pleiotropic effects (Hartung and Guay-Woodford 2014).
4. Molecular cause (Harris and Rossetti 2004):
   1. Mutations in the *PKHD1* gene on chromosome 6p21.1-p12 (Zerres et al. 1994), encoding a putative receptor protein, fibrocystin (or polyductin)
   2. The ARPKD protein, fibrocystin, is predicted to be an integral membrane, receptor-like protein containing multiple copies of an Ig-like domain (TIG).
   3. Fibrocystin is localized to the branching ureteric bud, collecting and biliary ducts, consistent with the disease phenotype and often absent from ARPKD tissue.
   4. In common with other PKD-related proteins, fibrocystin is localized to the primary cilia of renal epithelial cells, reinforcing the link between ciliary dysfunction and cyst development.
   5. The majority of patients are compound heterozygotes, and preliminary genotype/phenotype studies associate two truncating mutations with severe disease.
   6. The complexities of *PKHD1*, marked allelic heterogeneity, and high level of missense changes complicate gene-based diagnostics.
5. Genotype-phenotype correlations (Denamur et al. 2010):
   1. All patients carrying two truncating mutations displayed a severe phenotype with

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perinatal or neonatal demise (Bergmann et al. 2003; Dell and Avner 2011).
2. Patients who survive have at least one missense mutation.

6. The next challenges will be to determine how various factors, such as specific mutations in the *PKHD1* gene, variations in modifying gene loci, modulation by as yet unspecified environmental factors, or gene-environment interactions, contribute to the marked variability in survival and disease expression observed among ARPKD patients (Guay-Woodford and Desmond 2003).

Clinical Features

1. The most common heritable cystic renal disease manifesting in infancy and childhood (Lonergan et al. 2000).
2. A wide variable clinical spectrum (Zerres et al. 2003; Adeva et al. 2006), ranging from severe renal impairment, and a high mortality rate in infancy to older children and adolescents with minimal renal disease and complications of congenital hepatic fibrosis, cholangitis, and portal hypertension.
3. Principal manifestations:
   1. Fusiform dilatation of renal collecting ducts and distal tubuli
   2. Dysgenesis of the hepatic portal triad
4. Clinical characteristics at presentation: variable clinical spectrum:
   1. Zero to 1 month:
      1. Prenatal diagnosis made
      2. Positive family history
      3. Pneumothorax
      4. Flank mass
      5. Hypertension
      6. Renal insufficiency
   2. >1 month–1 year:
      1. Frank mass
      2. Hepatomegaly
      3. Hypertension
      4. Urinary tract infection
   3. >1–5 years:
      1. Hepatomegaly
      2. Portal hypertension
   4. >5 years:
      1. Hepatomegaly
      2. Hypertension
      3. Renal insufficiency
      4. Portal hypertension
   5. Predominance of renal abnormalities in younger children.
   6. Predominance of hepatic disease in older children and adolescents.
   7. Tendency of inverse relative degrees of kidney and liver involvement:
      1. Children with severe renal disease usually with milder hepatic disease
      2. Children with severe hepatic disease with milder renal impairment
   8. ARPKD may be underdiagnosed in adulthood because the sonographic data are not specific. Moreover, a correlation between age and hepatic involvement is not always seen, so this disease must be suspected when portal hypertension is present in a young adult with renal failure (Pérez et al. 1998).
5. "Potter" phenotype developed in affected fetuses:
   1. Pulmonary hypoplasia, often incompatible with life
   2. Characteristic face:
      1. Short and snubbed nose
      2. Deep eye creases
      3. Micrognathia
      4. Low-set flattened ears
   3. Deformities of the spine and limbs (clubfoot)
6. Renal manifestations:
   1. Frequent loss of concentrating ability of the kidney
   2. Common recurrent urinary tract infections
   3. Proteinuria
   4. Hematuria
   5. Creatinine clearance improving early but declining progressively during adolescence
   6. Hypertension early in life but usually regresses
   7. Enlarged kidneys
   8. End-stage renal disease

7. Hepatic manifestations:
    1. Congenital hepatic fibrosis (Lieberman et al. 1971):
        1. Invariably present but only occasionally do hepatic symptoms predominate.
        2. Two predominant features characterizing the liver in ARPKD:
            1. Bile ducts: abnormally/irregularly formed, often increased in number, and dilated intrahepatic bile ducts
            2. Portal tracts: enlarged and fibrotic
        3. Normal hepatic parenchyma.
        4. Hepatocellular function almost always normal in affected patients, even when they have relatively severe portal tract disease.
        5. Not by itself a diagnostic (not pathognomonic) sign. Congenital hepatic fibrosis has been observed in the following situations (Lonergan et al. 2000):
            1. Meckel-Gruber syndrome
            2. Vaginal atresia
            3. Tuberous sclerosis
            4. Juvenile nephronophthisis
            5. Rarely autosomal dominant polycystic kidney disease
    2. Caroli disease:
        1. Congenital hepatic fibrosis accompanied by a nonobstructive dilation of the intrahepatic bile ducts
        2. Clinical risk of secondary complications:
            1. Stone formation
            2. Recurrent cholangitis: may result from ectatic bile ducts
            3. Hepatic abscesses
            4. Rare cholangiocarcinoma
    3. Hepatomegaly
    4. Portal hypertension (Lonergan et al. 2000):
        1. The most common sequelae of congenital hepatic fibrosis
        2. Splenomegaly
        3. Variceal bleeding
        4. Hypersplenism:
            1. Leukopenia
            2. Thrombocytopenia
            3. Anemia
            4. Increased susceptibility to infections resulting from leukopenia associated with splenic sequestration
    5. Ascending cholangitis (Lonergan et al. 2000):
        1. Presumably caused by entry of nonsterile gastrointestinal contents into the dilated intrahepatic bile ducts
        2. Common in patients with macroscopically dilated bile ducts
        3. Clinical features:
            1. Abdominal pain
            2. Fever
            3. Elevation in levels of hepatic enzymes
        4. Tends to recur
        5. May lead to hepatic abscess formation, sepsis, and death
8. Cerebral aneurysm, a common feature of ADPKD, reported in an adult with ARPKD
9. Prognosis:
    1. Thirty to fifty percent of affected neonates die shortly after birth in respiratory insufficiency due to pulmonary hypoplasia.
    2. Most neonates without severe pulmonary hypoplasia will survive (Sumfest et al. 1993).
    3. Recent trend with improved prognosis.
    4. Sixty-seven percent of children who survive the newborn period with life-sustaining renal function at 15 years of age.

Diagnostic Investigations

1. Radiography in neonates and infants with moderate to severe renal disease:
    1. Smoothly enlarged kidneys because of the numerous dilated collecting ducts
    2. Abdominal distension
    3. Gas-filled bowel loops often deviated centrally
    4. Pulmonary hypoplasia and small thorax in the baby with severe kidney disease
    5. Pneumothorax common at birth following assisted ventilation
2. Ultrasonography:
    1. The absence of renal cysts in both parents as demonstrated by ultrasound examination

2. Neonatal ultrasonography with more marked renal cystic disease:
    1. Massive enlarged kidneys
    2. Increased echogenicity of the entire parenchyma
    3. Loss of corticomedullary differentiation
    4. Loss of central echo complex
    5. Small macrocysts (unusual focal rosettes consisting of a cluster of the radially oriented, dilated collecting tubules) (Stein-Wexler and Jain 2003)
    6. Usually small bladder
    7. Increased hepatic echogenicity, mainly in medulla
3. Ultrasonography in children with more prominent hepatic fibrosis:
    1. Massive kidney enlargement
    2. Increased hepatic echogenicity, mainly in medulla
    3. Macrocysts:
        1. Less than 2 cm in diameter
        2. Tend to become larger and more numerous over time
    4. Enlarged echogenic liver
    5. Hepatic cysts
    6. Pancreatic cysts
    7. Splenomegaly secondary to portal hypertension
    8. Hepatofugal-flow duplex and color-flow Doppler

3. CT scan:
    1. Nonenhanced CT: smooth, enlarged, and low-attenuating kidneys, likely the reflection of the large fluid volume in the dilated ducts
    2. CT with contrast:
        1. Kidneys with a striated pattern representing accumulation of contrast material in the dilated tubules
        2. Linear opacifications representing retention of contrast medium in dilated medullary collecting ducts
        3. Macrocysts appearing as well-circumscribed rounded lucent defects
        4. Time of delay in visualizing the contrast medium in the kidneys, proportionate to the severity of renal impairment
4. Ultrasonography and magnetic resonance cholangiography to investigate the presence of an extent of Caroli disease in children with autosomal recessive polycystic kidney disease
5. MRI of affected children (perinatal, neonatal, and infantile course) (Kern et al. 1999):
    1. Kidney appearance:
        1. Enlarged, humpy but still reniform in shape
        2. Homogeneously grainy parenchyma
    2. Signal intensity:
        1. Hypointense on T1-W spin-echo sequences
        2. Hyperintense on T2-W turbo spin-echo sequences
    3. Rapid acquisition with relaxation enhancement (RARE)-MR urography:
        1. Hyperintense, linear radial pattern seen in the cortex and medulla representing the characteristic microcystic dilatation of collecting ducts
        2. Possible few circumscribed small subcapsular cysts
    4. MR cholangiography: a valuable method to establish the diagnosis and demonstrate the extent of Caroli disease by showing the entire biliary free from different angles (Jung et al. 1999)
6. Histopathology of the kidney and liver (Sherwani et al. 2010):
    1. Kidneys: Grossly enlarged with multiple cysts on the external surface that involve the cortex and medulla and are located in collecting ducts and tubules, lined by cuboidal epithelium.
    2. Liver:
        1. Grossly, cysts are also present in an enlarged liver where they form due to enlarged portal areas forming anastomosing channels, with the biliary structures forming dilated sacs.
        2. Hepatic fibrosis is an essential diagnostic criterion for this autosomal recessive disease.
    3. The involvement of the renal collecting system and hepatic ductal plate malformation is due to the failure of terminal

differentiation of the collecting duct and biliary systems, causing oligohydramnios leading to pulmonary hypoplasia which is the cause of morbidity, in 30% of cases.

7. Molecular diagnosis:
    1. Linkage analysis of the affected family using 6p21 markers demonstrating linkage to the *ARPKD1* gene with the affected proband.
    2. 33 different mutations detected on 57 alleles (Rossetti et al. 2003):
        1. 51.1% in ARPKD
        2. 32.1% in congenital hepatic fibrosis/Caroli disease
        3. Two frequent truncating mutations:
            1. 9689delA (9 alleles)
            2. 589insA (8 alleles)
        4. Mutation detection rate:
            1. High in severely affected patients (85%)
            2. Lower in moderate severe ARPKD (41.9%)
            3. Low, but significant, in adults with congenital hepatic fibrosis/Caroli disease (323.1%)
        5. Complications for the prospects for gene-based diagnostics:
            1. Large gene size
            2. Marked allelic heterogeneity
            3. Clinical diversity of the ARPKD phenotype
    3. Direct DNA analysis – available clinically:
        1. Mutation scanning
        2. Sequence analysis
        3. Targeted mutation analysis
        4. Deletion/duplication analysis
        5. Linkage analysis
    4. Next-generation sequencing of the PKHD1 gene is a very useful method of molecular diagnosis in patients with a full clinical picture of ARPKD, and it has a high detection rate. Furthermore, its relatively low costs and rapidity allow the molecular genetic analysis of patients without the full clinical criteria of ARPKD, who might also have mutations in the PKHD1 gene (Obeidova et al. 2015). The estimated costs and the time invested for molecular screening of genes with large size and allelic heterogeneity such as PKHD1 demand the use of next-generation sequencing (NGS) technologies for a fast, accurate, and cost-effective molecular diagnostic tool for identifying mutations in targeted genes sequence analysis (Edrees et al. 2016; Melchionda et al. 2016).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: 25%
    2. Patient's offspring: not increased (theoretical risk 0.7%)
2. Prenatal diagnosis:
    1. Ultrasonography in most severely affected fetuses:
        1. Enlarged, echogenic kidneys (main US signs of ARPKD) (Zerres et al. 1988)
        2. Dilated collecting ducts
        3. Characteristic hepatic ductal plate malformation
        4. A small or nonvisualized bladder
        5. Oligohydramnios attributable to poor fetal renal output
        6. Unreliable especially in early pregnancy
    2. Molecular genetic testing by mutation scanning of *PKHD1* is available clinically by analysis of fetal DNA obtained by amniocentesis or CVS. Both disease-causing alleles of an affected family member must be identified, or linkage has been established in the family before prenatal testing can be performed. The ARPKD locus mapped to proximal chromosome 6p allowing haplotype-based prenatal diagnosis in "at-risk" family with a previously affected child in whom prior family studies have identified informative linked markers (Zerres et al. 1998a). An absolute prerequisite for these studies is an accurate diagnosis of ARPKD in the previously affected sib (Zerres et al. 1998b; Dell 2011).
    3. Preimplantation genetic diagnosis may be available for families in which the disease-

causing mutations have been identified (Sweeney and Avner 2014).

3. Management (Dell 2011):
    1. Initial management of affected infants to focus on stabilization of respiratory function. Mechanical ventilation may be necessary to treat both pulmonary hypoplasia and respiratory compromise from massively enlarged kidneys.
    2. Water and electrolyte balance.
    3. Peritoneal dialysis may be required for neonates with oliguria or anuria within the first days of life.
    4. Vigorous treatment of systemic hypertension with antihypertensive agents:
        1. ACE inhibitors
        2. Calcium channel blockers
        3. Beta blockers
        4. Judicious use of diuretics (e.g., thiazides, loop diuretics)
    5. Importance of early detection and appropriate management of systemic and portal hypertension (Roy et al. 1997).
    6. Antibiotics for treatment of urinary tract infections.
    7. Management of renal osteodystrophy in children with ARPKD and chronic renal insufficiency:
        1. Calcium supplements
        2. Phosphate binders
        3. 1,25-Dihydroxyvitamin D3 to suppress parathyroid hormone (PTH)
        4. Erythropoietin (EPO):
            1. Increases hemoglobin levels
            2. Improves the overall well-being of the child
    8. Potential use of recombinant human growth hormone therapy to improve the growth of children with uremia (Lilova et al. 2003).
    9. Therapeutic options available for the treatment of portal hypertension in children (Lonergan et al. 2000):
        1. Conservative management
        2. Control of variceal bleeding:
            1. Sclerotherapy effective in controlling bleeding
            2. Banding of varices
            3. Placement of portosystemic shunts occasionally necessary to reduce bleeding and the formation of additional varices
        3. Prompt management with antibiotics and, when indicated, surgical drainage to help reduce morbidity and mortality associated with ascending cholangitis
        4. Splenectomy for hypersplenism
        5. Liver transplantation in patients with severe hepatic dysfunction or chronic cholangitis
    10. Replacement therapy for renal failure:
        1. Renal dialysis
        2. Renal transplant
    11. Kidney transplantation (Jamil et al. 1999):
        1. Liver disease did not progress rapidly after initiation of renal replacement therapy and did not subsequently present a clinical problem.
        2. When it occurs, recurrent bleeding appears to be controllable with sclerotherapy.
        3. Cholangitis is not a significant problem.
        4. Renal transplantation is appropriate for patients with ARPKD and that prophylactic portacaval shunting or combined liver/kidney transplantation is unnecessary.

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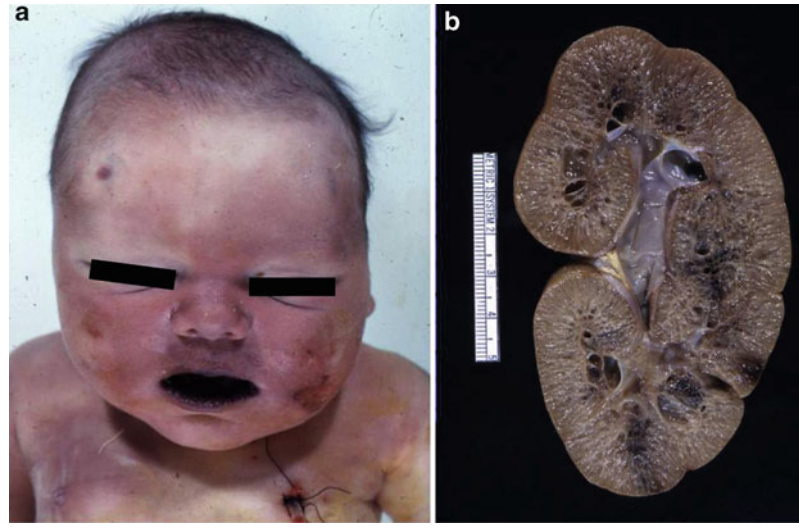

Fig. 1 A newborn with ARPKD showing Potter facies (**a**). The spongy appearing cut surface of a kidney from the same patient is due to generalized dilatation of the collecting ducts in both cortex and medulla (**b**)

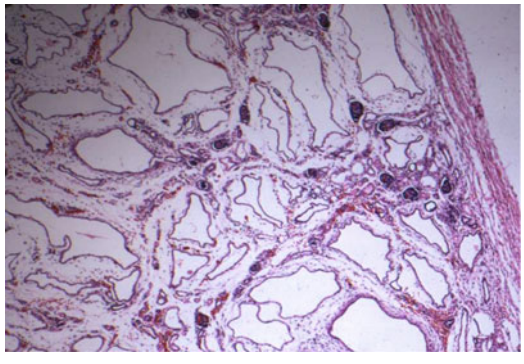

Fig. 2 Photomicrograph of a kidney of a neonate (37 weeks gestation) with ARPKD showing markedly dilated collecting ducts in the medulla (*top*) and the cortex (*bottom*). The infant also had intrahepatic bile duct proliferation and mild cystic changes and pulmonary hypoplasia

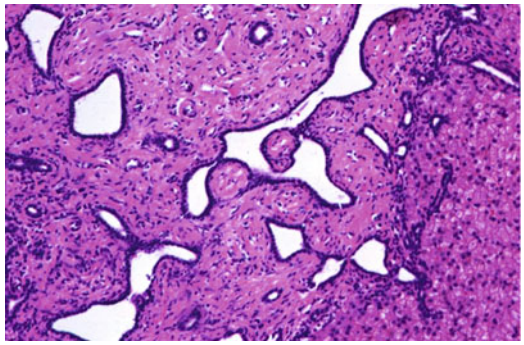

Fig. 3 Photomicrograph of the liver of a 2-year-old girl with congenital hepatic fibrosis, consistent with ARPKD. Note the irregularly dilated branching bile ducts. There is abundant fibrous connective tissue in this enlarged portal tract

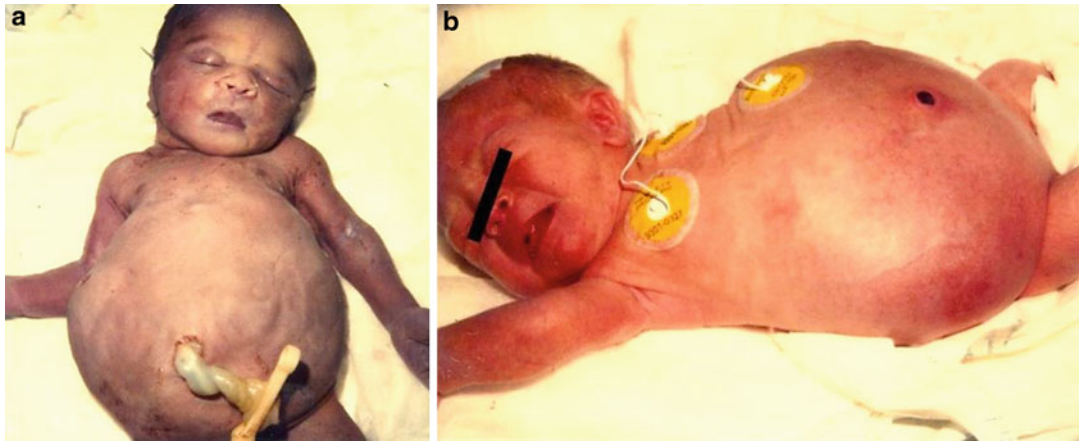

Fig. 4 Two neonates (**a**, **b**) with ARPKD showing markedly distended abdomen

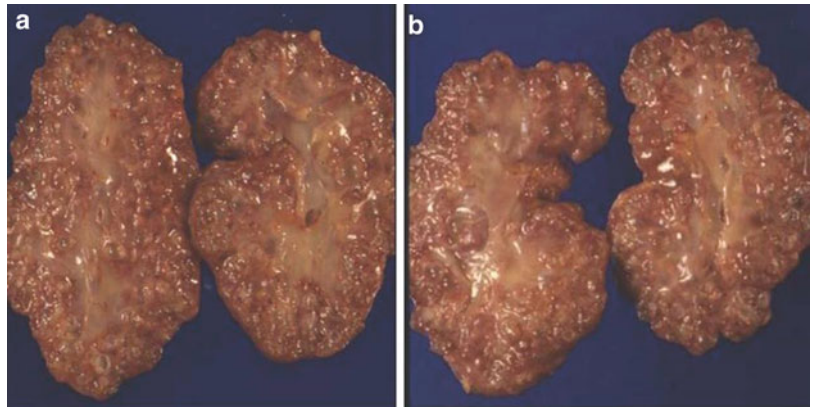

Fig. 5 (**a**, **b**) Kidneys in another neonates with ARPKD

Popliteal Pterygium Syndrome

Contents

In *1968*, Gorlin et al. (1968) described an autosomal dominant form of popliteal pterygium syndrome (PPS), a syndrome comprising cleft lip and palate, popliteal and intercrural pterygia, and digital and genital anomalies. Van der Woude syndrome (VWS) is one of the most common oral cleft syndromes. It accounts for about 2% of all cleft lip and palate cases. Both syndromes are caused by *IRF6* mutations.

In *1972*, Bartsocas and Papas (1972) reported on four sibs of third-cousin parents with a severe, presumably autosomal-recessive form of popliteal pterygium syndrome.

Synonyms and Related Disorders

Bartsocas-Papas syndrome; Cocoon syndrome; *IRF6*-Related Disorders including Van der Woude syndrome

Genetics/Basic Defects

1. Interferon regulatory factor 6 (*IRF6*) encodes a member of the IRF family of transcription factors (de Lima et al. 2009).
2. Mutations in *IRF6* cause popliteal pterygium syndrome and Van der Woude syndrome: interfamilial as well as intrafamilial variability has been described in IRF6-related disorders (Ferreira de Lima et al. 2009; Little et al. 2009; Durda and Schutte 2014; Busche et al. 2016).
3. Mutations in *RIPK4* gene on chromosome 21 cause the autosomal-recessive form of popliteal pterygium syndrome (Kalay et al. 2012).
4. Heterozygous mutations in *IRF6* cause popliteal pterygium syndrome (PPS), while homozygous mutations in *RIPK4* or *CHUK* (*IKKA*) cause the more severe Bartsocas-Papas syndrome (BPS) and Cocoon syndrome, respectively (Leslie et al. 2015). The most extreme end of this spectrum of disorders may be the lethal condition known as Cocoon syndrome (MIM 613630). This disorder, which has been described as an extreme form of Bartsocas-Papas syndrome, is caused by mutations in CHUK (also known as inhibitor of nuclear factor kappa-B kinase subunit alpha or IKKA) (Lahtela et al. 2010).
5. Popliteal pterygium syndrome (PPS)
   1. Inherited as an autosomal dominant trait.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_195

2. Exonic mutations in *IRF6* are found in nearly all families with PPS (De Lima et al. 2009).
3. First case of autosomal-recessive PPS reported (Leslie et al. 2015): Using a combination of Sanger and exome sequencing, the first case of an autosomal-recessive popliteal pterygium syndrome caused by homozygous mutation of *IRF6* and the first case of uniparental disomy of chromosome 21 leading to a recessive disorder.

6. Van der Woude syndrome (VWS)
   1. Inherited as an autosomal dominant trait with high penetrance (96.7%) but with variable expression.
   2. A nonsense mutation in the interferon regulatory factor 6 (*IRF6*) gene in the affected sib of two monozygotic twins discordant for VWS, suggesting *IRF6* as a candidate for VWS (Kondo et al. 2002).
   3. This hypothesis was confirmed in the same study by the detection of *IRF6* mutations in 45 additional unrelated families with VWS. In addition, a unique set of mutations in *IRF6* was discovered in 13 families with PPS, demonstrating that VWS and PPS as allelic, as previously suggested (Lees et al. 1999).
   4. Subsequently, mutations in *IRF6* were identified in 56 additional families with VWS and three with PPS (de Lima et al. 2009).
   5. Exonic mutations in *IRF6* are found in 68% of families with VWS.
7. Bartsocas-Papas syndrome (BPS)
   1. Inherited as an autosomal-recessive trait (Papadia and Zimbalatti 1984; Reich et al. 1984; Martinez-Frias et al. 1991; Massoud et al. 1998)
   2. Early lethality

Clinical Features

1. Autosomal dominant popliteal pterygium syndrome
   1. Cleft lip with or without cleft palate.
   2. Fistula of the lower lip.
   3. Filiform synechiae may connect the upper and lower jaws (syngnathia) or the upper and lower eyelids (ankyloblepharon).
   4. Syngnathia seen in nearly 40% of PPS patients are usually fibrous in type, limiting jaw excursion and creating difficulties in breathing and feeding (Froster-Iskenius 1990; Gahm et al. 2007).
   5. Webbing of the skin extending from the ischial tuberosities to the heels.
   6. Bifid scrotum and cryptorchidism in males.
   7. Hypoplasia of the labia majora in females.
   8. Syndactyly of fingers and/or toes.
   9. Anomalies of the skin around the nails: A characteristic pyramidal fold of the skin overlying the nail of the hallux is almost pathognomonic (Froster-Iskenius 1990; Mubungu et al. 2014).
   10. Normal growth and intelligence.
2. Autosomal-recessive popliteal pterygium syndrome (Kalay et al. 2012)
   1. Alopecia
   2. Ankyloblepharon filiforme adnatum
   3. Hypoplastic oral cavity and filiform bands between the jaws
   4. Limb abnormalities
      1. Digital hypoplasia
      2. Syndactyly
      3. Nail hypoplasia
      4. Arthrogryposis
      5. Clubfeet
      6. Popliteal, axillary, and inguinal pterygia
   5. Hypoplastic labia major
3. Van der Woude syndrome (Gorlin et al. 2001; Tripathi et al. 2014)
   1. Variable expressivity
   2. The most common oral cleft syndrome and accounts for 2% of complete cleft lip and palate cases (Katsube et al. 2015)
   3. Congenital lower-lip fistulae (pits)
      1. Usually bilateral and paramedian.
      2. The phenotype of the lower lip varies from a single barely evident depression to bilateral fistulae of the lower lip.
      3. Phenotypes of the orofacial cleft vary from a bifid uvula to a complete cleft lip and palate.

4. Cleft lip with or without cleft palate and cleft palate only
5. Hypodontia
6. Cleft or bifid uvula
7. Ankyloglossia
8. Less common features
    1. Syndactyly of the fingers
    2. Syngnathia
    3. Ankyloblepharon
9. Normal growth and intelligence

4. Autosomal-recessive Bartsocas-Papas syndrome (Hall et al. 1982; Erturan et al. 2016)
    1. Craniofacial
        1. Ankyloblepharon
        2. Facial cleft
        3. Hypotrichosis
        4. Microcephaly
        5. Filiform bands
        6. Hypoplastic nose
        7. Microphthalmia
        8. Eyelid colobomas
        9. Corneal opacities
        10. Salivary pits (with absent mouth)
    2. Musculoskeletal
        1. Synostosis of the hands and feet
        2. Talipes equinovarus
        3. Pelvic hypoplasia
        4. Popliteal and axillary webbing
        5. Single palmar crease
        6. Short sternum
        7. Syndactyly
        8. Laterally displaced nipples
        9. Diaphragmatic hypoplasia
    3. Genitourinary
        1. Ambiguous genitalia
        2. Renal agenesis (Hennekam et al. 1994)
        3. Penile shaft agenesis
        4. Urethral agenesis
        5. Dilated bladder
        6. Dysplastic kidneys
    4. Gastrointestinal
        1. Low-set umbilicus
        2. Stenotic anal orifice
        3. Esophageal atresia (Hennekam et al. 1994)
    5. Cardiothoracic: pulmonary stenosis.
    6. Developmental/cognitive: mental retardation.
    7. Early lethality is common, but about one-fourth of cases could survive (Giannotti et al. 1992).
    8. Causes of death
        1. Bronchopneumonia
        2. Respiratory distress
        3. Sepsis

5. VWS–PPS spectrum (Houweling et al. 2009)
    1. VWS and PPS may be regarded as mild and more severe manifestations of a single syndrome with intrafamilial and interfamilial variability.
    2. Instead of labeling VWS and PPS as separate syndromes, VWS–PPS spectrum, as recently published by De Medeiros et al. (2008), might prove to be more accurate.
    3. Lethal multiple pterygium syndrome (please see the chapter on "▶ Lethal Multiple Pterygium Syndrome").

Diagnostic Investigations

1. The role of MRI in evaluating the normal or abnormal position of the popliteal artery and peroneal nerve provides useful information for preoperative planning for surgical correction of the popliteal pterygium (Qasim and Shaukat 2012).
2. Histology of popliteal pterygium (Gorlin et al. 1968)
    1. Bilateral pterygium extending from the heel to the ischial tuberosity.
    2. Limiting extension and abduction as well as rotation of the leg.
    3. A hard, inelastic subcutaneous cord or fibrous band runs along the free edge of the pterygium.
    4. The sciatic nerve lies free within the pterygium deep to the fibrous band about halfway between the free edge and the apex being covered by fibromuscular septa.
    5. The popliteal vessels are normally situated deep in the popliteal space.
    6. Absence of muscle groups or abnormal muscle insertions in many cases.

3. Molecular genetic testing by sequence analysis of the *IRF6* coding region (exons 1–9) (Schutte 2014)
    1. Detects mutations in approximately 70% of individuals with the Van der Woude syndrome phenotype
    2. Detects mutations in approximately 97% of individuals with the popliteal pterygium syndrome phenotype
4. Exome Sequence Identifies RIPK4 as the Bartsocas-Papas Syndrome Locus (Mitchell et al. 2012).

Genetic Counseling

1. Recurrence risk for autosomal dominant *IRF6*-related disorders
    1. Patient's sib
        1. Appears to be low when parents are clinically unaffected, but the possibility of incomplete penetrance in a parent or of germline mosaicism need to be considered.
        2. Fifty percent of a parent of the proband is affected or has an *IRF6* mutations.
    2. Patient's offspring
        1. Each child of an individual with an *IRF6* mutation has a 50% chance of inheriting the mutation.
        2. The clinical manifestations of *IRF6*-related disorders are variable and cannot be predicted in the offspring.
2. Recurrence risk for autosomal-recessive PPS and BPS
    1. Patient's sib: 25%
    2. Patient's offspring: not increased unless the spouse is a carrier
3. Prenatal diagnosis
    1. Ultrasonography
        1. Oral cleft
        2. Popliteal pterygium
    2. Molecular genetic testing
        1. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing allele of an affected family member is previously identified.
        2. Preimplantation genetic diagnosis (Durda and Schutte 2014): may be available for families in which the disease-causing mutation has been identified in an affected family member.
4. Management (Gahm et al. 2007)
    1. Early surgical treatment is of importance to enable and preserve oral feeding.
    2. Syngnathia in patients with PPS has raised concerns regarding oral feeds and airway compromise: need for thorough neonatal airway assessment (Posey et al. 2014).
    3. Intranasal flexible fiber intubation with the patient awake is a possible anesthetic strategy to secure the airway prior to surgery in patients with multiple or extensive interalveolar syngnathia.
    4. Surgical removal for synechiae.
    5. Cleft lip/cleft palate: surgical and orthodontic management.
    6. Speech therapy and audiologic evaluation for cleft palate.
    7. Surgery for lip pits for cosmetic purpose.
    8. Syndactyly may require surgery.
    9. To accomplish knee extension (Gardetto and Piza-Katzer 2003)
        1. Resect fibrous bands.
        2. Free the sciatic nerve.
        3. Z-lengthening of the Achilles tendon and multiple Z-plasties.
        4. Surgery result: 1 year after surgery, the patient can put his heel on the ground and has almost complete range of motion in the knee and ankle joints.
    10. Operations include excision of the fibrous band, mobilization of nerves and vessels and Z-plasty of the skin (Herold et al. 1986). Recurrence of flexion contracture is noted in some cases. Gradual soft tissue lengthening with an Ilizarov external fixator can be one of the optimal procedures when excision of a fibrous band and Z-plasty is not possible due to severe adhesion of the nerves and vessels into a fibrotic band (Kim et al. 2009).
    11. Excision of symptomatic accessory medial meniscus resulted in resolution of the symptoms (Funk et al. 2015).

12. Orthopedic care and physical therapy may be needed.

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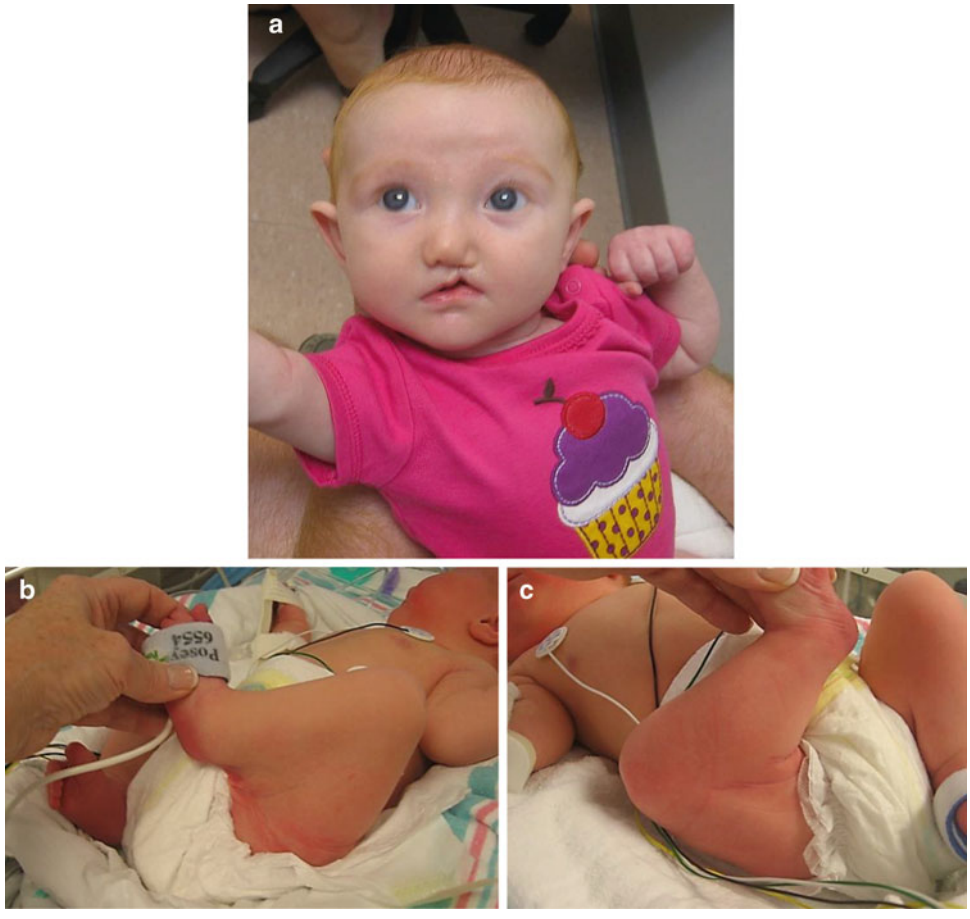

Fig. 1 (**a**–**c**) The newborn (**b**, **c**) was evaluated for multiple congenital anomalies, consisting of ankyloblepharon connecting upper and lower eyelids by fimbria (thin threadlike connective tissue); unilateral cleft lip and palate; thin strings of connective tissue connecting the upper and lower alveolar ridge on both sides; absence of labia majora, a clitoral hood, and a sacral dimple; hypoplastic labia minor; popliteal pterygium (webbing of the skin extending from the ischial tuberosities to the heels); skin over the nails of her great toes giving the nail a somewhat triangular shape with a flat base; and syndactyly over second to fifth toes bilaterally. The clinical diagnosis of popliteal pterygium syndrome (**a**) was confirmed by molecular genetic analysis of *IRF6* gene which showed a missense mutation of exon 4 [c252G > A or p. Arg841His (R84H)]

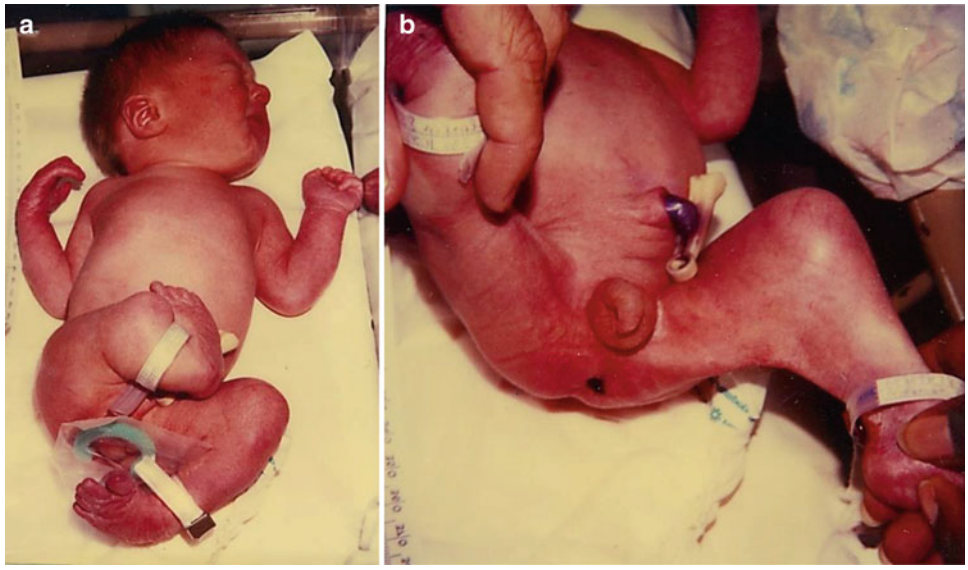

Fig. 2 (**a**, **b**) Another baby with popliteal pterygium syndrome

Prader-Willi Syndrome

Contents

Prader-Willi syndrome is a neurogenetic disorder characterized by hypotonia and feeding difficulties in infancy, followed by hyperphagia, hypogonadism, mental retardation, and short stature. It was the first recognized microdeletion syndrome identified with high-resolution chromosome analysis, the first recognized human genomic imprinting disorder, and the first recognized disorder resulting from uniparental disomy. The incidence of Prader-Willi syndrome is approximately 1/10,000–1/15,000 individuals.

Genetics/Basic Defects

1. Inheritance:
   1. Usually sporadic events (de novo deletions of 15q11-q13) (Ledbetter et al. 1981)
   2. Rare familial transmission (balanced translocations involving 15q11-q13) (<1%)
2. A contiguous gene syndrome involving multiple paternally expressed genes.
3. Caused by the lack of expression of normally active paternally inherited genes at chromosome 15q11-q13 because of a phenomenon called genomic imprinting (Horsthemke et al. 1997; Hanel and Wevrick 2001)
   1. The relevant region on chromosome 15q11-q13: normally expressed on the paternally derived chromosome and imprinted on maternally derived chromosome.
   2. The imprinted maternal allele is unable to produce functional protein since the normally expressed paternal copy is often deleted in Prader-Willi syndrome.
4. Prader-Willi syndrome can also be caused by disruption of the SNRPN gene (Ozçelik et al. 1992; Kuslich 1999).
5. Molecular subclassification of Prader-Willi syndrome: All involving loss of paternal gene expression from chromosome 15q11-q13 (Cassidy 1997; Buiting 2010):
   1. Paternal deletion 15q11-q13 (de novo) (70% of cases: microdeletion of the actively transcribed segment on the paternally derived chromosome 15q11-q13)
   2. Maternal uniparental disomy (UPD15) (inheritance of both copies of chromosome 15 from the mother) (Nicholls et al. 1989; Mascari et al. 1992) (25–30% of cases):
      1. Uniparental disomy (UPD) in humans is caused primarily by meiotic nondisjunction events, followed by trisomy or monosomy "rescue' (Ledbetter and Engel 1995).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Inheritance of two copies of the maternal chromosome without paternal contribution.
3. In normal individuals, the paternally donated chromosome expresses multiple genes in the Prader-Willi syndrome region, while the maternal chromosome is largely silent.
4. In case of maternal uniparental disomy, without the presence of a chromosome donated from the father, normal imprinting on the two maternally donated chromosomes leads to the absence of gene expression in this region.

3. Mutation in the imprinting control center:
   1. Deletion of the imprinting center (1% of the cases) of the *s*mall *n*uclear *r*ibonucleoprotein *p*olypeptide *N* (SNRPN) gene causing inability to establish the normal methylation status
   2. Without imprinting center deletion (1% of cases)

6. Prader-Willi syndrome and Angelman syndrome: sister imprinted disorders (Nicholls 1993; Glenn et al. 1997; Cassidy and Schwartz 1998; Cassidy 2000; Buiting 2010):
   1. The most frequent genetic lesions in both disorders:
      1. A de novo deletion of the chromosomal region 15q11-q13
      2. A uniparental disomy 15 (Fridman 2000)
      3. An imprinting defect
      4. In the case of AS, a mutation of the UBE3A gene
   2. Angelman and Prader-Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion (Knoll et al. 1989): In contrast to the paternal inheritance of the deleted chromosome 15 observed in the majority of PWS patients, maternal inheritance of the deleted chromosome 15 was demonstrated in the AS patients by restriction fragment length polymorphisms (RFLPs).
   3. Imprinting in Prader-Willi and Angelman syndrome (Nicholls et al. 1998): PWS involves loss of function of multiple paternally expressed genes, while mutations in a single gene, UBE3A, which is subject to spatially restricted imprinting, occur in some AS patients.
   4. Genomic imprinting in an Angelman and Prader-Willi translocation family (Hultén et al. 1991):
      1. By genomic imprinting, we would expect to find translocation and inversion families with both AS and PWS children, dependent on transmitting parental sex.
      2. Such a translocation family have been reported. The index child with classic AS has a maternally derived unbalanced translocation, leading to a deletion 15pter- > q13 and a duplication 22pter- > q11. Another branch of this family has two children with PWS, having the same unbalanced translocation but of paternal derivation (Fernandez et al. 1987).
      3. This result has important clinical implications for genetic counseling. The carrier females are at high risk of having children with AS, while their brothers have a high risk of having PWS children.
   5. Prader-Willi syndrome and Angelman syndrome in cousins from a family with a translocation between chromosomes 6 and 15 (Smeets et al. 1992):
      1. One of the two female first cousins has PWS and the other has AS.
      2. Cytogenetic and molecular studies revealed that both syndromes resulted from a familial translocation between chromosomes 6 and 15, leading to a deletion in the paternally derived chromosome 15 in the patient with PWS and to the inheritance of two different copies of chromosome 15 from the father in the patient with AS.
   6. Microdeletions in a small number of patients with PWS and AS have led to the identification of the chromosome 15 imprinting center (IC). The IC consists of two critical elements, which act in cis to regulate imprinting in the whole chromosome 15q11-q13 imprinted domain.

7. The human small nuclear ribonucleoprotein polypeptide N (SNRPN) gene (Glenn et al. 1996):
    1. One of the gene families that encode proteins involved in pre-mRNA splicing and map to the smallest deletion region involved in the Prader-Willi syndrome (PWS) within chromosome 15q11-q13.
    2. Paternal only expression of SNRPN has previously been demonstrated by the use of cell lines from PWS patients (maternal allele only) and Angelman syndrome (AS) patients (paternal allele only).
8. Highly restricted deletion of the *SNORD116* region is implicated in Prader-Willi Syndrome (Bieth et al. 2015):
    1. A 23-year-old woman presented clinical criteria of PWS, including the behavioral and nutritional features, obesity, developmental delay, and endocrine dysfunctions with hyperghrelinemia.
    2. A paternally transmitted highly restricted deletion of the *SNORD116* gene cluster, the shortest described to date (118 kb), was found. This deletion was also present in the father.
    3. This finding strongly supports the current hypothesis that lack of the paternal *SNORD116* gene cluster has a determinant role in the pathogenesis of PWS.
    4. Moreover, targeted analysis of the SNORD116 gene cluster, complementary to SNRPN methylation analysis, should be carried out in subjects with a phenotype suggestive of PWS.
    5. The absence of a small nucleolar organizing RNA gene, *SNORD116*, seems to reproduce many of the clinical features. Sibling recurrence risk is typically $<1\%$, but higher risks may pertain in certain cases (Cassidy et al. 2012).

Clinical Features

1. Fetal presentation (McCandless and Committee on Genetics 2011):
    1. Breech presentation
    2. Reduced fetal activity
    3. Polyhydramnios
2. Growth:
    1. Short stature.
    2. Poor weight gain (failure to thrive) in infancy.
    3. Central obesity: PWS is the most common syndromal cause of obesity (Butler 1990).
3. Neonatal presentation:
    1. Central hypotonia in infancy (Miller et al. 1999)
    2. Poor feeding/sucking
    3. Genital hypoplasia/hypogonadism
    4. Diminished deep tendon reflexes
    5. Abnormal squeaky weak cry (Aughton and Cassidy 1990)
4. Developmental delay
5. Mild dysmorphic features:
    1. Almond-shaped eyes
    2. Dolichocephaly
    3. Narrow bifrontal diameter
    4. Narrow nasal bridge
    5. Small mandible
    6. Small mouth
    7. High-arched palate
    8. Down-turned lips
    9. Thick viscous saliva (Hart 1998)
6. Hyperphagia after the first–second postnatal years:
    1. Due to decreased satiation rather than increased hunger (Lindgren et al. 2000).
    2. Hyperghrelinemia (elevated circulating total ghrelin levels) in Prader-Willi syndrome begins in early infancy long before the onset of hyperphagia (Kweh et al. 2015).
7. Severe obesity without significant intervention
8. Retinal hypopigmentation
9. Small hands and feet (acromicria) (Bray et al. 1983)
10. Cryptorchidism
11. Mild to moderate mental retardation
12. Hypothalamic insufficiency suggested by several autonomic dysfunctions that affect appetite regulation, growth, pubertal development, control of breathing, and alertness

13. Behavioral (Curfs and Fryns 1992; Einfeld et al. 1999) and psychiatric difficulties:
    1. Excessive food-seeking behaviors
    2. Obsessions
    3. Compulsions
    4. Mood lability
    5. Depression
14. Other manifestations:
    1. Infantile lethargy
    2. Sleep disturbance and/or sleep apnea (Hertz et al. 1995)
    3. Hypopigmentation
    4. Skin sores from constant picking (Martin et al. 1998)
    5. Esotropia/myopia
    6. Speech articulation defects
    7. High pain threshold
    8. Ineffective thermoregulation
    9. Early adrenarche
    10. Osteoporosis
    11. Kyphoscoliosis
15. Adults with Prader-Willi syndrome (Greenswag 1987):
    1. Most were short, overweight, cognitively impaired, and emotionally labile, had poor gross motor skills, and were always hungry.
    2. Males were taller and heavier than females, and both sexes were far shorter and heavier than US norms.
    3. Micropenis and cryptorchidism in males and primary amenorrhea, late menarche, and irregular menstrual cycles in females indicated hypogenitalism in both sexes.
    4. Of 106 with chromosome analysis, 54 had an abnormality on chromosome 15, primarily a deletion.
16. Clinical features and common medical problems in adult PWS (Scheermeyer 2013; Ho-Ming 2016):
    1. Signs and symptoms that warrant referral to genetic service for genetic assessment of PWS in adult:
        1. History of hypotonia, poor sucking, and feeding problems during infancy
        2. Short stature
        3. Hypogenitalism
        4. Hyperphagia
        5. Obesity
        6. Small hands and feet
        7. Intellectual disability and/or behavioral problems
        8. Thick, viscous saliva
    2. Common medical problems in adult PWS:
        1. Cardiovascular: hypertension, hyperlipidemia
        2. Respiratory: breathing-related sleep disorder, infection like pneumonia
        3. Endocrine: type 2 diabetes mellitus, hypothyroidism, hypogonadism
        4. Psychological: psychosis, behavioral problems, sexuality, abuse
        5. Dermatological: skin picking, soft tissue infection like erysipelas
        6. Musculoskeletal: osteoporosis
        7. Iatrogenic: growth hormone-related side effects
17. Prognosis:
    1. Obesity: the major cause of morbidity and mortality
    2. Cardiopulmonary compromise (Pickwickian syndrome) resulting from excessive obesity: the presence of a primary disturbance of central respiratory control in patients with Prader-Willi syndrome which may be worsened by the development of obesity (Schlüter et al. 1997)
    3. Most common causes of death: respiratory insufficiency or infections (Tauber et al. 2008)
18. Clinical spectrum and molecular diagnosis of Angelman and Prader-Willi syndrome patients with an imprinting mutation (Saitoh et al. 1997):
    1. Detailed clinical findings of five AS imprinting mutation patients (three families) and two PWS imprinting mutation patients (one new family) were described.
    2. All these patients have essentially the classical clinical phenotype for the respective syndrome, except that the incidence of microcephaly is lower in imprinting mutation AS patients than in deletion AS patients.
    3. Furthermore, imprinting mutation AS and PWS patients do not typically have

hypopigmentation, which is commonly found in patients with the usual large deletion.

19. Diagnostic criteria (adapted from Holm et al. 1993; Scheimann 2015) – five points for children under 3 years (three from major criteria) and eight points for children above 3 years (four from major criteria):
    1. Major criteria (one point each):
        1. Infantile central hypotonia
        2. Infantile feeding problems/failure to thrive
        3. Rapid weight gain between 1 and 6 years
        4. Characteristic facial features
        5. Hypogonadism (genital hypoplasia, pubertal deficiency)
        6. Developmental delay/mental retardation
    2. Minor criteria (1/2 point each):
        1. Decreased fetal movement and infantile lethargy
        2. Typical behavioral problems
        3. Sleep disturbance/sleep apnea
        4. Short stature for the family by age 15 years
        5. Hypopigmentation
        6. Small hands and feet for height age
        7. Narrow hands with straight ulnar border
        8. Esotropia/myopia
        9. Thick viscous saliva
        10. Speech articulation defects
        11. Skin picking
    3. Supportive criteria (no points):
        1. High pain threshold
        2. Decreased vomiting
        3. Temperature control problems
        4. Scoliosis/kyphosis
        5. Early adrenarche
        6. Osteoporosis
        7. Unusual skill with jigsaw puzzles
        8. Normal neuromuscular studies
20. Genotype-phenotype correlations (Driscoll et al. 2016):
    1. UPD:
        1. Post-term delivery is more common with UPD (Butler et al. 2009).
        2. Individuals with UPD are less likely to have the typical facial appearance, hypopigmentation, or skill with jigsaw puzzles (Dykens 2002); they also have a somewhat higher verbal IQ and milder behavior problems (Dykens et al. 1999; Roof et al. 2000; Hartley et al. 2005).
        3. Individuals with UPD are more likely to have psychosis (Holland et al. 2003; Yang et al. 2013) and autism spectrum disorders (Veltman et al. 2004, 2005; Whittington et al. 2004; Descheemaeker et al. 2006). Studies suggest that as many as 62% of those with UPD develop atypical psychosis compared with 16% of those with a deletion (Soni et al. 2007).
    2. Deletion:
        1. Individuals with a deletion showed a higher frequency of need for special feeding techniques, sleep disturbance, hypopigmentation, and speech articulation defects in a recent study of 91 children (Torrado et al. 2007).
        2. Individuals with the slightly larger, type 1 deletions have been reported to have more compulsions and poorer adaptive behavior, intellectual ability, and academic achievement than those with type 2 deletions (Butler et al. 2004; Hartley et al. 2005).
        3. Two other studies found much less clinically significant differences between individuals with these two deletion types (Milner et al. 2005; Varela et al. 2005). Larger studies are needed to determine whether there are significant clinical differences between the two most frequent deletion classes.

Diagnostic Investigations

1. Cytogenetic studies:
    1. Diagnostic testing methods (Delach et al. 1994; ASHG/ACMG Test and Technology Transfer Committee 1996):

1. High-resolution chromosome analysis
2. FISH
3. PCR to detect UPD
4. Methylation analysis

2. Microscopic or submicroscopic del(15)(q11-q13) confirmed by fluorescence in situ hybridization (FISH probe for *SNRPN*) (60–80%)
3. Paternally derived chromosome 15 that is deleted
4. De novo events in most cases with cytogenetically normal father's chromosomes
5. Balanced chromosomal rearrangement with break in 15q11-q13 (<1%)

2. Molecular analyses:
   1. Uniparental disomy identified by using microsatellite repeat sequences of chromosome 15 in the patient and both parents:
      1. Maternal uniparental disomy for chromosome 15 in most of nondeletion cases (20–40%)
      2. Inheriting both copies of chromosome 15 from the mother
      3. The absence of the paternally inherited copy of chromosome 15q11-q13
   2. Rare Prader-Willi syndrome in a brother and sister without cytogenetic or detectable molecular genetic abnormality at chromosome 15q11q13: paternally inherited submicroscopic deletions are possible explanations for the sib occurrence in this family (Orstavik et al. 1992).
   3. Rare familial Prader-Willi syndrome: associated with very small mutations in 15q11-q13 region leading to the loss of expression of multiple genes from the paternal chromosome.
   4. DNA methylation analyses (Gillessen-Kaesbach et al. 1995) (by Southern blotting and PCR) of the *SNRPN* or PW71 (D15S63) (Gillessen-Kaesbach et al. 1995) loci to detect the absence of paternal methylation patterns on the basis of deletion, uniparental disomy, or defective methylation: detects over 99% of cases and is highly specific.
   5. Because methylation analysis can detect all three major classes of genetic defects associated with PWS (deletion, UPD, or imprinting mutations), methylation analysis with either PW71 or SNRPN is an efficient primary screening test to rule out a diagnosis of PWS. Only patients with an abnormal methylation result require further diagnostic investigation by FISH or DNA polymorphism analysis to distinguish among the three classes for accurate genetic counseling and recurrence-risk assessment (Kubota et al. 1996b).
   6. The SNRPN expression test is rapid and reliable in the molecular diagnosis of Prader-Willi syndrome (Wevrick and Francke 1996).
   7. Imprinting defect (Cassidy and Schwartz 2009):
      1. Presumed to be present in individuals with an abnormality in the parent-specific methylation imprint without evidence of a deletion of UPD (Driscoll et al. 1992; Ohta et al. 1999).
      2. Imprinting defects caused by microdeletions are detected using sequence analysis or MLPA of the PWS-SRO (smallest region of overlap).
      3. Most imprinting defects are epimutations (i.e., alterations in the imprint, not the DNA) and cannot be detected by sequence analysis (Buiting et al. 1998; Buiting et al. 2003; Horsthemke and Buiting 2006).
   8. As all typical PWS cases showed either a deletion or disomy of 15q11.2-q12, molecular examination should provide a reliable diagnostic tool (Robinson et al. 1991).
3. Polysomnography (Schlüter et al. 1997):
   1. An increased number of apneas per hour of sleep
   2. A decreased nadir of oxygen saturation
   3. An increased maximum of the instantaneous heart rate
   4. A decreased respiratory responses to hypercapnia during quiet sleep
4. Growth standard charts of infants with PWS available when examining infants with PWS and evaluating growth for comparison purposes, monitoring for growth patterns,

nutritional assessment, and recording responses to growth hormone therapy, commonly used in infants and children with PWS (Butler et al. 2011). Growth charts for nongrowth hormone-treated Prader-Willi syndrome are also available (Butler et al. 2015).

Genetic Counseling

1. Recurrence risks (Cassidy 1987; Cassidy and Schwartz 2009; Buiting 2010):
    1. Patient's sib:
        1. De novo deletion or maternal uniparental disomy in an affected child: a low recurrence risk ($\leq$1% due to possible paternal balanced insertion or gonadal mosaicism):
            1. Imprinting center mutation in an affected child
            2. No imprinting center deletion: $<$1%
        2. With imprinting center deletion: up to 50% recurrence risk
        3. Apparently de novo-balanced chromosome translocation breaking within the PWS/AS-critical region: $<$1%
        4. The presence of a parental balanced chromosomal rearrangement: up to 25% recurrence risk
        5. Two families with a microdeletion affecting the chromosome 15 imprinting center (IC) (Buiting et al. 2000):
            1. Carrier males have a 50% risk of having children with an imprinting defect leading to PWS, and in one of the two families, a father has two affected daughters.
            2. In the other family, diagnostic testing was confounded by the presence of a neutral microdeletion close to the IC. The silent transmission of PWS IC deletions through the female germline and the occurrence of neutral microdeletions close to the IC can impose considerable problems on diagnostic testing and genetic counseling in affected families.
    2. Patient's offspring (Cassidy and Schwartz 2009):
        1. With rare exception, individuals with PWS do not reproduce.
        2. The risk to the child of an affected individual depends on the etiology of the absence of the paternally derived PWS critical region and the sex of the affected individual.
        3. If the proband has PWS as the result of a deletion, the offspring have a 50% risk of having Angelman syndrome (AS) if the proband is female (reported once) and PWS if the proband is male (never reported).
        4. If the proband has UPD, there is a theoretical risk of the offspring inheriting two chromosomes 15 from the proband, which could lead to: (1) fetal demise if trisomy rescue does not occur, (2) PWS if the proband is female, and (3) AS if the proband is male. None of these possibilities have been reported. There is a single report of a female with PWS caused by UPD having a normal child (Schulze et al. 2001).
        5. If the proband has PWS as the result of an imprinting mutation, the offspring has a theoretical risk of $\leq$50% of having PWS (never reported).
        6. If the proband has a chromosomal translocation, there is a theoretical increased risk to offspring of having PWS or AS, depending on the sex of the proband (never reported).
        7. A pair of siblings affected by PWS was described. Neither demonstrates a microscopically visible deletion in 15q11q13 or maternal disomy. Methylation studies at D15S63 and at the SNRPN locus confirm the diagnosis of PWS. Molecular studies reveal biparental inheritance in both siblings with the exception of D15S128 and D15S63 where no paternal contribution is present indicating a deletion of the imprinting center. Family studies indicate that the father of the siblings carries the

deletion which he has inherited from his mother. The recurrence risk for PWS in his offspring is 50% (McEntagart et al. 2000).

3. Differentiated recurrence-risk estimations in the Prader-Willi syndrome (Kennerknecht 1992):
    1. A deletion at 15q has not been found in a familial case of PWS, except in those cases where del(15q) is due to familial structural chromosome rearrangements. Hence, with de novo deletion, the recurrence risk should be nearly zero.
    2. In cases with familial translocation, risk estimates depend on the variable nature of the familial chromosome mutation.
    3. If only one child is affected and has no deletion at 15q, this may be a sporadic or an isolated familial case. For this situation, an estimate of an overall recurrence risk of 0.4%.
    4. If two or more sibs are affected, consider a risk of 50% that the next sib may also be affected.
4. Fertility in Prader-Willi syndrome (Schulze et al. 2001):
    1. There is a variable degree of reduced fertility in untreated females with PWS of any molecular genetic etiology and that infertility may not be a consistent feature in females with this condition.
    2. There are no reports on fertility in PWS males.
    3. The risk for the offspring of an AS male of having PWS would be 1 in 2.

2. Molecular defects and recurrence risks in PWS (Ramsden et al. 2010):
    1. De novo deletion of 15q11-q13 on the paternal chromosome (75–80%): <1% recurrence risk
    2. Maternal uniparental disomy (UPD) of chromosome 15 (20–25%): <1% recurrence risk
    3. Imprinting defects (with an imprinting center deletion excluded) (about 1%): <1% recurrence risk
    4. Imprinting center deletion (about 10–15% of patients with an imprinting defect): up to 50% (if present in father) recurrence risk

3. Prenatal diagnosis:
    1. High-risk pregnancies:
        1. Parents who have had a previous child with Prader-Willi syndrome, caused by deletion or uniparental disomy, are not routinely offered prenatal testing in subsequent pregnancies but could be offered such testing for assurance.
        2. Parents who have had a previous child with Prader-Willi syndrome, caused by a defect in the imprinting control center, should be offered prenatal testing because of the high recurrence risk; methylation analysis can also be used in these cases.
        3. Prenatal testing for an inherited translocation involving chromosome 15 and resulting in a deletion is relevant because of the theoretical 25% risk of Prader-Willi syndrome in the offspring.
    2. PWS may be a possibility for low-risk pregnancies in which no family history of Prader-Willi syndrome exists – prenatal detection (ASHG/ACMG Test and Technology Transfer Committee 1996):
        1. Cytogenetic study to detect del(15q11-q13) from amniocytes, cordocentesis (Le Bris-Quillevere et al. 1990), or CVS cells performs FISH with SNRPN or other PWS/AS-critical region probes for confirmation. Parent-of-origin studies should be performed after confirmation of a deletion to determine if the deletion is paternally derived (fetus has PWS). (If the deletion is maternally derived, the fetus has Angelman syndrome.)
        2. If trisomy 15 or mosaic trisomy 15 (Christian et al. 1996) is detected on CVS and if subsequent amniocentesis reveals 46 chromosomes, the possibility of trisomy rescue (Roberts et al. 1997) leading to PWS (maternal UPD) through loss of a parental chromosome 15 [or leading to Angelman syndrome (maternal UPD) through loss of a maternal chromosome 15] can be considered. In this instance, parent-of-origin (UPD) studies or methylation analysis (Glenn

et al. 2000) on amniocytes or chorionic villus sampling should be considered (European Collaborative Research on Mosaicism in CVS 1999; Shaffer et al. 2001):
    1. If maternal UPD is present, PWS is confirmed.
    2. If paternal UPD is present, AS is confirmed.
    3. If an inherited or de novo translocation involving chromosome 15 is present or if a supernumerary chromosome derived from chromosome 15 is detected, FISH (to rule out a deletion) and parent-of-origin studies (to rule out the possibility of UPD) are indicated.
  3. Molecular studies of uniparental disomy 15 using microsatellite dinucleotide polymorphism analysis of amniocytes and parental DNA.
  4. DNA methylation analysis of amniocytes.
  5. SNRPN, but not PW71, methylation analysis may be useful for diagnosis of PWS/AS on lymphoblast cell lines, cultured amniotic fluid, or chorionic villus samples and will allow prenatal diagnosis for families known to carry imprinting center defects (Kubota et al. 1996a).
4. Preimplantation genetic diagnosis (PGD) (Driscoll et al. 2016):
  1. May be available for families in which a mutation in the imprinting control element has been identified
  2. Also can be used in cases of familial translocation to rule out UPD
5. Management (Greenswag and Alexander 1995; Cassidy 2001):
  1. Manage feeding problems with special nipples or gavage feeding if needed to assure adequate nutrition, to avoid failure to thrive, and to improve hypotonia.
  2. Early intervention programs with speech, physical, and occupational therapies after careful educational, behavioral, and psychological assessments.
  3. Dietary control (Holm and Pipes 1976):
    1. Monitoring of weight and nutritional counseling
    2. Low-calorie and well-balanced diet combined with a regular exercise program
    3. Limit access to food
    4. Close supervision to minimize food stealing
  4. Management of endocrine problems:
    1. Growth hormone treatment improves growth, physical phenotype, and body composition (Ritzen et al. 1999; Cassidy and Driscoll 2009; Wolfgram et al. 2013) and requires close monitoring for adverse events (Irizarry et al. 2016).
    2. Testosterone treatment in males to improve changes in voice and body hair, beard growth, genital size, body mass and strength, and self-image.
    3. Treatment with estrogen, cycling hormones, or birth control pills in females has resulted in increasing breast size and menstrual periods.
  5. Management of scoliosis as in the general population.
  6. Behavioral management (Dykens et al. 1996a):
    1. Firm limit setting and enforcement.
    2. Consult with a behavioral psychologist or other behavior specialist for behavioral management programs.
  7. Psychiatric management:
    1. Psychosis
    2. Manic-depressive illness
    3. Obsessive-compulsive disorder (Dykens et al. 1996b)
  8. Treatment of complications resulting from excessive obesity:
    1. Cardiopulmonary compromise
    2. Type II diabetes mellitus
    3. Thrombophlebitis
    4. Management of skin picking, chronic skin changes, and peripheral edema

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Fig. 1 A 10-month-old girl with Prader-Willi syndrome showing severe hypotonia, strabismus, and small hands and feet. Parent-of-origin-specific DNA methylation studies at 15q11-q13 for Prader-Willi syndrome revealed the presence of maternal 4.2 kb hybridization band only but not paternal 0.9 kb band consistent with Prader-Willi syndrome. Uniparental disomy DNA analysis revealed that the patient has only maternal alleles based on the Mendelian inheritance of two informative markers (D15S205 and D15S1002) and two partial informative markers (D15S130 and D15S1007), indicative of uniparental disomy for chromosome 15

Fig. 2 A 17-month-old boy with Prader-Willi syndrome showing severe hypotonia. Methylation-specific PCR using SNRPN flanking primers revealed the absence of paternal SNRPN and presence of maternal SNRPN, confirming the diagnosis of Prader-Willi syndrome

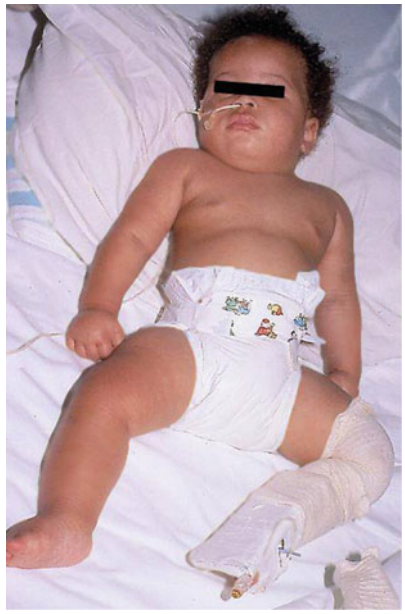

Fig. 3 An infant with Prader-Willi syndrome [del(15)(q11-q13)] showing hypotonia and failure to thrive

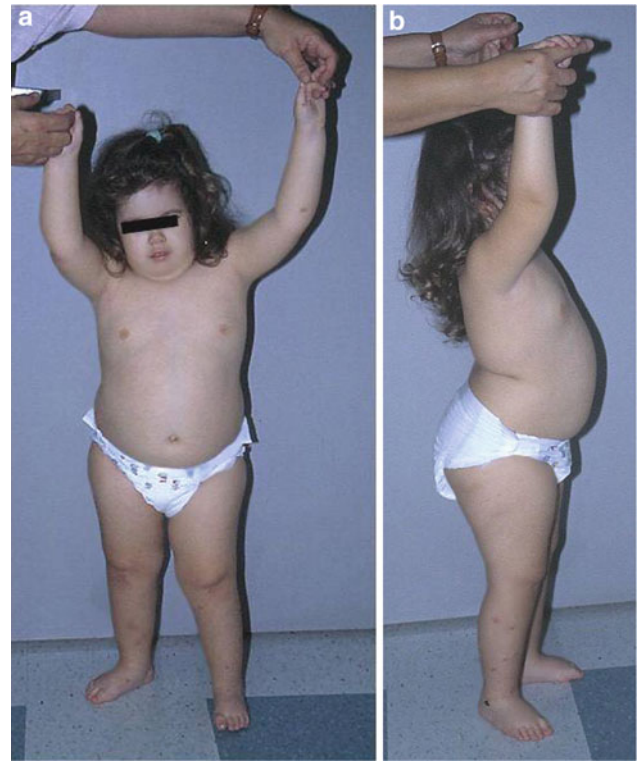

Fig. 4 (**a**, **b**) A girl with Prader-Willi syndrome [del(15)(q11-q13)] showing obesity, short stature, almond-shaped eyes, and small hands and feet

Fig. 5 (**a**, **b**) A boy with Prader-Willi syndrome [del (15)(q11-q13)] showing obesity, almond-shaped eyes, and bitemporal narrowing

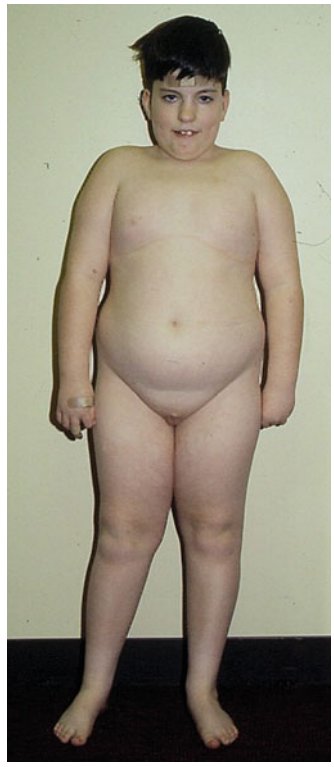

Fig. 6 A boy with Prader-Willi syndrome [del(15)(q11-q13)] showing almond-shaped eyes, bitemporal narrowing, obesity, hypogenitalism, and small hands and feet

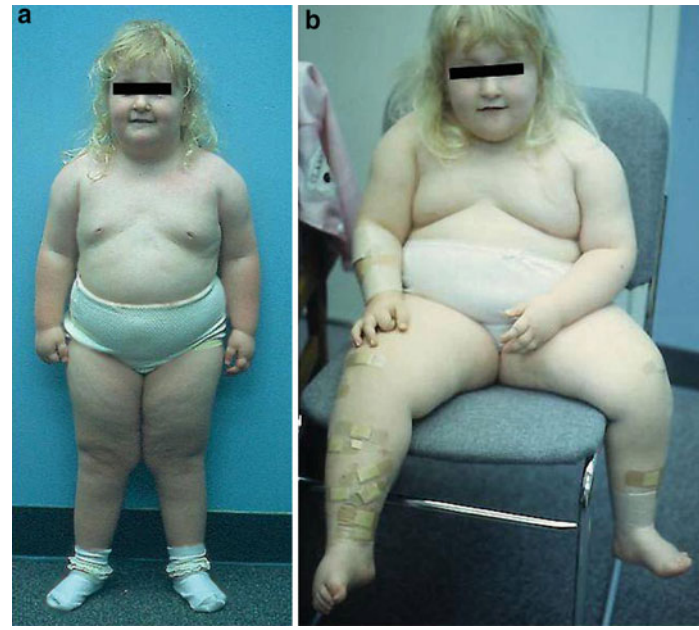

Fig. 7 (**a**, **b**) A girl with Prader-Willi syndrome [del(15)(q11-q13)] showing extreme obesity, characteristic facial appearance, small hands and feet, and multiple skin sores from constant picking

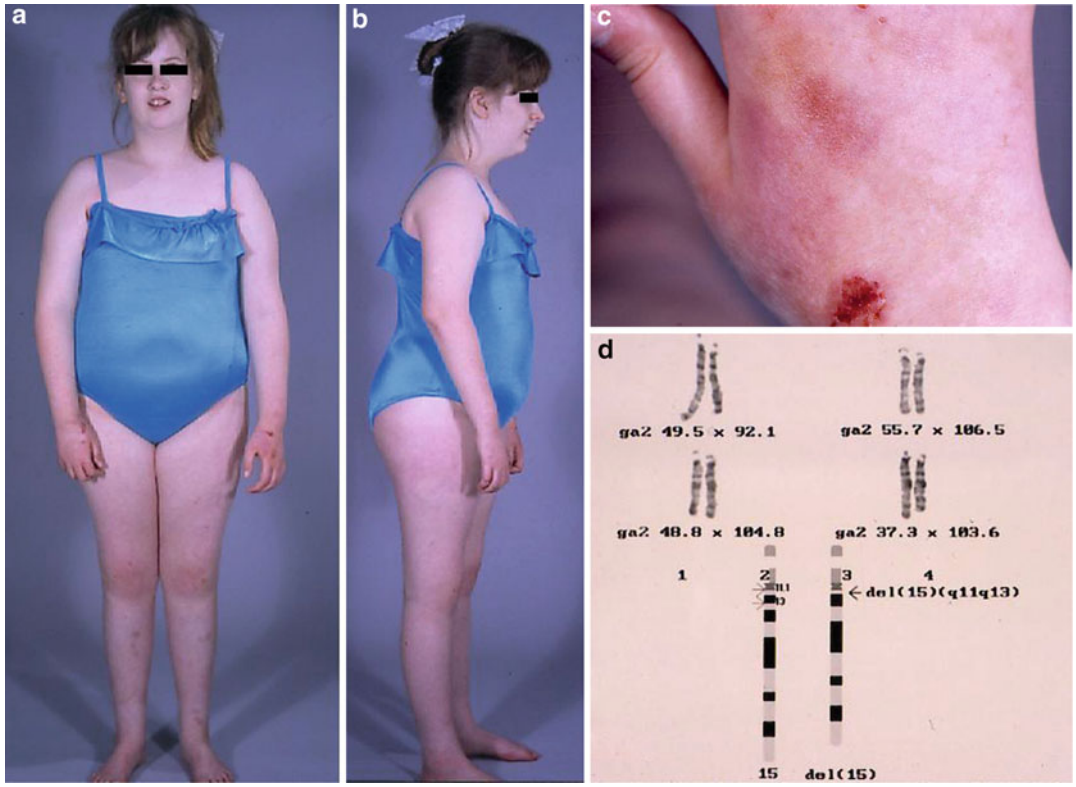

Fig. 8 (**a**–**d**) A patient with Prader-Willi syndrome [del(15)(q11-q13)] (shown by partial karyotypes and ideogram) and trimethylaminuria showing sores on the skin

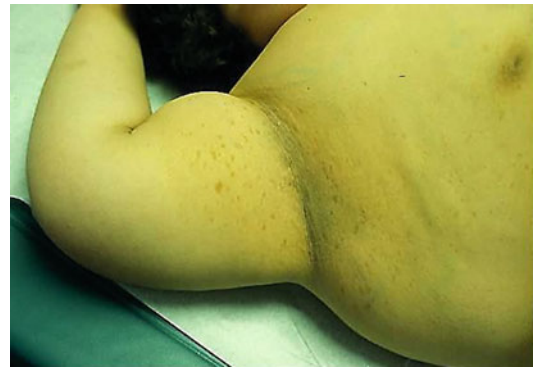

Fig. 9 A woman with Prader-Willi syndrome [del(15)(q11-q13)] and neurofibromatosis 1 showing obesity and axillary freckles

Primary Microcephaly

Contents

Primary microcephaly (MCPH) is a rare autosomal recessive neurodevelopmental disorder characterized by two principal features, microcephaly present at birth and nonprogressive mental retardation (Woods et al. 2005). The incidence is about 1 in 10,000 in consanguineous populations (Thornton and Woods 2009), less in non-consanguineous populations (between 1 in 30,000 and 1 in 2 million).

Synonyms and Related Disorders

Autosomal recessive primary microcephaly; Premature chromosome condensation (PCC) syndrome; Premature chromosome condensation with microcephaly and mental retardation syndrome

Genetics/Basic Defects

1. Inheritance; autosomal recessive
2. Cytogenetic features (Neitzel et al. 2002)
   (a) Premature chromosome condensation in G2 phase associated with autosomal recessive microcephaly and mental retardation in two siblings from consanguineous parents
   (b) A high frequency of prophase-like cells (>10%) in lymphocytes, fibroblasts, and lymphoblast cell lines with an otherwise normal karyotype
3. Molecular genetics (Kaindl et al. 2010; Mahmood et al. 2011)
   (a) MCPH1
      (i) Chromosome: 8p23.1
      (ii) Gene: *MCPH1* (microcephalin)
      (iii) Cellular location: nucleus/chromatin
      (iv) Proposed function: DNA damage repair, chromosome condensation
   (b) MCPH2
      (i) Chromosome: 19q13.12-q13.2
      (ii) Gene: *WDR62* (WD repeat-containing protein 62)
      (iii) Cellular location: nucleus, centrosomal during mitosis
      (iv) Proposed function: not yet established (expression pattern resembles with *ASPM*)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_268

(c) MCPH3
  (i) Chromosome: 9q33.2
  (ii) Gene: *CDKSRAP2* (cyclin-dependent kinase 5 regulatory associated protein 2)
  (iii) Cellular location: centrosome/midbody
  (iv) Proposed function: regulation of microtubule function/centrosome maturation
(d) MCPH4
  (i) Chromosome: 15q15.1
  (ii) Gene: *CASC5* (cancer susceptibility candidate 5)
  (iii) Cellular location: kinetocore
  (iv) Proposed function: kinetochore integrity
(e) MCPH5
  (i) Chromosome: 1q31.3
  (ii) Gene: *ASPM* (abnormal spindle-like, microcephaly)
  (iii) Cellular location: pericentrosomal/midbody
  (iv) Proposed function: orientation of mitotic spindles during embryonic neurogenesis
(f) MCPH6
  (i) Chromosome: 13q12.12
  (ii) Gene: *CENPJ* (centromeric protein J)
  (iii) Cellular location: centrosome/midbody
  (iv) Proposed function: centriole length control/microtubule function
(g) MCPH7
  (i) Chromosome: 1p33
  (ii) Gene: *STIL* (SCL/TAL1-interrupting locus)
  (iii) Cellular location: pericentrosomal
  (iv) Proposed function: spindle organization/cell cycle progression
(h) MCPH8 (Hussain et al. 2012)
  (i) Chromosome: 4q12
  (ii) Gene: *CEP135*
  (iii) Cellular location: centrosome
  (iv) Proposed function: disorganized microtubule networks and mutant protein not localized to the centrosome
(i) MCPH9 (Genin et al. 2012)
  (i) Chromosome: 15q21.1
  (ii) Gene: *CEP152* (centrosomal protein 152)
  (iii) Cellular location: centrosome
  (iv) Proposed function: involved in centriole duplication
(j) MCPH10 (Yang et al. 2012)
  (i) Chromosome: 20q13.12
  (ii) Gene: *ZNF335* (zinc finger protein 335)
  (iii) Cellular location: neuronal cells
  (iv) Proposed function: disrupts the proliferation and proper differentiation of neuronal cells
(k) MCHP11 (Awad et al. 2013)
  (i) Chromosome: 12p13.31
  (ii) Gene: *PHC1* (polyhomeotic-like 1)
  (iii) Cellular location: chromatin
  (iv) Proposed function: abnormalities in chromatin regulation

Clinical Features

1. Main features (Woods et al. 2005; Mahmood et al. 2011)
  (a) Microcephaly (2 SD below the mean) at birth, further "relative" reduction of head circumference in the first years of life
  (b) Reduction in cerebral cortex volume
  (c) Simplification of gyral pattern
  (d) Mild to severe nonprogressive mental retardation (borderline IQ possible)
2. Inconsistent features
  (a) Neurological/neuropsychological
    (i) Seizures (tonic-clonic, focal, generalized): very rare but cannot exclude the diagnosis (*ASPM*)
    (ii) Delay in early motor milestone, especially speech delay
    (iii) Behavior pattern: sometimes aggressive but otherwise have a happy effect and easy to handle
    (iv) Sleep disorder
  (b) Other features
    (i) Sloping forehead common but is not always associated

(ii) Short stature in some cases (*MCHP1*)
(iii) Early puberty

3. Differential diagnosis
   (a) Nongenetic and genetic causes of "primary microcephaly with mental retardation," e.g.,
      (i) Congenital infection with toxoplasma
      (ii) Maternal alcohol overconsumption during pregnancy
      (iii) Rubinstein-Taybi syndrome
   (b) Secondary microcephaly: indicates a progressive neurodegenerative condition

Diagnostic Investigations

1. Plain X-ray films: microcephaly
2. MRI (Mahmood et al. 2011)
   (a) Reduction of cerebral cortical volume (neuronal proliferation defect) and simplification of gyral pattern in most cases
   (b) Pachygyria with cortical thickening as well as hypoplasia/agenesis of the corpus callosum (neuronal migration defect) in some cases (*ASPM*, *WER62*)
   (c) Lissencephaly, schizencephaly, polymicrogyria, and cerebellar hypoplasia in few cases (*WDR62*)
3. Abnormal cytogenetic findings: high proportion of prophase-like cells due to premature chromosome condensation reported in *MCPH1*-related MCPH (Jackson et al. 2002; Trimborn et al. 2004, 2005)
4. Molecular genetic analysis (clinical research laboratories listed in www.GeneTests.org)

Genetic Counseling

1. Recurrence risk
   (a) Autosomal recessive inheritance
      (i) Patient's sib: 25%
      (ii) Patient's offspring: not increased unless the spouse is also a carrier
   (b) The empiric recurrence risk for a non-consanguineous couple who have had one child with a diagnosis of MCPH: 1 in 5 if detailed chromosome studies and neuroimaging yield normal results (Tolmie et al. 1987)
   (c) There may be a phenotype in heterozygous carriers of MCPH mutations, because of an increased frequency of intellectual impairment in parents of individuals with recessive microcephaly (Kloepfer et al. 1964; Qazi and Reed 1975)
2. Prenatal diagnosis
   (a) Ultrasonography: microcephaly
   (b) Prenatal MRI studies of affected families: the frontal lobes of the cerebral cortex to be particularly affected (Desir et al. 2008; Saadi et al. 2008)
   (c) Molecular genetic analysis: currently available
3. Management: symptomatic
   (a) Early intervention
   (b) Speech therapy
   (c) Physical therapy
   (d) Occupational therapy
   (e) Behavior management
   (f) Seizure management

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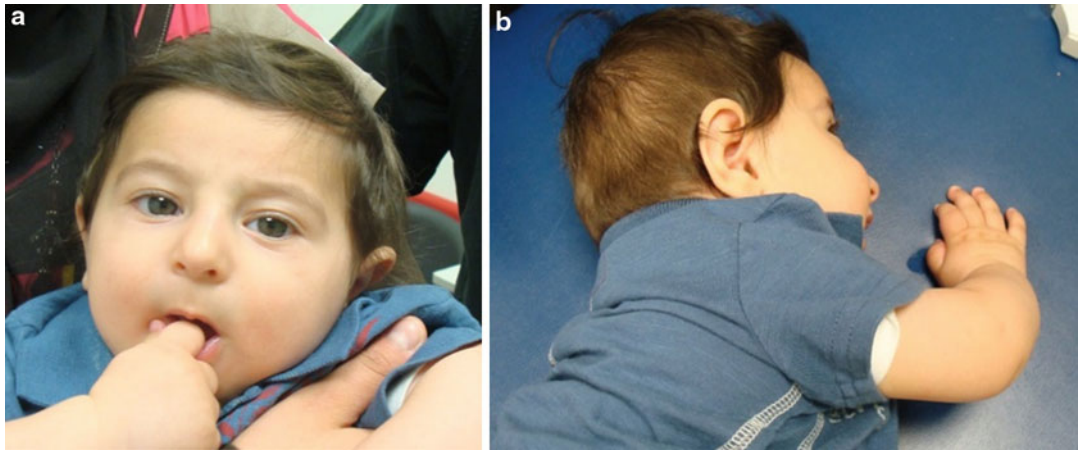

Fig. 1 (**a**, **b**) An 8-month-old Arabic boy was evaluated for developmental delay and microcephaly. Her older sister who expired at 15 months of age had microcephaly, developmental delay, and hypotonia. Normal laboratory tests include chromosome microarray analysis, chromosome analysis, plasma amino acids, urine organic acids, acylcarnitine profile, and VLCFA for peroxisomal disorders. Since two siblings are similarly affected in a family, the disorder most likely represents an autosomal recessive disorder of primary microcephaly

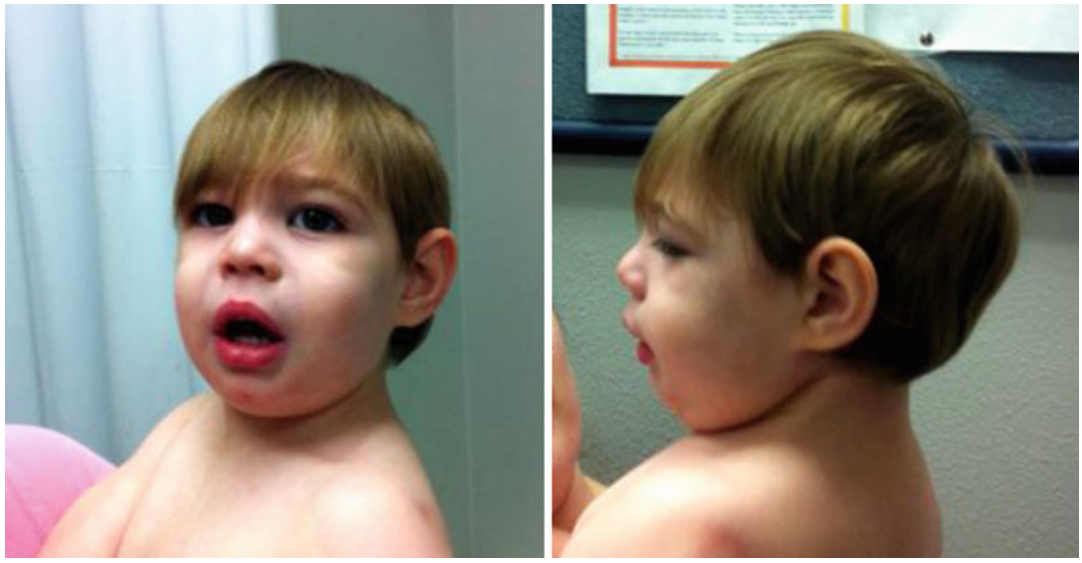

Fig. 2 (**a**, **b**) This 3-year-old Caucasian boy was evaluated for primary microcephaly. He had slightly sloping forehead with a very small cranial vault, slightly prominent ears, and mild retromicrognathia. He was born after 40 weeks gestation. It was a normal spontaneous delivery. The birth weight was 3,180 g, birth length 45.9 cm, and HC 29.5 cm (−3 standard deviations). TORCH titers were negative. He had unremarkable 3D CT. MRI of the brain showed a significantly decreased cranial to facial proportion with a sloping forehead and flattened occiput, abnormal cortical gyral/sulcal development with unusually broad and shallow gyri, and simplified sulcal pattern with generalized prominence of the extra-axial CSF space and thickening of the cortical mantle. The corpus callosum was small. The pituitary and midline structures were normal. This findings are compatible with group I primary microcephaly with an abnormal simplified gyral pattern, but with normal myelination. Craniosynostosis was not present. He has a history of seizures. Currently, he has developmental delay and receives speech and occupational therapy (Courtesy of Dr. Susanne Ursin)

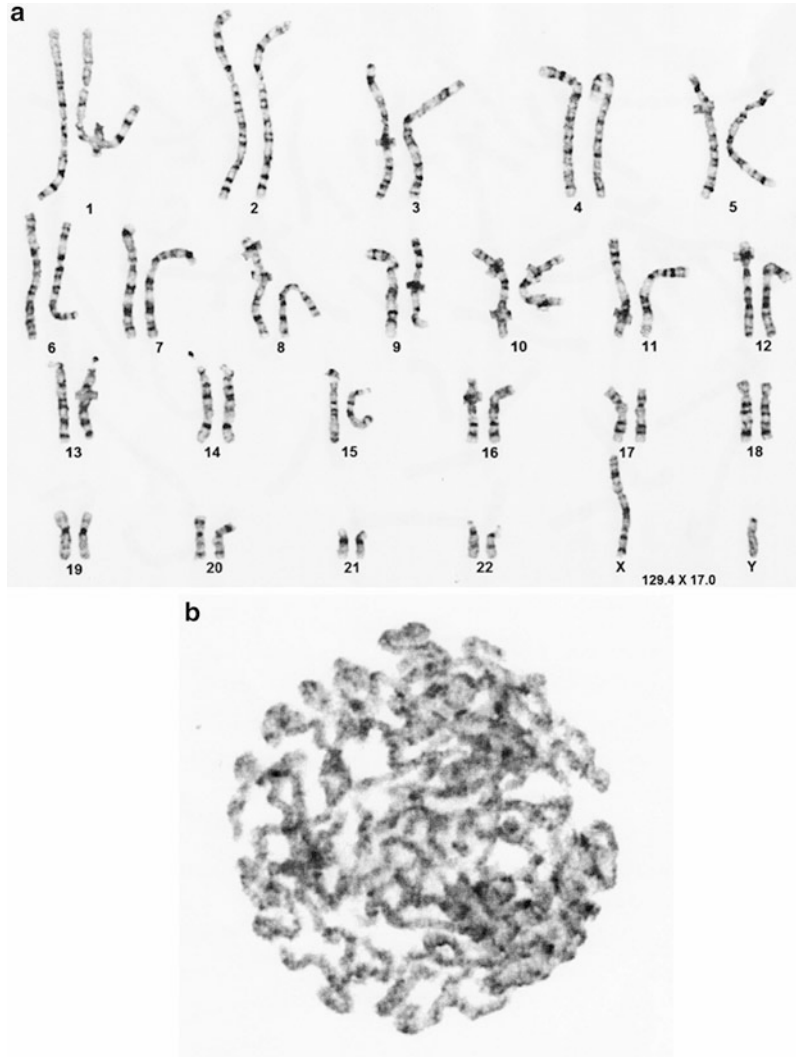

Fig. 3 (**a**, **b**) High-resolution cytogenetic analysis of metaphase cells from blood lymphocytes showed a cytogenetic male (**a**). However, approximately 14% of cells (normal reference range of <2% showed prophase-like cells) (**b**). Increased number of prophase-like cells has been reported in primary microcephaly in the literature. *MCPH1* gene sequencing did not identify any mutation in the *MCPH1* gene. However, the diagnosis cannot be completely ruled out due to mutations not detected by this assay or mutations in another gene. The frequency of mutations in the *MCPH1* gene ranges from 3.4% to 8.25% of the population affected with primary microcephaly (Courtesy of Dr. Leonard Prouty)

Progeria

Contents

In 1886, Hutchinson (1886) described a boy with congenital alopecia, wrinkled atrophic skin, an odd facies, joint contractures, and normal intelligence. Subsequently in 1904, Gilford (1904) reported a second patient with similar features and suggested the term progeria, from the Greek word *geras* meaning old age, to describe the premature senile characteristics of the patients. Thus, the syndrome is also known as Hutchinson-Gilford progeria syndrome (HGPS) (Thomson and Forfar 1950).

Progeria is an extremely rare condition with characteristic clinical findings of premature and accelerated aging. Its incidence was estimated to be one per eight million live births in the United States. Male to female ratio is about 1.5:1. Most reported patients are Caucasians (Badame 1989).

Synonyms and Related Disorders

Hutchinson-Gilford progeria syndrome; Progeroid syndrome

Genetics/Basic Defects

1. Inheritance:
    1. Autosomal dominant inheritance (Khalifa 1989):
        1. Advanced paternal age effect observed
        2. Germinal mosaicism responsible for rare instances of affected sibs
    2. Possible autosomal recessive inheritance: affected siblings in a family (Monu et al. 1990; Parkash et al. 1990; Pollex and Hegele 2004)
2. Basic defects:
    1. Caused by mutations in lamin A (*LMNA*) gene (Cao and Hegele 2003; Pollex and Hegele 2004):
        1. *LMNA* gene encodes two protein products, lamins A and C, representing major constituent of the inner nuclear membrane lamina.
        2. Mutations in *LMNA*:
            1. About 90% of patients have an identifiable mutation.
            2. Most common mutation (Fukuchi et al. 2004): a de novo single-base substitution, G608G (GGC > GGT) in exon 11. G608G mutation responsible for the majority of progeria arises in the paternal germline (D'Apice et al. 2004).
            3. A second mutation in the same codon, G608S (GGC > AGC).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. E145K (exon 2) observed in a phenotypically unusual HGPS.

3. Mutations in *LMNA* also cause the following different recessive and dominant disorders (Eriksson et al. 2003):
   1. Emery-Dreifuss muscular dystrophy type 1 (EMD1) (autosomal dominant)
   2. Emery-Dreifuss muscular dystrophy type 2 (EMD2) (autosomal recessive)
   3. A familial dilated cardiomyopathy and conduction system defects (CMD1A) (autosomal dominant)
   4. Dunnigan-type familial partial lipodystrophy (FPLD) (autosomal dominant)
   5. Limb-girdle muscular dystrophy type 1B (LGMD1B) (autosomal dominant)
   6. Charcot-Marie-Tooth disorder type 2B1 (CMT2B1) (autosomal recessive axonal neuropathy)
   7. Mandibuloacral dysplasia (MAD) (autosomal recessive)

2. Del(1)(q23) reported in a patient with Hutchinson-Gilford progeria (Luengo et al. 2002).
3. Inv ins(1;1)(q32;q44q23) reported in the postmortem skin biopsy specimens from identical twins raising the possibility that a gene for progeria may be located at the breakpoint site of the inserted chromosome segment.
4. Hutchinson-Gilford progeria syndrome gene localized to chromosome 1q by observing two cases of uniparental isodisomy of 1q and one case with a 6-megabase paternal interstitial deletion (Eriksson et al. 2003).
5. Increased hyaluronic acid production by progeric fibroblasts postulated as the underlying metabolic abnormality in progeria:
   1. Urinary excretion of hyaluronic acid found to be increased in some patients.
   2. Elevated levels of hyaluronic acid may result in growth failure and accelerated senescence by inhibiting the growth of blood vessels.
6. Accumulation of type IV collagen due to an interaction between activated T lymphocytes and fibroblasts.
7. Current results of microarray analysis: further support the notion that patients with progeria experience an accelerated form of aging.
8. Reduced growth capacity in vitro in the skin fibroblasts from progeria patients with conflicting evidence on whether progeric cells can repair single-strand DNA breaks induced by X- or gamma irradiation.
9. Fibroblasts from progeric tissue (Ackerman and Gilbert-Barness 2002):
   1. Inability to subculture
   2. Having short telomeres
   3. Uncertain as to whether aging is the consequence of shortened telomeres with reduced cell replication, impaired telomerase activity, or the culmination of the effects of reactive oxygen species

3. Aging- and progeria-related disorders (Evangelisti et al. 2016):
   1. *LMNA*-linked progeroid syndromes
      1. Hutchinson-Gilford progeria syndrome (HGPS)
      2. Mandibuloacral dysplasia types A and B (MADA and MADB, respectively)
      3. Atypical Werner syndrome (A-WS)
   2. Nucleotide excision repair (NER)-linked progeroid syndromes
      1. Xeroderma pigmentosum (XP)
      2. Cockayne syndrome (CS)
      3. Trichothiodystrophy (TTD)
   3. RecQ-associated progeria-related syndromes
      1. Bloom syndrome (BS)
      2. Werner syndrome (WS)
      3. Rothmund-Thomson syndrome (RTS)
   4. DNA polymerase-linked progeroid syndromes:
      1. A variant form of XP (known as XP-V)
      2. A form of mandibuloacral dysplasia: the mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL)

Clinical Features

1. General features (Ackerman and Gilbert-Barness 2002):
   1. Normal appearance at birth
   2. Normal intelligence and personality
   3. High-pitched voice
2. Growth (Cooke 1953):
   1. Profound growth failure/failure to thrive starting around 6 months to 1 year of age
   2. Extreme short stature
   3. No rapid growth during puberty
   4. Markedly diminished subcutaneous fat, especially on the face and limbs
   5. Absent sexual maturation
3. Skin:
   1. Unremarkable at birth
   2. Generalized nonpitting edema suggestive of scleroderma shortly after birth
   3. "Sclerodermatous" skin over the lower abdomen and proximal thighs, in which irregular bumps give appearance of lipodystrophy
   4. Becoming thin, dry, taut, and shiny in some areas, but lax and wrinkled in others, most commonly over the fingers and toes, by the second year
   5. Striking loss of subcutaneous tissue
   6. Prominent venous pattern
   7. Easy bruising
   8. Diminished eccrine sweating in some cases
   9. Progressive freckle-like hyperpigmentation (most evident in sun-exposed areas) and thickened sclerotic areas (usually on the lower parts of the trunk or thighs) after several years
4. Hair:
   1. Partial alopecia progressing to generalized alopecia often beginning at birth or in the first year and becoming prominent by the end of the second year
   2. Few remaining hairs: white or blond, fine, and fuzzy
   3. Body hair as well as scalp and facial hair: equally affected
5. Nails:
   1. Short, thin, and dystrophic fingernails and toenails
   2. Koilonychia (spoon nails)
   3. Onychogryposis (deformed overgrowth of the nails)
6. A striking facies after few months of life:
   1. Typical "plucked bird" appearance related to disproportionate craniofacial growth
   2. Disproportionately large cranium
   3. Relatively small face
   4. Prominent eyes
   5. Prominent scalp veins
   6. Sparse to absent scalp hair (alopecia, balding, hypotrichosis)
   7. Absent eyebrows and eyelashes
   8. Thin lips
   9. Circumoral cyanosis
   10. Protruded ears with absent earlobes
   11. "Beaked," pinched nose with sculptured tip
   12. Micrognathia
7. Teeth (Yu and Zeng 1991):
   1. Anodontia/hypodontia, especially permanent teeth
   2. Delayed and incomplete dentition
   3. Discoloration (yellowish brownish)
   4. Crowded, rotated, displaced, overlapped, and maloccluded, especially the anterior teeth
   5. High incidence of caries
   6. Poor oral hygiene/gingivitis
   7. Irregularity in size and shape of the odontoblasts
   8. Delayed in ossification of the crown of the permanent teeth
   9. Narrow pulp chambers and root canals
   10. Reticular atrophy of pulp
   11. Calcification along the nerve fibers and the vascular walls
   12. Irregular width of predentin, secondary dentin, and cementum
   13. Osteoclastic resorption at apical portion
   14. Incomplete formation of roots of deciduous molars
8. Endocrine manifestations:
   1. Incomplete sexual maturation
   2. Occasional hypoplastic nipples

9. Cardiovascular disease (Baker et al. 1981):
    1. Premature severe atherosclerotic heart disease and aortic stenosis (Makous et al. 1962).
    2. Calcification of the aortic and mitral valves, coronary arteries, and aorta.
    3. Premature coronary artery disease leads to ischemic changes in the myocardium, including well-defined infarcts.
    4. Death from coronary artery disease is frequent and may occur before 10 years of age.
    5. Angina pectoris.
    6. Myocardial infarction.
    7. Congestive heart failure.
    8. Epidural hematoma formation after a mild head injury possibly due to progressive atherosclerosis of intracranial vessels.
10. Musculoskeletal abnormalities (Moen 1982; Hamer et al. 1988):
    1. Generalized osteoporosis with pathologic fractures
    2. Osteolysis
    3. Marked delay in bone healing after fractures
    4. Skull: osteopenic and widened and unossified cranial sutures
    5. Short/dystrophic clavicles
    6. Hypoplasia of the mandible and maxilla
    7. Coxa plana and coxa valga
    8. Arthropathy
    9. Avascular necrosis of the femoral capital epiphysis
    10. Distal phalangeal osteolysis
    11. Delayed closure and persistently patent anterior fontanelle
    12. Joint contractures with contracted hands, elbows, and knees
    13. Dislocation of the hip
    14. Mild flexion of the knees resulting in a wide-gaited "horse-riding" stance and wide-based shuffling gait
    15. Short, tapered distal phalanges
    16. Thin limbs
    17. Muscle atrophy
11. Prognosis (Badame 1989):
    1. The absence of other factors associated with aging such as cancers, cataracts, and senility (not considered to be a phenocopy of normal aging)
    2. Death due to cardiovascular abnormalities in approximately 75% of patients
    3. Main cause of death due to cardiovascular complications:
        1. Myocardial infarction
        2. Congestive heart failure
    4. Other causes of death:
        1. Marasmus
        2. Inanition
        3. Convulsions
        4. Accidental head trauma due to thinned cortical bones
    5. Average life expectancy: 13 years (7–27 years)
12. Existence of a more severe prenatal form or "accelerated form" of progeria (Runge et al. 1978; Rodríguez and Pérez-Alonso 1999; Rodríguez et al. 1999):
    1. Intrauterine growth retardation
    2. Premature aging
    3. The absence of subcutaneous fat
    4. Brachydactyly
    5. Absent nipples
    6. Hypoplastic external genitalia
    7. Abnormal ear lobes
13. Progeroid syndromes:
    1. Acrogeria:
        1. Also known as Gottron syndrome (Gottron 1941)
        2. Characterized by premature aging, more specifically in the form of unusually fragile, thin skin on the hands and feet
    2. Werner syndrome (WS) (Muftuoglu et al. 2008; Goto et al. 2013):
        1. Characterized by premature aging which is clinically apparent during 20–30 years old.
        2. WS patients show abnormal physical development such as a birdlike face, short stature, and slender limbs.
        3. They also display a high-pitched voice, remarkable loss and graying of hair, and scleroderma-like skin changes. Other common clinical presentations include bilateral cataracts, type

2 diabetes mellitus, hypogonadism (with reduced fertility), skin ulcers, premature arteriosclerosis, osteoporosis, and cancer predisposition.
4. Many WS patients develop similar cardiovascular complications but also have an increased predisposition to developing multiple rare malignancies (Swahari and Nakamura 2016).
5. Ninety percent of WS is linked to mutations on WRN, a member of the RecQ family responsible for stable genome maintenance. Owing to autosomal recessive inheritance, biallelic mutation on WRN is pathogenic (Cheung et al. 2015).

3. Cockayne syndrome (CS) (Laugel 2012):
1. A rare autosomal recessive disorder: spans a phenotypic spectrum that includes CS type I (classic or moderate form), CS type II (more severe form), CS type III (a milder form), and xeroderma pigmentosum-Cockayne syndrome (XP-CS).
2. Characterized by dwarfism, progressive pigmentary retinopathy, birdlike facies, and photosensitivity.
3. The two genes in which mutations are known to cause Cockayne syndrome are ERCC6 (65% of individuals) and ERCC8 (35% of individuals).

4. Progeroid syndrome with characteristic facial appearance and hand anomalies in father and son: a new autosomal dominant disorder (Giannotti et al. 1997)

Diagnostic Investigations

1. Histopathology (Badame 1989):
1. Skin lesions indistinguishable from scleroderma:
1. Progressive hyalinization of dermal collagen (hyaline fibrosis)
2. Loss of subcutaneous tissue
3. Decreased sebaceous and sweat glands and hair follicles
4. Scleroderma-like skin lesions (Jansen and Romiti 2000)

2. Progeria is associated with hyperplastic scars or keloid-like lesions with an unusual accumulation of type IV collagen, which may be formed through interaction between activated T cells and fibroblasts after minor traumas (Jimbow et al. 1988).
3. Bone lesions:
1. Osteoporosis
2. Osteolysis prominent in distal phalanges and clavicles
3. Skeletal dysplasia manifesting as coxa plana, coxa valga, and attenuated diaphyses with dystrophic metaphyses
4. Avascular hip necrosis
5. Nonunion of fractures
6. Hip dislocations

4. Cardiovascular lesions:
1. Severe, progressive atherosclerosis with widely variable age of clinical manifestation
2. The presence of atherosclerotic plaques in the large and small arteries
3. Calcifications in the mitral and aortic valves as well as aorta, coronary, cerebral, subclavian, and axillary arteries
4. Myocardial ischemia and infarction resulting from the coronary artery disease
5. Diffuse interstitial myocardial fibrosis and lipofuscin pigment (Reichel and Garcia-Bunuel 1970)
6. Ventricular dilatation and hypertrophy

5. Increased lipofuscin in the brain, adrenal cortex, kidney, testis, liver, and heart.
6. Gonads:
1. Aspermatogenesis in males
2. The presence of primordial follicles and corpora albicans in females with evidence of ovulation

7. Arterial biopsy:
1. Premature atherosclerosis
2. Subintimal fibrosis

8. Abnormal mesangial collagen distribution in progeria kidney (Delahunt et al. 2000).

9. Autopsy findings of a case: scleroderma-like skin atrophy, elastotic degeneration of the skin, arteriosclerosis, and atrophy of the endocrine glands (Ishii 1976).

2. Radiography (Runge et al. 1978; Badame 1989; Gillar et al. 1991):
   1. Widespread degenerative changes of bone in the first or second year of life
   2. Skull and facial bones:
      1. Craniofacial disproportion
      2. Patent fontanelles
      3. Wormian bones with skull fractures
      4. Facial bone hypoplasia
      5. Mandibular hypoplasia with dental crowding
      6. Delayed and abnormal dentition
      7. Normal base of skull
   3. Thorax:
      1. Clavicular resorption: thinning and resorption of distal clavicles (a progressive process)
      2. Rib tapering: narrowing of ribs, particularly of posterior segments
   4. Long bones:
      1. Development of bizarre indentations with subsequent pathologic fractures
      2. Thinned cortices and poorly defined trabeculae
      3. Widened, poorly tubulated metaphyses
      4. Severe coxa valga
      5. Moderate genu valgum
      6. Normal capital femoral epiphyses
   5. Phalanges:
      1. Progressive resorption of the bone from distal phalanges of fingers and/or toes, one of the hallmarks of the disease
      2. Progressive osteolysis (Ozonoff and Clemett 1967)
      3. Radiolucent terminal phalanges (acroosteolysis) (Jansen and Romiti 2000)
   6. Others:
      1. Diffuse osteopenia/osteoporosis
      2. Ovoid and fish-mouth vertebral bodies
      3. Soft tissue loss
      4. Generally normal bone age
3. Blood chemistry for hyperlipidemia:
   1. Increased low-density lipoprotein levels
   2. Increased β-lipoprotein and pre–βlipoprotein levels of high-density lipoprotein
   3. Increased serum cholesterol levels
4. Metabolic workup – inconsistent results:
   1. Insulin resistance (Rosenbloom et al. 1983)
   2. Abnormal collagen formation
   3. Increased metabolic rate: could be the cause of the failure to thrive seen in progeria
   4. Elevated growth hormone levels
5. Urine test:
   1. Excessive excretion of glycosaminoglycans
   2. Excessive excretion of hyaluronic acid (unreliable)
6. Cultured skin fibroblasts:
   1. Exhibit 76.1% DNA repair capacity compared to normal (Sarkar and Shinton 2001).
   2. Decreased cell growth in culture.
   3. Short telomeres.
   4. Whether aging is the consequence of shortened telomeres with reduced cell replication, impaired telomerase activity, or the culmination of the effects of reactive oxygen species is uncertain.
   5. The cultured skin fibroblast from both the homozygous affected individual and the heterozygous parents can be distinguished from normals by decreased cell growth in culture (Danes 1971). Mitotic activity, DNA synthesis, and cloning efficiency are markedly reduced.
7. Immunofluorescence of cultured fibroblasts with antibodies directed against lamin A demonstrating visible abnormalities of the nuclear membrane in many cells
8. Molecular genetic analysis to detect *LMNA* p. gly608Gly point mutation – clinically available:
   1. Sequence analysis
   2. Targeted mutation analysis

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib:
      1. The lamin A gene mutations not found in patient's parents suggesting that it occurs

spontaneously in each patient and does not pass from parent to child
    2. Recurrence risk very low, estimated at 1 in 500 with each subsequent pregnancy due to germline mutations (Wuyts et al. 2005)
    3. Rare reports of siblings with progeria from consanguineous or nonconsanguineous marriages
    4. Reported cases of monozygous twins with progeria
  2. Patient's offspring: inability of patients to reproduce
2. Prenatal diagnosis and preimplantation genetic diagnosis: possible in families in which the disease-causing mutation has been identified in a family member (Gordon et al. 2015)
3. Management (Gordon et al. 2015):
  1. Regular diet
  2. Combined nutritional treatment and growth hormone treatment:
    1. Improve growth.
    2. Increase the levels of growth factors.
    3. Paradoxically result in a decreased BMR.
    4. Response decreases over time.
    5. Do not prevent the progression of atherosclerotic disease (Abdenur et al. 1997).
  3. Early and definitive surgical intervention for symptomatic oral pathosis (Batstone and Macleod 2002):
    1. Abnormal facial morphology
    2. Dermal inelasticity
    3. Potential anesthetic difficulties
    4. Progressive ongoing deterioration in the medical condition
    5. Importance of special and early dental care by a dentist, oral surgeon, and orthodontist, leading to a reduction in oral pathologies and a higher quality of life (Reichert et al. 2014).
  4. Orthopedic cares for musculoskeletal abnormalities:
    1. Routine treatment of fractures.
    2. Conservative treatment for hip dislocation. Avoid surgery if possible.
    3. Routine physical therapy to maintain joint range of motion.
  5. Management of cardiovascular complications:
    1. Routine anticongestive therapy for congestive heart failure.
    2. Nitroglycerin for angina.
    3. Low doses of aspirin help delay heart attacks and strokes.
  6. Anesthesia in progeria: intubation difficulty (Liessmann 2001; Nguyen and Mayhew 2001).
  7. Farnesyltransferase inhibitors (FTIs) have been widely used in the treatment of progeria (Kieran et al. 2007). The results of the first clinical trials taught us that some improvements of the disease phenotypes can be achieved by FTI treatment, but they also made clear that we need a much better understanding of the underlying disease mechanisms to be able to tackle specific aspects of the disease in a more focused approach (Vidak and Foisner 2016).
  8. Potential therapeutic effects of mTOR inhibitors (Evangelisti et al. 2016):
    1. Rapamycin
    2. Rapalogs
    3. Resveratrol
    4. Metformin
  9. mTOR molecular pathways in aging (Evangelisti et al. 2016):
    1. Protein translation
    2. Autophagy
    3. Stem cell pool turnover
    4. Regulation of the inflammatory response
    5. Cellular senescence
  10. mTOR inhibitors and progeria-related disorders (Evangelisti et al. 2016):
    1. Regulation of autophagy and protein accumulation
    2. mTOR inhibitors and lamin A/C-dependent progeroid syndromes: HGPS and MADA
    3. mTOR inhibitors and other progeria-related disorders
    4. mTOR inhibitors and other aging-related diseases

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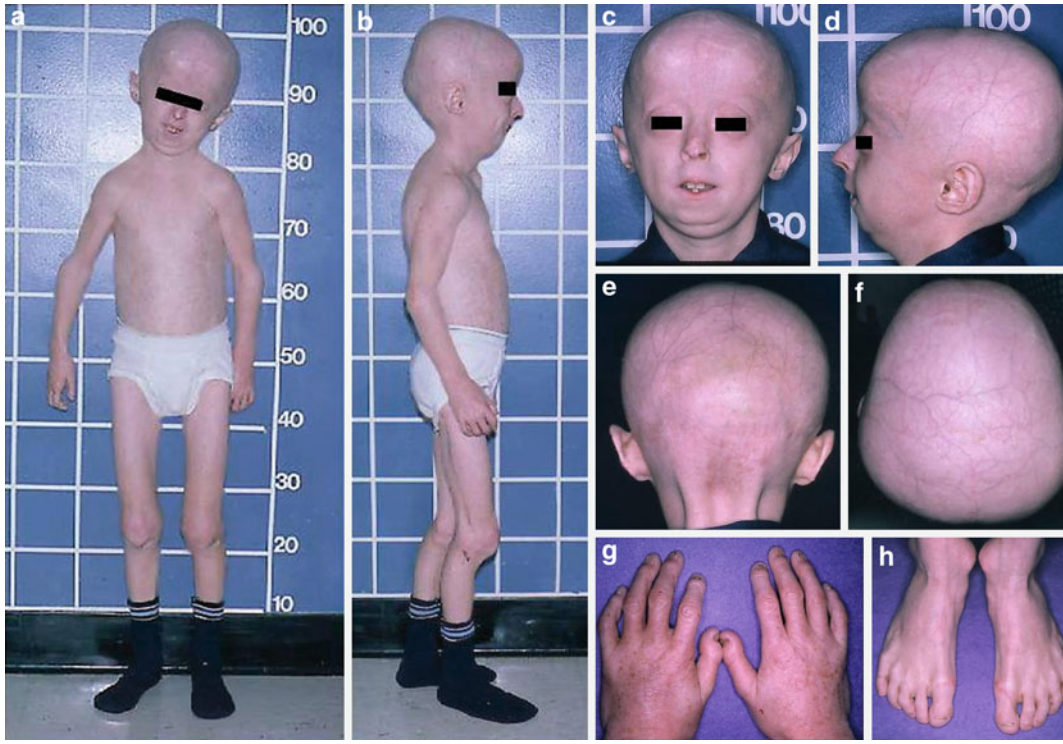

Fig. 1 (**a**–**h**) A boy with progeria (**a**, **b**) showing short stature; senile appearance; small face in comparison with large cranial vault (craniofacial disproportion); alopecia with prominent scalp veins; absent eyelashes and eyebrows; prominent eyes; beak-like nose; mandibular hypoplasia; absent earlobes (**c**–**f**); contracted hands, elbows, and knees (**a**, **b**); short, tapered terminal phalanges; enlarged joints; and dry, brittle, hypoplastic nails (**g**, **h**)

Prune Belly Syndrome

Contents

In 1895, Parker described the congenital triad of deficient abdominal musculature, cryptorchidism, and urinary tract abnormalities. Subsequently, the term "prune belly syndrome" was coined for this condition based on the characteristic wrinkled appearance of the abdomen. The incidence of the syndrome is estimated to be 1 in 35,000 to 1 in 50,000 live births.

Synonyms and Related Disorders

Absence of abdominal muscles with urinary tract abnormality and cryptorchidism; Eagle-Barrett syndrome; Potter sequence

Genetics/Basic Defects

1. Etiologies
    1. Questionable genetic inheritance.
    1. Questionable autosomal dominant inheritance
    2. Autosomal recessive inheritance suggested by some authors
2. Fetal abdominal distension caused by urinary tract obstruction (Burton and Dillerd 1984).
    1. The most common cause of prune belly syndrome
    2. Urethral obstruction causing dilatation of the fetal bladder and upper tracts, thereby attenuating the abdominal musculature
    3. Spontaneous relief of the urethral obstruction in some cases prenatally decompresses the abdomen, producing the shriveled, prune-like appearance of the baby's abdomen
    4. Persistent urethral obstruction causing huge distention of the urinary bladder, bilateral hydronephrosis, and hydroureter complicated by oligohydramnios in more severe cases
3. Fetal ascites from whatever cause: abdominal decompression during intrauterine life leading to prune belly appearance of the abdomen.
4. Prostatic hypoplasia resulting in a functional urethral obstruction leading to development of the prune belly syndrome (Hoagland et al. 1988).
5. Primary mesodermal defect simultaneously affecting the formation of abdominal

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musculature and abnormalities in the lower urinary tract (Mouriquand et al. 2001).

6. Rare association of chromosome abnormalities.
   1. Trisomy 13
   2. Trisomy 18
   3. Turner syndrome with fetal ascites (pathogenetic mechanism thought to involve abdominal distention by ascites rather than by urinary obstruction)
   4. Ring X chromosome lacking *XIST* (Guillen et al. 1997)
   5. Cat eye syndrome
   6. Rarely with trisomy 21
   7. Mosaic unbalanced chromosome constitution of chromosome 16
   8. Presence of a small additional chromosome fragment
   9. Interstitial deletion of chromosome 1 [del(1)(q25q32)] (Scarbrough et al. 1988)
7. One genomic *HNF1β* mutation was detected in 3% of patients with prune belly syndrome but found to be functionally normal. Thus, functionally significant *HNF1β* mutations are uncommon in prune belly syndrome, despite case reports of *HNF1β* deletions (Granberg et al. 2012).
8. R179H mutation in *ACTA2* was reported in a child with prune belly sequence (Richer et al. 2012).

2. Pathogenesis (Pagon et al. 1979; Stranb and Spranger 1981): abdominal wall muscle deficiency (hypoplasia) as a nonspecific lesion resulting from fetal abdominal distension of various causes
3. Terminologies
   1. Prune belly: a descriptive term for a wrinkled and flaccid abdominal wall secondary to stretched skin, soft tissues, and muscles of the abdomen
   2. Prune belly syndrome generally used to indicate the condition having prune belly, cryptorchidism, and abnormalities of the urinary tract
4. Causes of urine flow impairment/obstruction (Mouriquand et al. 2001)
   1. Renal causes
      1. Pelviureteric junction anomaly
      2. Vesicoureteric junction anomaly
      3. Posterior urethral valves
      4. Duplex systems
      5. Ureterocele/ectopic ureter
      6. Urethral atresia
      7. Cloacal anomaly
      8. Vesicoureteric reflux
      9. Megaureter
      10. Megacystis microcolon
      11. Hypoperistalsis syndrome
   2. Extrarenal causes
      1. Sacrococcygeal teratoma
      2. Hydrometacolpos
      3. Other pelvic masses

Clinical Features

1. Broad spectrum in severity
2. Nearly 95% of cases occurring in males
3. Potter face
   1. Mandibular micrognathia
   2. Wide-set eyes
   3. Flattened palpebral fissures
   4. Prominent epicanthus
   5. Flattened nasal bridge
   6. Large, low-set ears with lacking cartilage
4. Abdomen (Nunn and Stephens 1961)
   1. Partial or complete absence of the abdominal musculature (Eagle and Berret 1950; Lattimer 1958; Ives 1974; Welch and kearney 1974)
   2. Thin/lax protruding abdominal wall
   3. Wrinkled abdominal skin
   4. Visible intra-abdominal intestinal patterns through thin abdominal wall
5. Pulmonary (58%): pulmonary hypoplasia (Hassett et al. 2012)
6. Other associated gastrointestinal abnormalities (Woods and Brandon 2007)

1. Malrotation: midgut anomaly, intestines abnormally rotated or become twisted during embryological development
2. Atresia: failure of the intestinal tract to completely form, causing absence of a normal opening
3. Stenosis: narrowing of the center passage within the intestines
4. Volvulus: intestines or stomach lack normal attachments of the body, causing the intestines to become twisted, resulting in a lack of blood supply
5. Clinical symptoms
    1. Bilious vomiting
    2. Abdominal distention
    3. Abdominal tenderness
    4. Failure to pass meconium
    5. Rectal bleeding
    6. Signs of shock and sepsis

7. Genitourinary anomalies (Harley et al. 1972; Rogers and Ostrow 1973; Pramanik et al. 1977; Tuch and Smith 1978; Woodhouse et al. 1982)
    1. Urethral obstruction
    2. Dilated/hypertrophic bladder
    3. Dilated urethra, particularly the prostatic urethra
    4. Dilated/tortuous ureters
    5. Renal dysplasia/hypoplasia with cystic changes
    6. Hydronephrosis
    7. Absence or hypoplasia of the prostate
    8. Ventral body wall defects
        1. Cloacal exstrophy
        2. Bladder exstrophy
        3. Hypo-/epispadias
    9. Genitalia
        1. Bilateral cryptorchidism in males
        2. Pseudohermaphroditism in females
    10. Potter sequence
        1. Oligohydramnios
        2. Potter face
        3. Pulmonary hypoplasia
        4. Other deformations

8. Secondary malformations
    1. Gastrointestinal (24%) (Hassett et al. 2012)
        1. Malrotation (40%)
        2. Atresia of small bowel and colon
        3. Splenic torsion
        4. Imperforate anus
        5. Anorectal agenesis
        6. Omphalocele
        7. Cloacal anomaly
    2. Limb (Genest et al. 1991) and other skeletal abnormalities believed to be the direct result of oligohydramnios with resultant fetal crowding (Green et al. 1993)
        1. Talipes equinovarus
        2. Metatarsus adductus
        3. Vertical talus
        4. Hip dislocation
        5. Arthrogryposis
        6. Pectus excavatum/carinatum
        7. Congenital muscular torticollis
        8. Bell shaped chest
        9. Infantile scoliosis
        10. Severe leg maldevelopment
            1. Generalized hypoplasia
            2. Complete absence
            3. Terminal defects
    3. Cardiacvascular (25%) (Hassett et al. 2012)
        1. Patent ductus arteriosus
        2. Tetralogy of Fallot
        3. Ventriculoseptal defect
        4. Atrioseptal defect
        5. Vascular anomalies
    4. Cleft lip
    5. Spina bifida
    6. Association with diverse chromosome syndromes (Qazi et al. 1978)
        1. Trisomy 13 (Beckman et al. 1984)
        2. Trisomy 18 (Frydman et al. 1983)
        3. Turner syndrome (Lubinsky et al. 1980)
        4. Cat-eye syndrome
        5. Trisomy 21 (Amacker et al. 1986)
        6. Others

9. Grading of patients according to severity of renal and pulmonary malformations (Herman and Siegel 2009)
    1. Grade 1: those with oligohydramnios-induced pulmonary hypoplasia and Potter's facies
    2. Grade 2: moderate-to-marked neonatal and infantile urinary tract involvement without pulmonary hypoplasia or Potter facies
    3. Grade 3: mild renal involvement
10. Prognosis
    1. High mortality although compatible with long-term survival
        1. Stillbirth or death by 1 month of age in 20% of cases
        2. Death by the second year for additional 30% of cases
    2. Causes of death (Christopher et al. 1982)
        1. Renal failure secondary to renal dysplasia present at birth
        2. Pulmonary complications including lung hypoplasia
        3. Infection associated with urinary stasis or operative interventions

Diagnostic Investigations

1. Renal and bladder ultrasound
2. Contrast voiding cystourethrogram
3. Radiography
    1. Hypoplastic lungs with flared lower ribs secondary to the distended abdomen
    2. Diffusely distended flanks
    3. Dilated/dysplastic calyces of the kidneys
    4. Markedly dilated/tortuous ureters
    5. Vertical and trabeculated bladder
    6. A wide and long posterior urethra
    7. Cryptorchidism
4. Histology of the abdominal wall (Moerman et al. 1984a, b)
    1. Muscle atrophy (degeneration of already formed muscle), not of primitive muscle.
    2. The finding supports the theory that the abdominal muscle hypoplasia is a nonspecific lesion, resulting from fetal abdominal distension of various causes.
5. Chromosome analysis for multiple congenital anomalies

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased unless in autosomal recessive inheritance (which is still unclear)
    2. Patient's offspring: not increased
2. Prenatal diagnosis by 2D and 3D ultrasonography (Leeners et al. 2000; Chen et al. 2010)
    1. Signs of fetal abdominal laxity (characteristic abdominal appearance) associated with fetal urinary tract abnormalities
        1. Amniotic fluid wave produced by fetal movement
        2. Sinusoidal undulation of the fetal anterior abdominal wall produced by tapping the maternal abdomen
    2. A distended bladder (megacystis) (Cooperberg et al. 1979) and ureters
    3. Cryptorchidism
    4. Oligohydramnios
    5. Fetal ascites (Monie and Monie 1979; Stevenson et al. 1987)
    6. Lung hypoplasia
    7. Associated anomalies
        1. Other renal anomalies (25%)
        2. Extrarenal abnormalities (12%)
            1. Anorectal anomalies
            2. VATER syndrome
            3. Esophageal atresia
            4. Pattern compatible to specific chromosomal abnormality
3. Management
    1. Orchidopexy for cryptorchidism
    2. Treatment of vesicoureteral dysfunction
        1. Temporary diversion
        2. Ureteral reconstruction
    3. Treatment of vesicourethral dysfunction
        1. Reduction cystoplasty
        2. Internal urethrotomy
        3. Megalourethra repair

4. Abdominal wall reconstruction
5. Vesicoamniotic shunting with percutaneous-placed catheters: useful in some lower urinary tract obstructions such as those that occur with prune belly syndrome (Woods and Brandon 2007). However, vesicoamniotic shunt placement for suspected prenatal obstructive uropathy remains controversial (Freedman et al. 1996)
6. Urological surgical procedures (Seidel et al. 2015)
    1. Urethral surgery (13.0%): urethral dilation, urethrotomy
    2. Bladder surgery (47.8%): vesicostomy, appendicovesicostomy, reduction cystoplasty, tumor resection, Casale procedure, cystostomy, cystolithotomy
    3. Testicular surgery (93.2%)
    4. Renal surgery (23.9%): nephrectomy, transplant, nephrostomy
    5. Ureteral surgery (47.8%): reimplantation, ureterectomy, pyeloplasty
7. Renal transplantation (Hassett et al. 2012)
    1. Nearly a third of PBS patients outside the postnatal period will progress to renal failure requiring transplantation.
    2. Early identifiable risk factors are renal cystic disease and dysplasia reported in approximately 50% of infants with prune belly syndrome.
    3. The most accurate marker of significant renal dysplasia is nadir creatinine; that is the lowest consistent creatinine level in the first 12 months of life.
    4. The commonest indications for a renal transplant in prune belly syndrome patients are renal failure secondary to chronic pyelonephritis and renal dysplasia

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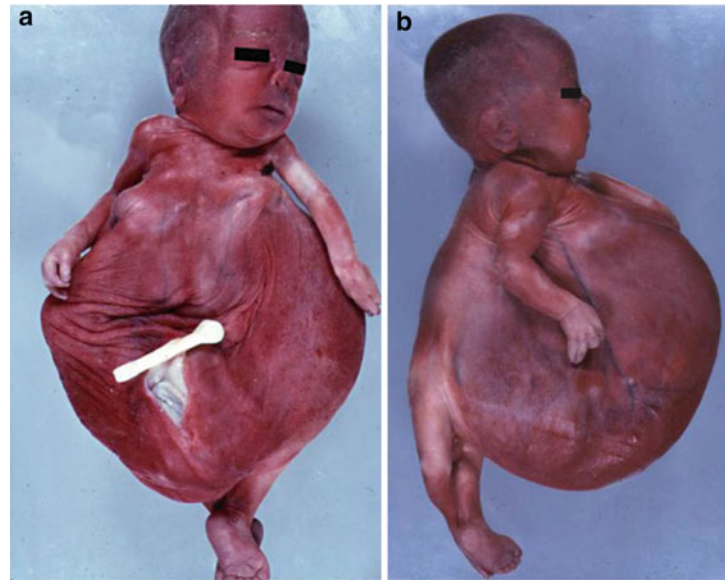

Fig. 1 (**a**, **b**) A premature male neonate with prune belly syndrome due to urethral atresia. He lived for 2 h. There was a massive dilation and hypertrophy of the urinary bladder. Mild hydronephrosis was seen in one kidney, but the second kidney was hypoplastic. The anterior abdominal wall showed muscle deficiency. Additional anomalies included imperforate anus with vesicorectal fistula, secundum-type atrial septal defect of the heart, mild coarctation of the aorta, and bilateral talipes equinovarus

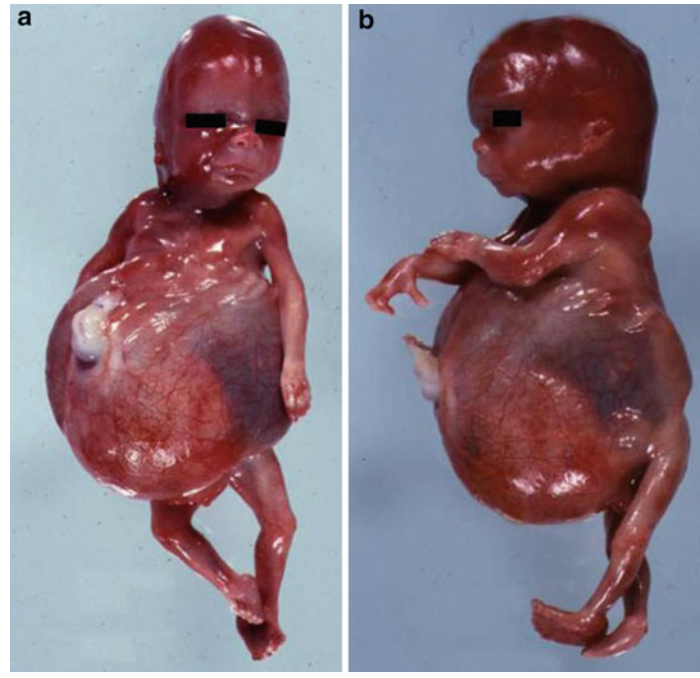

Fig. 2 (**a**, **b**) A male fetus with prune belly syndrome due to severe urethral stenosis. There were marked dilatations of the proximal urethra, bladder, and bilateral ureters. Mild hydronephrosis and cystic renal dysplasia were seen in both kidneys. There were no other anomalies

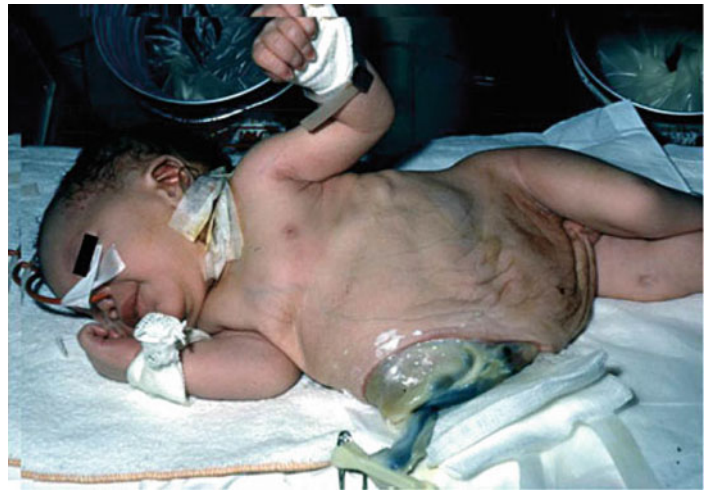

Fig. 3 An infant with prune belly syndrome showing thin, flaccid abdominal wall through which intra-abdominal intestinal patterns are visible

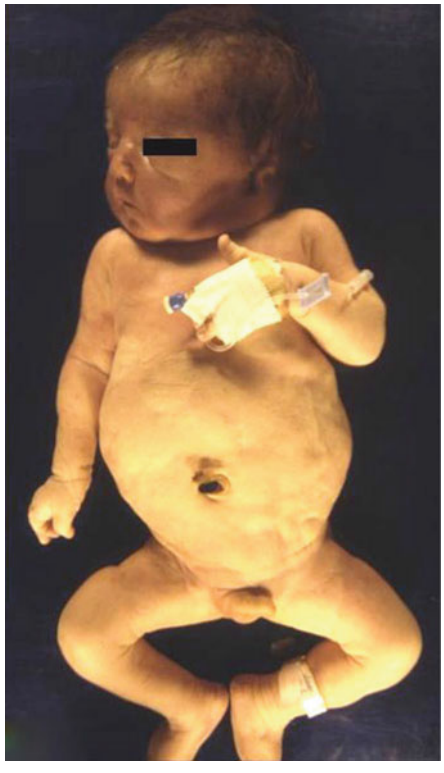

Fig. 4 A postmortem infant with prune belly syndrome showing flaccid and wrinkling abdominal wall with visible intestinal patterns

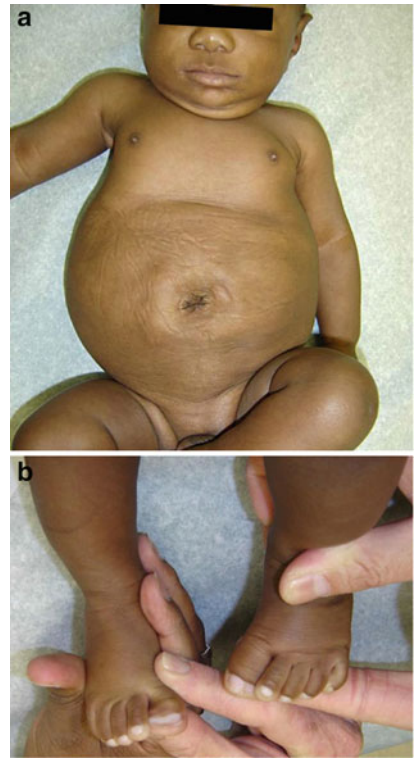

Fig. 5 (**a**, **b**) A neonate with prune belly syndrome showing wrinkling abdominal wall due to multicystic kidneys. The infant also has duplicated great toes

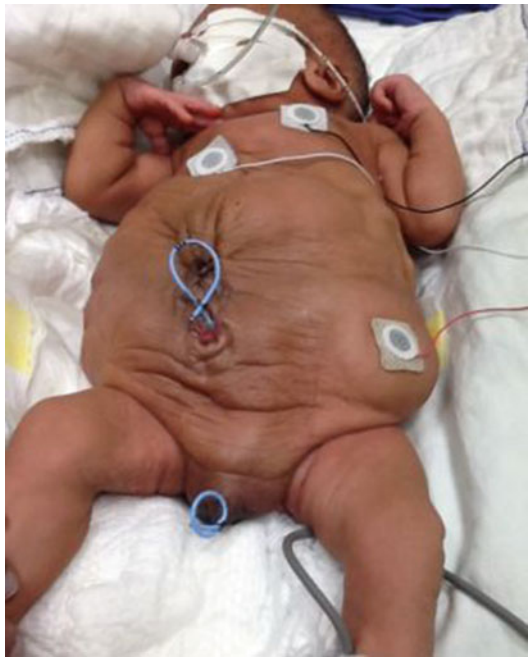

Fig. 6 This infant boy was evaluated for prune belly syndrome. Prenatal ultrasound showed oligohydramnios, bilateral hydronephrosis, and ascites. A wrinkled abdominal wall was noted at birth. The bladder was palpable up to the umbilicus. Bilateral kidneys were enlarged, left more than right. A clear fluid appeared oozing out from the umbilicus (patent urachus). He had a small penis with cryptorchidism. Also seen in the figure is a catheter in the urethra after ureterostomy and ligation of urachus (Courtesy of Dr. Barty Manchandia)

Pseudoachondroplasia

Contents

Pseudoachondroplasia (PSACH) is a type of short-limbed dwarfism, deriving its name from phenotypic similarity to achondroplasia. It is characterized by normal facies, short-limbed dwarfism, joint laxity, and epiphyseal and metaphyseal abnormalities in the growing child.

Synonyms and Related Disorders

Peudoachondroplastic spondyloepiphyseal dysplasia; Pseudoachondroplastic dysplasia

Genetics/Basic Defects

1. Inheritance
    1. Autosomal dominant with complete penetrance: multiple affected Ovitz family members (Muensterer et al. 2012)
    2. Autosomal recessive unlikely (Ferguson et al. 1997)
        1. Somatic mosaicism was demonstrated in two pseudoachondroplasia families that were originally considered to represent autosomal recessive inheritance.
        2. The results suggest that autosomal recessive inheritance is unlikely, and all cases of pseudoachondroplasia should be studied for mutations in *COMP*.
2. Cause
    1. Mutations in the gene encoding cartilage oligomeric matrix protein (*COMP*) on the centromeric region of 19p (19p13.1-p12) (Briggs et al. 1993; Hecht et al. 1995; Ikegawa et al. 1998).
        1. Deletions: Approximately 40–50% of cases of pseudoachondroplasia have deletion mutations in exon 13 of the *COMP* gene.
        2. Specific base substitutions
        3. Duplications
    2. The c. 1352_1353ins TGTCCCTGG is a novel mutation responsible for severe familial PSACH (Dai et al. 2011).
    3. The variant, c.1160_1162del of the COMP gene, was identified as a novel mutation responsible for the spontaneous form of PSACH (Luo et al. 2016).
    4. Can be caused by spontaneous or parental gonadal mosaicism in cases of unaffected parent and no COMP mutation identified in a child (Ferguson et al. 1997; Hall et al. 1987; Xie et al. 2013).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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5. Increase of the range of mutations in COMP that cause PSACH and provides additional evidence for the importance of the calcium-binding domains and the globular domain to the function of COMP (Deere et al. 1998).
6. Allelic to multiple epiphyseal dysplasia, which is also caused by *COMP* mutations (Song et al. 2003).
7. All mutations associated with pseudoachondroplasia and multiple epiphyseal dysplasia (MED): found in exons encoding the type III repeat region or C-terminal domain of *COMP*.
8. PSACH and MED (Briggs and Chapman 2002; Briggs et al. 1995, 1998; Jackson et al. 2012).
    1. Constitute a bone dysplasia family which is both genetically and phenotypically heterogeneous.
    2. The disease spectrum ranges from mild MED, which manifests with pain and stiffness in the joints and delayed and irregular ossification of the epiphyses, to the more severe PSACH, which is characterized by marked short stature, deformity of the legs, and ligamentous laxity.
    3. PSACH is almost exclusively caused by mutations in cartilage oligomeric matrix protein (COMP).
    4. AD-MED is genetically heterogenous and can also result from mutations in matrilin-3 (MATN3) and type IX collagen (*COL9A1*, *COL9A2*, and *COL9A3*).
    5. In contrast, autosomal recessive MED (rMED) appears to result exclusively from mutations in sulfate transporter solute carrier family 26 (*SLC26A2*).

Clinical Features

1. Variable clinical features (Hall 1975; Maroteaux et al. 1980)
2. Normal at birth
3. Normal intelligence
4. Normal craniofacial appearance
5. Waddling gait and diminished linear growth at about 2 years of age
6. Chronic pain in weight-bearing joints (Gamble et al. 2015)
    1. One of the earliest manifestations of PSACH
    2. Most frequently involves knees, hips, and back
    3. Significantly interferes with overall quality of life
7. Rhizomelic short-limbed dwarfism
    1. Body proportion resembling achondroplasia
    2. Usually detectable at age 2–4 years
8. Spine
    1. Accentuated lumbar lordosis
    2. Scoliosis
    3. Kyphosis
    4. Chronic compression myelopathy secondary to habitual atlantoaxial dislocation
9. Extremities
    1. Bowing of the long bones
    2. Deformities of the lower limbs
        1. Secondary to ligamentous laxity
        2. Ranging from genu varum (bowed legs), genu valgum (knock-knees), and genu recurvatum
        3. A "wind-swept deformity" (bowleg on one side and knock-knee on the other side)
    3. Markedly shortened hands (without trident configuration) and feet
    4. Ulnar deviation of the wrist
    5. Flexion contractures of the elbow and knees
    6. Brachydactyly
    7. "Telescoping" fingers
10. Joint
    1. Lax ligament
    2. Premature osteoarthritis
    3. Contractures of the hips
11. Prognosis
    1. Good survival.
    2. Early arthrosis, notably in the hip and knee joints.
    3. PSACH individuals are generally healthy but have problems associated with debilitating osteoarthritis (McKeand et al. 1996).

4. Possible myelopathy secondary to atlantoaxial dislocations.

12. Genotype-phenotype correlation (Briggs et al. 2014)
    1. Mutations in specific residues and/or regions of the type III repeats of COMP are significantly associated with either PSACH or MED.
    2. This newly derived genotype to phenotype correlation may aid in determining the prognosis of PSACH and MED, including the prediction of disease severity, and in the long term guide genetic counseling and contribute to the clinical management of patients with these diseases.
13. Differential diagnosis (Briggs and Wright 2015)
    1. Dominant multiple epiphyseal dysplasia (see the chapter of "▶ Multiple Epiphyseal Dysplasia"): Mutations in *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, or *MATN3* genes can be demonstrated in about 50% of cases.
    2. Recessive multiple epiphyseal dysplasia (see the chapter).
        1. *SLC26A2* (*DTDST*) is the only gene known to be associated with recessive multiple epiphyseal dysplasia.
        2. Diagnosis can be confirmed by molecular genetic testing of the *SLC26A2* gene.
    3. Other forms of spondyloepimetaphyseal dysplasia: need complete skeletal survey for diagnosis.

Diagnostic Investigations

1. Radiography (Heselson et al. 1977)
    1. Tubular bones
        1. Irregularities and fragmentations of the developing epiphyses
        2. Shortened tubular bones
        3. Flaring of metaphyses
        4. Brachydactyly
        5. Delayed epiphyseal ossification (delayed bone age)
        6. Small phalangeal epiphyses (miniepiphyses)
        7. Small, irregular carpal bones
        8. Irregular, widened (frayed), mushroomed metaphyses
        9. Coxa vara
    2. Pelvis
        1. Delayed ossification of the capital femoral epiphyses, which become flattened and small when ossified
        2. Commonly observed sclerosis and irregularity of the acetabular roof
    3. Vertebrae
        1. Characteristic anterior beaking or tonguing (in lateral view of the lumbar spines)
            1. Due to delayed ossification of the annular epiphyses
            2. Vertebrae becoming more normal in appearance after puberty
        2. Some degree of vertebral end-plate malformation
        3. Characteristic platyspondyly in childhood
        4. Kyphoscoliosis
        5. Lumbar lordosis
        6. Odontoid hypoplasia
        7. Atlantoaxial dislocations
    4. Ribs: spatulate
    5. Radiographically, both PSACH and MED are characterized by abnormalities of the epiphyses of the hands, long bones, and hips (Cohn et al. 1996). PSACH also shows marked metaphyseal irregularities as well as characteristic anterior beaking of the vertebrae. The metaphyses and spine in MED are usually normal.
2. Histology of growth plates
    1. Irregular arrangement of chondrocytes without column formation
    2. Irregular provisional calcification
    3. Intracytoplasmic inclusions in chondrocytes
3. EM of chondrocytes (Cooper et al. 1973)
    1. Showing distinctive giant rough endoplasmic reticulum cisternae filled with punctuate material

2. The material composed of alternating electron-lucent and electron-dense layers in a unique lamellar appearance
4. Serum COMP concentration may be suggested as an additional diagnostic marker to aid clinical findings in suspected cases of Pseudoachondroplasia (Liu et al. 2010).
5. Molecular diagnosis
   1. Important to confirm suspected pseudoachondroplasia (Newman et al. 2000)
   2. Sequence analysis of selected exons or the entire coding region (Briggs and Wright 2015)
      1. Detect p.Asp473del (about 30%)
      2. Detect missense and small in-frame deletions (about 70%)
   3. Particularly useful in adult patients where radiological diagnosis can be difficult

Genetic Counseling

1. Recurrence risk: according to autosomal dominant inheritance (Briggs and Wright 2015)
   1. Patient's sib
      1. Fifty percent if one of the parent is affected.
      2. Not increased if parents are normal.
      3. If the disease-causing mutation identified in the proband cannot be detected in the DNA of either parent, two possible explanations are germ line mosaicism in a parent or a de novo mutation in the proband.
         1. The risk to the sibs of the proband depends on the probability of germ line mosaicism in a parent of the proband and the spontaneous mutation rate of *COMP*.
         2. Germ line mosaicism for a *COMP* mutation has been reported (Hall et al. 1987; Ferguson et al. 1997), but the frequency is unknown and the empiric risk to sibs of a proband has not been determined.
   2. Patient's offspring: 50%
2. Prenatal diagnosis
   1. Prenatal ultrasonography unlikely to detects the skeletal changes which will not manifest until about 2 years of age.
   2. Prenatal diagnosis and preimplantation genetic diagnosis: possible in the family at risk and the disease-causing *COMP* mutation has been characterized in an affected individual (Briggs and Wright 2015).
3. Management
   1. Supportive
   2. Surgical correction of the leg deformities
   3. Hip replacement for severe hip contractures
   4. Cervical stabilization procedures for cervical cord compression with progressive neurologic symptoms and signs

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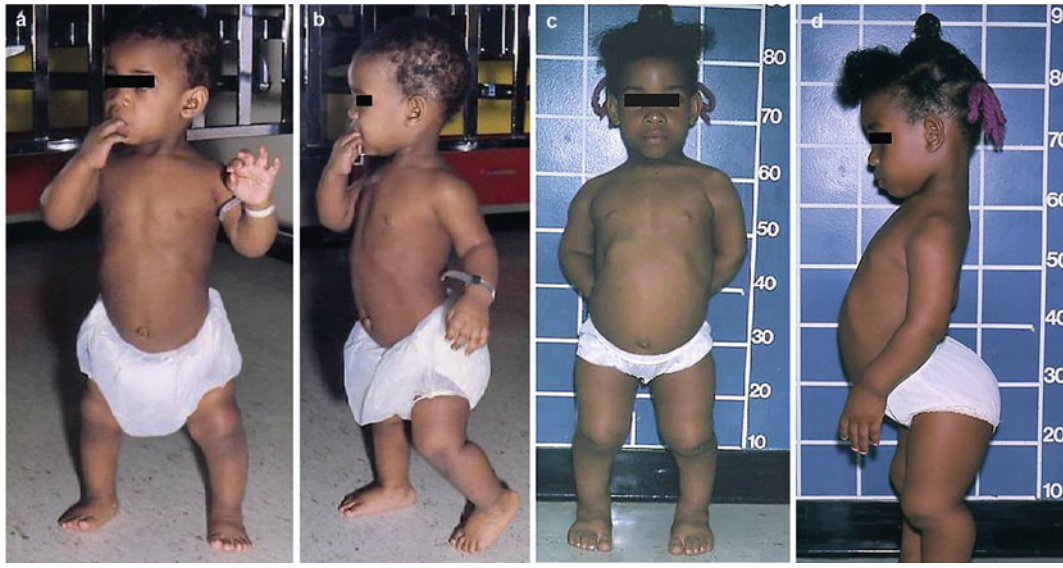

Fig. 1 (**a**–**d**) A girl with pseudoachondroplasia at 2½ years (**a**, **b**) with normal craniofacial appearance, mild short stature, and waddling gate and at 6 years (**c**, **d**) with short limbs, accentuated lumbar lordosis, and short stature

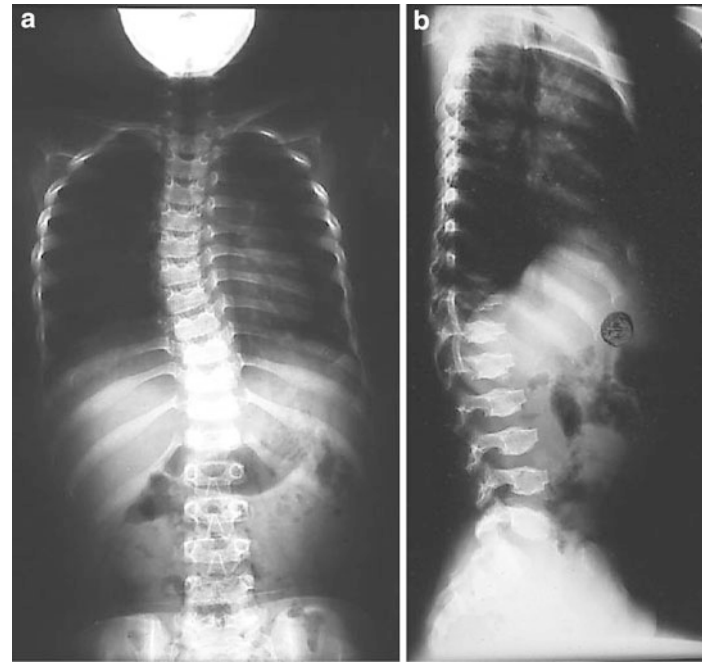

Fig. 2 (**a**, **b**) Radiographs of the spine show characteristic anterior beaking of the lumbar spine and mild scoliosis

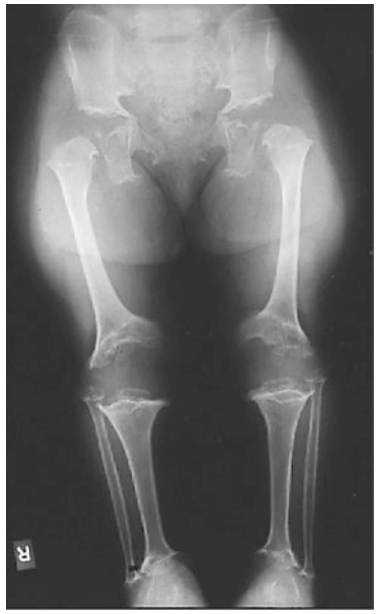

Fig. 3 Radiographs of the pelvis and lower extremities showing irregular, horizontal acetabular roof, delayed epiphyseal ossification, and wide mushroom-shaped metaphyses

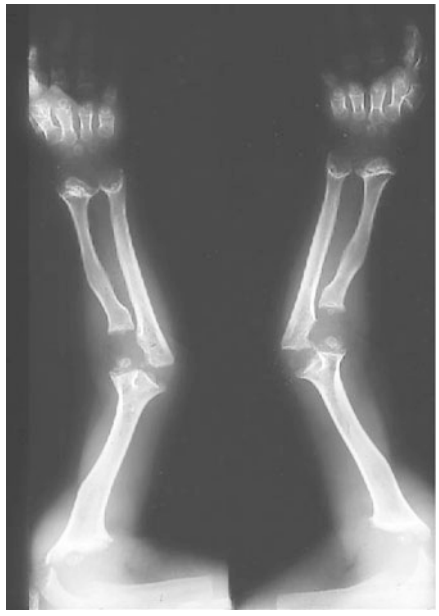

Fig. 4 Radiograph of the upper extremities showing markedly widened and defective metaphyseal and epiphyseal ossifications in the proximal humerus, distal radius, and ulna

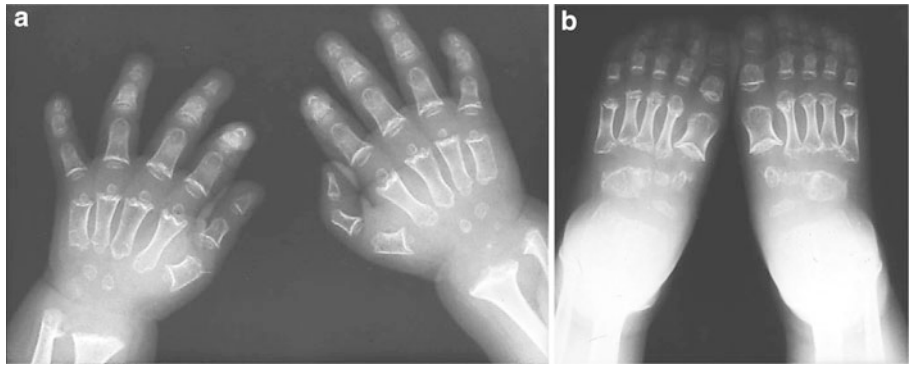

Fig. 5 (**a**, **b**) Radiographs of the hands (**a**) and feet (**b**) show grossly disturbed metaphyseal and epiphyseal ossification, short and stubby tubular bones, somewhat widened metacarpals and metatarsals, and small and markedly irregular carpal and tarsal bones

R(18) Syndrome

Contents

In 1962, Wang et al. (1962) reported the first observation of the ring chromosome 18. Ring chromosome 18 syndrome is a rare chromosome disorder resulting from loss (deletion) of genetic material from one or both ends of a chromosome 18 and joining of the chromosomal ends to form a ring.

Ring chromosome 18 has been reported in many cases of liveborns. The phenotype may vary greatly in range and severity from normal fertile persons in a majority of cases to those with severe malformations, depending upon the amount and location of lost genetic material. Ring chromosome 18 is usually caused by spontaneous (de novo) errors very early in the development of the embryo.

Synonyms and Related Disorders

Mosaic ring chromosome 18 syndrome; Ring chromosome 18 syndrome

Genetics/Basic Defects

1. Formation of a ring chromosome 18
    1. Ring chromosomes arise from chromosomal breakages occurring on either side of the centromere and subsequent rejoining of the segment containing the centromere.
    2. One of the breakpoints is generally at or adjacent to the centromere. Thus, two types of ring chromosomes may arise:
        1. One derived from the short arm
        2. One derived from the long arm
2. Supernumerary ring chromosome 18
    1. The r(18) was additional to the two existing chromosome 18 copies, leading to trisomy for the chromosome 18 segment carried on r(18).
    2. May show the characteristics of trisomy 18 or duplications of 18p or 18q.
3. Mosaic ring chromosome 18
    1. Ring chromosomes are known to be unstable and are often found in a mosaic state.
    2. Instability of a ring may lead to a monosomic cell line.
    3. A report of a deletion at 18pter and at 18qter and a mosaic partial trisomy of the pericentromeric region of chromosome 18 (Baumer et al. 2002).
4. Haploinsuficiency of several genes have been postulated to play a role in the 18q- and 18p- syndrome phenotypes:
    1. HPE4 (18p11.3): holoprosencephaly
    2. GALNR1 (18q23)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Growth hormone deficiency (Aritaki et al. 1996)
4. MBP (18q23): hypomyelination

5. Phenotypic variability depends on the extent of the deleted chromosome 8 segments: most patients show the symptoms of 18q- syndrome, 10p- syndrome, or combination of these two.
6. Chromosome 18 replaced by two ring chromosomes of chromosome 18 origin (Miller et al. 2003): clinical findings partly overlap with observations in 18p- and 18q-syndrome and are similar to some cases of ring chromosome 18.
7. Rare occurrence of a ring chromosome 18 together with a duplication of a segment of chromosome 18 or with a marker chromosome.
8. Familial case of ring chromosome 18 and monosomy 18 mosaicism (Yardin et al. 2001).
9. Rare occurrence of a ring chromosome in mother and daughter (Christensen et al. 1970) and mother and son (Donlan and Dolan 1986; Fryns et al. 1992; Jenderny et al. 1993; Balci et al. 2014).

Clinical Features

1. Clinical features of r(18) syndrome (Wertelecki and Gerald 1971; Karda et al. 2001; Stankiewicz et al. 2001; Carter et al. 2015):
    1. Growth and development
        1. Mental retardation
        2. Hypotonia
        3. Short stature
    2. Head/brain
        1. Microcephaly
        2. Dolichocephaly
        3. Holoprosencephaly spectrum (cebocephaly, arhinencephaly)
        4. Abnormal white matter
    3. Midface: flat
    4. Ears
        1. Asymmetric
        2. Low set
        3. Atretic external ear canals
        4. Prominent antihelix
        5. Hearing loss
    5. Eyes
        1. Deep set
        2. Hypertelorism
        3. Down slanting palpebral fissures
        4. Epicanthal folds
        5. Hyperopia
        6. Amblyopia
        7. Nystagmus
        8. Strabismus
        9. Astigmatism
        10. Ptosis
        11. Optic nerve hypoplasia
        12. Coloboma
    6. Nose
        1. Broad base
        2. Depressed nasal bridge
        3. Broad tip
        4. Choanal atresia
    7. Mouth
        1. Micrognathia
        2. Carp-like down-turned corners
        3. Thin upper and lower lips
        4. High/narrow/cleft palate
        5. Bifid uvula
        6. Dental caries
    8. Throat
        1. Tracheomalacia
        2. Laryngomalacia
    9. Neck: short
    10. Chest
        1. Pectus excavatum
        2. Wide-spaced nipples
    11. Congenital heart defect
        1. PDA
        2. PS
        3. VSD
        4. AS
    12. Abdomen
        1. Umbilical hernia
        2. Inguinal hernia
    13. Gastrointestinal
        1. Reflux
        2. Neonatal feeding difficulties
        3. Constipation
        4. G or NG tube/dysphagia

14. Genitourinary
    1. Male genitalia
        1. Cryptorchidism
        2. Hypoplastic scrotum
        3. Micropenis
    2. Female genitalia: hypoplastic labia minora
15. Pulmonary
    1. Neonatal respiratory difficulties
    2. Asthma
16. Musculoskeletal
    1. Spine: scoliosis/kyphosis
    2. Hands
        1. Clinodactyly
        2. Camptodactyly
        3. Short fingers
        4. Long tapering fingers
        5. Proximally placed thumbs
        6. Single transverse palmar crease
    3. Legs/feet
        1. Club feet (varus)
        2. Vertical talus
        3. Metatarsus adductus
        4. Pectus cavus
        5. Overriding toes
        6. Long/broad toes
        7. Genu valgum
17. Other features
    1. Hypothyroidism.
    2. Autoimmune thyroiditis (Dacou-Voutetakis et al. 1999).
    3. Hypoparathyroidism.
    4. Growth hormone deficiency.
    5. Some of the anomalies overlap with the VACTERL association (van der Veken et al. 2010).
18. Atypical features
    1. Van der Woude syndrome
    2. Insulin-dependent diabetes mellitus (Dacou-Voutetakis et al. 1999)
    3. Agammaglobulinemia (Litzman et al. 1998)

2. Most patients share the features of del(18q) syndrome which are highly variable depending on the extent of the terminal or interstitial 18q deletion:
    1. Mental retardation
    2. Hypotonia
    3. Microcephaly
    4. Short stature
    5. Flat midface
    6. Carp-shaped mouth
    7. Prominent antihelix and antitragus
    8. Atretic/stenotic ear canals
    9. Proximally placed thumbs
    10. Long tapering digits
    11. Foot deformity
    12. Abnormal male genitalia
3. Monosomy 18/r(18) mosaicism fetus with complex malformations (Eiben et al. 1992)
    1. Cebocephaly
    2. Hypotelorism
    3. Microphthalmia
    4. Severe defects of brain development
    5. Arrest of placental maturation
4. Some patients share the features of del(18p) syndrome which are highly variable depending on the extent of the terminal or interstitial 18p deletion:
    1. Mental retardation
    2. Speech delay
    3. Hypotonia
    4. Short stature
    5. Midface defects including holoprosencephaly
    6. Ptosis of eyelids
    7. Small mandible
    8. Dental caries
    9. Short neck
    10. IgA deficiency
5. Some patients share the combined features of del(18p) syndrome and del(18q) syndrome.
6. Genotype–phenotype correlation (Spreiz et al. 2013)
    1. Revealed extensive clinical variability but no characteristic r(18) phenotype.
    2. Severity of clinical signs were generally correlated with the size of the deletion.
    3. Patients with large deletions in 18p and small deletions in 18q exhibited mainly symptoms related to 18p-, whereas those with large deletions in 18q and small deletions in 18p had symptoms of 18q-

Diagnostic Investigations

1. MRI of the brain: abnormal myelination (Nakayama et al. 1997)
2. Conventional cytogenetic studies
   1. Nonmosaic r(18)
   2. Mosaic r(18)
3. Molecular cytogenetic studies using fluorescence in situ hybridization (FISH) technique
   1. Ring chromosome positive for chromosome 18 centromeric probe
   2. Absence of 18q subtelomeric probe
4. Microdissection followed by FISH to determine the origin of the marker chromosome
5. Using a number of microsatellite markers to determine the parental origin and possible mode of formation of the r(18)
6. Single-nucleotide polymorphism array-based characterization of ring chromosome 18 (Spreiz et al. 2013)
7. Whole-genome low-coverage sequencing: would improve the detection and prediction of genotype and phenotypic outcomes to direct postnatal medical care. (Yao et al. 2016)
8. Absent/low IgA (Stewart et al. 1970)

Genetic Counseling

1. Recurrence risk
   1. Patient sibling
      1. A low recurrence risk if both parents are normal phenotypically and karyotypically (in cases of de novo instances in majority of cases).
      2. Careful chromosome analysis to rule out parental mosaicism which may contribute to a recurrent risk of giving birth to a child with either partial trisomy or monosomy of different regions of chromosome 18.
      3. A ring chromosome 18 can be transmitted from a phenotypically normal parent with 46,XX or XY/47,XX or XY,+r(18) karyotype to offspring with a 46,XX or XY,r(18) karyotype.
   2. Patient's offspring
      1. Patients with an r(18): 50%
      2. Patients with mosaic form of an r(18): lower than 50% depends on the percentage of the marker chromosomes
2. Prenatal diagnosis
   1. Prenatal ultrasonography for congenital anomalies including abnormal facial profiles (Los et al. 1996)
   2. Chromosome analysis by amniocentesis or CVS
      1. Presence of an r(18) chromosome
      2. Presence of monosomy 18/r(18) mosaicism (Eiben et al. 1992)
      3. FISH with a chromosome 18 probe to identify chromosome 18
3. Management
   1. Mainly supportive
   2. Multidisciplinary team approach with physical, occupational, and speech therapies
   3. Supportive treatment for chronic sinopulmonary infections associated with IgA deficiency
   4. Treat endocrine dysfunction if present
   5. Surgery for congenital anomalies

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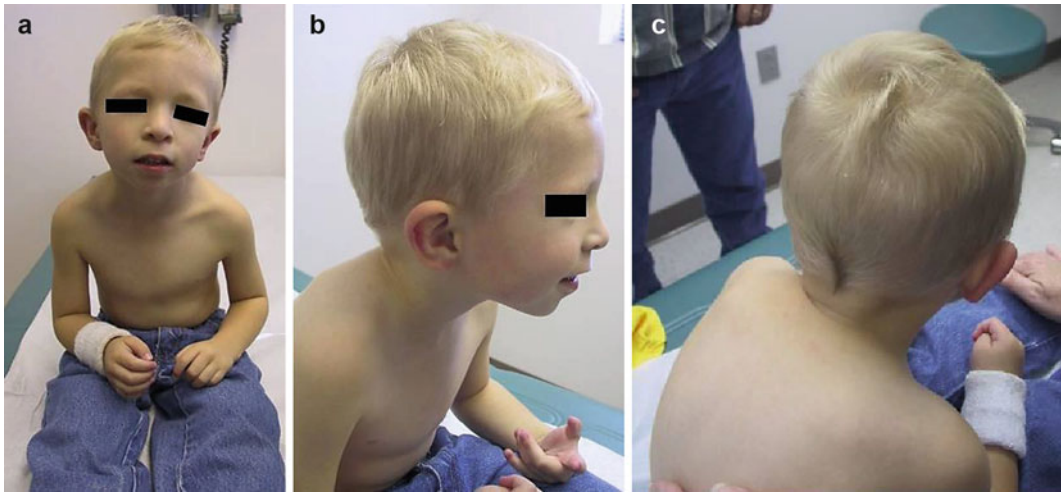

Fig. 1 (**a**–**c**) A 4-year-old boy with de novo r(18) syndrome showing growth deficiency (prenatal and postnatal), speech delay, hypertelorism, downward slanting of the palpebral fissures, strabismus, slightly low-set ears, mild pectus carinatum, clinodactyly of the 5th fingers, and syndactyly of toes. He also has IgA deficiency

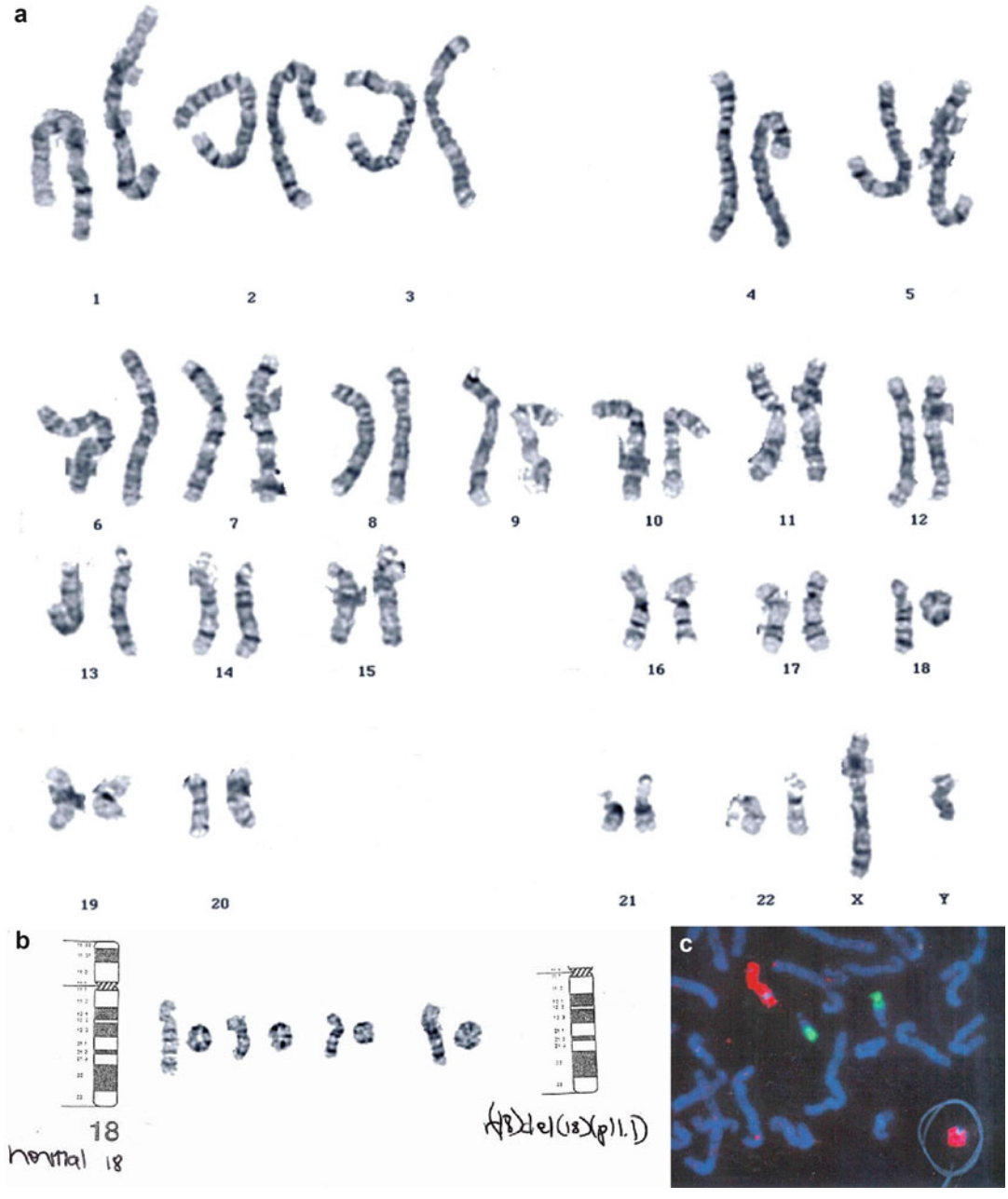

Fig. 2 (**a**–**c**) Chromosome analysis of the patient showed 46,XY,r(18), illustrated by a G-banded karyotype (**a**), a partial karyotype with idiograms (**b**), and FISH with whole chromosome 18 painting probe (**c**)

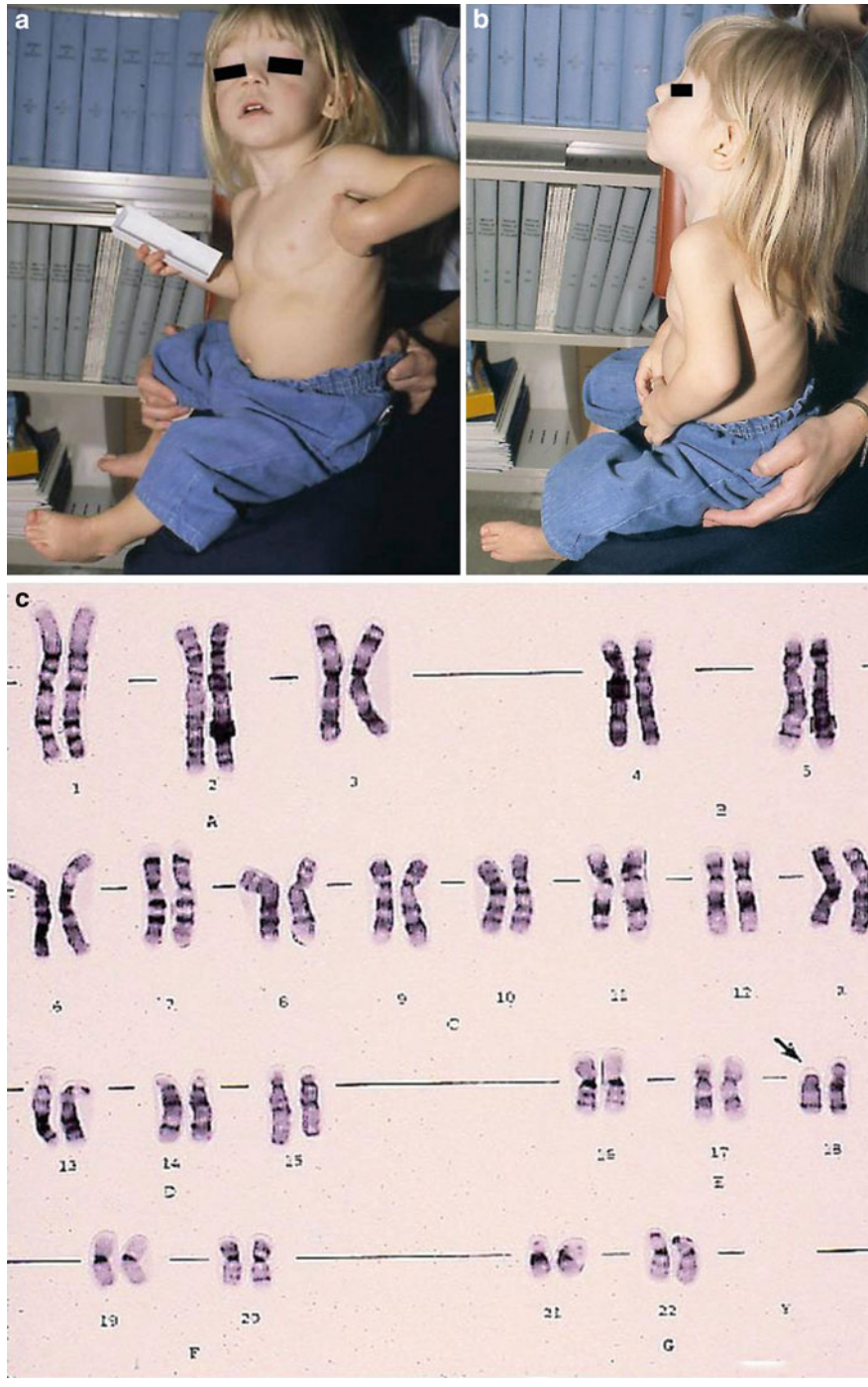

Fig. 3 (**a**–**c**) A girl (**a**, **b**) with del(18p) showing hypotonia, ptosis of the eyelids, and small mandible. The G-banded karyotype (**c**) shows deletion of the short arm of a chromosome 18 (*arrow*)

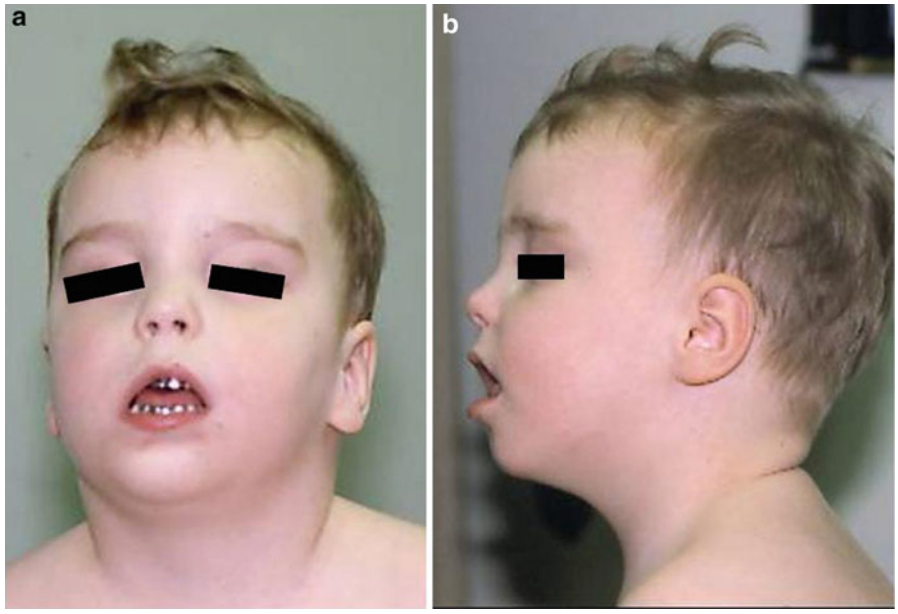

Fig. 4 (**a**, **b**) A boy with del(18q) showing hypotonia, ptosis of the eyelids, and carp-like mouth

Retinoid Embryopathy

Contents

Oral retinoids, isotretinoin (Accutane), and etretinate, uniquely effective in the treatment for severe cystic and keratinization disorders, are potent human teratogens.

Synonyms and Related Disorders

Isotretinoin embryopathy

Genetics/Basic Defects

1. Synthetic retinoids (isotretinoin, etretinate, acitretin)
    1. Closely resemble naturally occurring vitamin A, which is essential for the maintenance of visual and reproductive function and for proliferation and differentiation of epithelial tissues
    2. Isotretinoin and etretinate
        1. Released in the United States and Europe in 1982
        2. Isotretinoin (Brinker et al. 2002; Stashower 2003)
            1. Uniquely effective in severe cystic acne.
            2. Accutane is a powerfully effective therapy, but is not right for every patient.
            3. Estimate rate of pregnancy during Accutane therapy: Mitchell et al (1995) reported 402 pregnancies among 124,216 women completing follow-up for an incidence rate of 3.2 per 1000 women.
            4. From the rates of pregnancy documented during isotretinoin use, we can estimate an annual pregnancy rate during treatment of 16–24 per 1000 female users. Among the 118 live births were 11 (9.3%) cases of congenital malformation (Henry et al. 2016).
        3. Etretinate (and acitretin): uniquely effective in severe psoriasis and other keratinization disorders which proved recalcitrant to all other therapies, account for their availability on prescription despite their teratogenicity
    3. Acitretin released later to replace etretinate as it is more rapidly eliminated from the body

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Adverse reactions (Rademaker 2010)
    1. Isotretinoin is a very effective medication with a low adverse effect profile when used at lower doses (Rademaker 2010).
    2. Commonly reported adverse reactions: largely dose-related, of early onset, and reversible on discontinuation.
        1. Cheilitis
        2. Dryness of the lips, mouth, and eyes
        3. Eczema
        4. Tiredness
        5. Mood change (mental depression)
        6. Skin fragility
        7. Nose bleeds
        8. Joint and muscle aches
        9. Eye problems (altered vision)
        10. Hair loss
        11. Pruitis
    3. Less common and more severe idiosyncratic reactions
        1. Headache
        2. Abnormally raised serum transaminase levels
        3. Serum lipid changes
        4. Increased serum triglyceride and cholesterol levels
        5. An increase in low-density/high-density lipoprotein ratio
    4. Rare reactions
        1. Infections
        2. Severe hepatitis
        3. Diffuse hyperostosis of the spine
        4. Benign intracranial hypertension
5. Teratogenicity of retinoids
    1. Foreshadowed by animal studies with strong warnings against exposure during pregnancy
    2. Believed to interfere with the activity and migration of cranial neural crest cells during development and thus cause craniofacial, thymic conotruncal heart, and CNS malformations
    3. Intellectual deficits

2. Teratogenicity (Chan et al. 1996)
    1. Isotretinoin (Lammer et al. 1988; Lancaster 1988; Strauss et al. 1988)
        1. Teratogenic during the first trimester fetal exposure within the therapeutic dose range
        2. Has a short elimination half-life of about 20 h
        3. Recommended contraception period after cessation of therapy: 1 month
        4. Labeling guidelines be followed in an effort to reduce the risk of pregnancy among women taking isotretinoin (Brinker et al. 2002; Mitchell and Van Bennekom 2003)
        5. Risk of teratogenicity for isotretinoin
            1. Exposure within first trimester: about 28%.
            2. Pregnancy occurring within 1 month after cessation of treatment: about 4%.
            3. Pregnancy occurring after 1 month: the risk of fetal malformations returns to baseline (isotretinoin is no longer detectable in the maternal circulation) (Ellis and Krach 2001).
    2. Etretinate
        1. Readily absorbed into adipose tissue and slowly released from it
        2. Has a long elimination half-life ($\geq$120 days)
        3. Recommended contraception period after therapy: 2 years
        4. Risk for teratogenicity for exposure to etretinate
            1. During pregnancy: about 26%
            2. Within 2 years of treatment cessation: about 2%
    3. Acitretin
        1. A shorter elimination half-life of 50 h.
        2. Recommendation of a 2-year contraception period after therapy for acitretin; as in some women, there is conversion of acitretin to etretinate during therapy.

Clinical Features

1. Isotretinoin embryopathy (Braun et al. 1984; de la Cruz et al. 1984; Chan et al. 1996)

1. Craniofacial abnormalities (Fernhoff and Lammer 1984)
    1. Major auricular malformations (Jahn and Ganti 1987)
        1. Microtia/anotia
        2. Agenesis or marked stenosis of external ear canals
    2. Hypertelorism
    3. Depressed nasal bridge
    4. Micrognathia
    5. Cleft palate
    6. Low-set ears
    7. Asymmetric crying facies (Sarici et al. 2012)
2. Central nervous system abnormalities
    1. Hydrocephalus
    2. Dandy-Walker malformation
    3. Microcephaly
    4. Microophthalmia
    5. Cerebellar defects
        1. Hypoplasia
        2. Microdysgenesis
    6. Cortical defects
    7. Cortical blindness
    8. Facial nerve palsy
    9. Optic nerve hypoplasia
    10. Retinal defects
    11. Spina bifida
    12. Mental retardation
3. Cardiovascular abnormalities
    1. Conotruncal malformations
        1. Transposition of the great vessels
        2. Tetralogy of Fallot
        3. Truncus arteriosus
        4. Double-outlet right ventricle
        5. Ventricular septal defect
        6. Atrial septal defect
    2. Coarctation of the aorta
    3. Interrupted aortic arch
    4. Hypoplastic left ventricle
    5. Retroesophageal right subclavian artery
4. Other abnormalities
    1. Thymic abnormalities
        1. Ectopia
        2. Hypoplasia
        3. Aplasia
    2. Nystagmus
    3. Decreased muscle tone
    4. Hepatic abnormality
    5. Hydroureter
    6. Simian crease
    7. Limb reduction defects (Rizzo et al. 1991)
    8. An increased risk of spontaneous abortions (about 15%) but no long-term effects on fertility
2. Retinate embryopathy
    1. Craniofacial abnormalities
        1. Microtia
        2. Micrognathia
        3. Low-set ears
    2. Central nervous system abnormalities
        1. Menigomyelocele
        2. Anophthalmia
        3. Brain defect
    3. Skeletal abnormalities
        1. Syndactyly
        2. Shortened or absent digits
        3. Club foot
        4. Multiple synostosis

Diagnostic Investigations

1. Sonogram/CT/MRI of the brain for CNS anomalies
2. Radiography/CT for auditory canal malformations
3. Echocardiography for congenital heart defects
4. Audiological assessment by brainstem auditory evoked response
5. Visual and somatosensory evoked potential to detect cortical response
6. Electroencephalography

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased unless the mother exposes to retinoid again during the pregnancy
    2. Patient's offspring: not increased unless exposure to retinoid during pregnancy

2. Prenatal diagnosis
    1. History of maternal exposure to retinoid
    2. Prenatal ultrasonography
        1. Craniofacial anomalies
            1. Microtia/anotia
            2. Anophthalmia/microphthalmia
            3. Other facial abnormalities
        2. CNS anomalies
            1. Microcephaly
            2. Dandy-Walker malformation
            3. Hydrocephalus
        3. Cardiac defects by fetal echocardiography
        4. Skeletal abnormalities
3. Management (Dai et al. 1989; Atanackovic and Koren 1999a, b; Abroms et al. 2006)
    1. Pregnancy Prevention Program, developed by the manufacturer and the US Food and Drug Administration since 1988, to prevent fetal exposure to the drug Accutane (Pastuszak and Koren 1993; Pastuszak et al. 1994; Koren and Pastuszak 1997):
        1. Distribute printed material to prescribing physicians to be used in educating their female patients about the serious teratogenic effects.
        2. Instruct physicians to delay therapy until the second or third day of the patient's next normal menstrual period.
        3. Stress to patients the importance of using two forms of contraception concurrently.
        4. A consent form to be signed by female patients (Holmes et al. 1998):
            1. Acknowledging that they have been instructed through the program.
            2. Aware of the need to use two forms of contraception during isotretinoin therapy.
            3. Agree to undergo pregnancy testing before, during, and after the therapy.
        5. Still no full compliance to the isotretinoin pregnancy prevention program in many Western countries (Zomerdijk et al. 2014).
        6. Internet-based, performance-linked system called iPLEDGE (Abroms et al. 2006):
            1. The most recent and most stringent system
            2. To ensure that the drug is dispensed only when there is documentary proof that the patient is not pregnant and is using two forms of birth control
    2. Adhere to strict prescription guidelines, but exposure during pregnancy still occurs. The most common reasons for unwanted or mistimed pregnancies with isotretinoin therapy are (Perlman et al. 2001) as follows:
        1. Unsuccessful attempts at abstinence
        2. Use of ineffective contraception
        3. Inconsistent use of contraception
        4. Unexpected sexual activity
        5. Contraceptive failure
    3. Safe and optimal use of isotretinoin: summery and recommendations (Goldsmith et al. 2004).
    4. Currently, there appears to be no increased risk of retinoid embryopathy. However, according to current knowledge, topical retinoids cannot be advised for use during pregnancy because their risk/benefit ratio remains questionable (Panchaud et al. 2012).
    5. Physicians who cannot follow the program or are not experienced prescribers of oral isotretinoin should refer the patient to the most experienced practitioner available – to protect themselves and to serve their patients (Shear 1999).
    6. The need to improve pregnancy prevention programs (Crijns et al. 2011):
        1. Taking responsibility and enhancing the performance by health care professionals.
        2. Give explicit instructions.
        3. Monitor the performance and adjusting, if necessary.
    7. The medical community has a major role to play in ensuring that babies are not affected by prescription drugs taken during pregnancy. The continued occurrence of fetal exposure to isotretinoin highlights the need for improved practices. These

improvements will likely require intervention at multiple levels, including improved education for patients and healthcare providers, improved patient adherence with established safety protocols, and proper control of isotretinoin's distribution (Choi et al. 2013).

8. Encouraging the use of highly effective, patient-independent contraception and limiting abstinence to women who have never been sexually active may further reduce the rate of isotretinoin exposed pregnancies (Collins et al. 2014).
9. Increase adherence to contraceptive methods that will reduce and, hopefully, eliminate fetal exposure to isotretinoin (Altman 2014).
10. Since few clinicians provide women information on highly effective (i.e., intrauterine or subdermal) contraceptives, the iPLEDGE program increases anxiety about isotretinoin more than it helps women feel protected from the teratogenic risks of isotretinoin (Werner et al. 2014).
11. Surgical shunting for hydrocephalus.
12. Surgical repair of congenital heart defects.
13. Surgical reconstruction of the external ear canal and middle ear.
14. Orthopedic management of limb reduction.
15. Multidisciplinary approach to multiple handicapped conditions.

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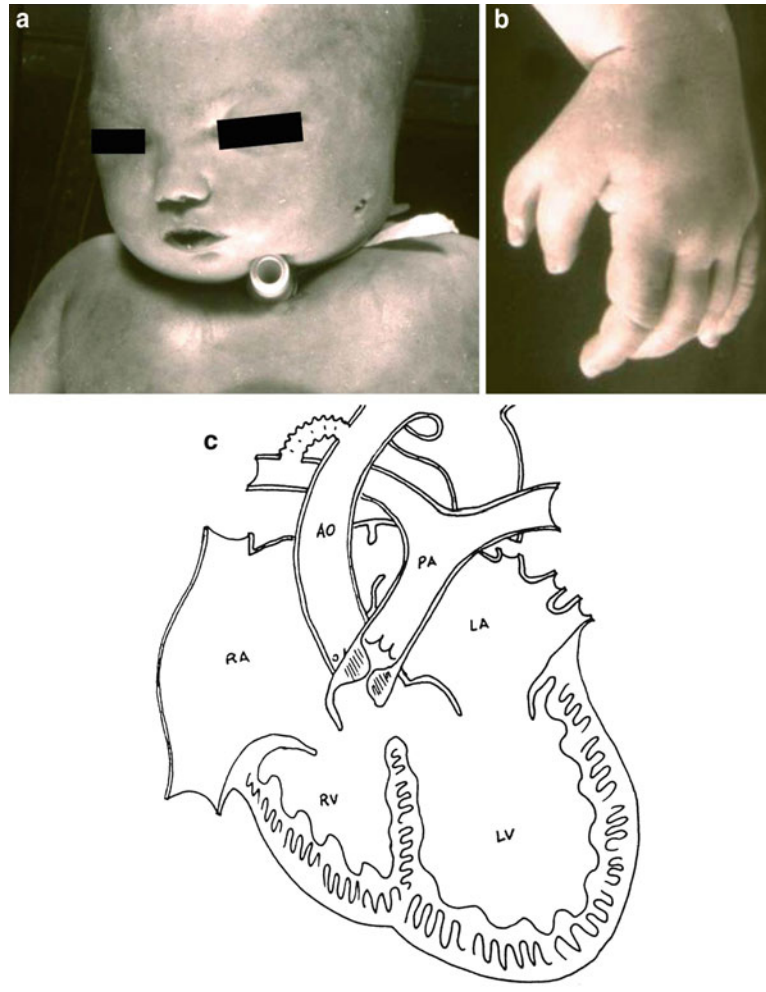

Fig. 1 (**a**–**c**) An infant with isotretinoin embryopathy (**a**, **b**). The mother took Accutane in the first trimester. Prenatal ultrasound examinations revealed intrauterine growth retardation, apparent ocular hypertelorism, flat nasal bridge, and tetralogy of Fallot. Parents elected to continue the pregnancy. The infant was born with dysmorphic craniofacial features (microcephaly, hypertelorism, flat nasal bridge, microretrognathia, cleft palate, absent ear canals and anotia, duplicated thumb on the left hand, anteriorly placed anus, and tetralogy of Fallot (illustrated in a drawing) (**c**))

Rett Syndrome

Contents

Rett syndrome (RTT), a neurodevelopmental disorder affecting girls almost exclusively, was first described by Rett (1966) in 1966. The disorder now bears his name and became widely known after a report of 35 cases by Hagberg et al. (1983). The prevalence is estimated to be 1/10,000–1/15,000 female births (Hagberg 1985); over 95% of cases arise de novo due to the fact that most females with Rett syndrome do not reproduce. Rett syndrome is considered to be one of the most common genetic causes of mental retardation in girls, second only to Down syndrome.

Synonyms and Related Disorders

Ataxia; Autism; Dementia; Loss of purposeful hand use

Genetics/Basic Defects

1. Inheritance:
    1. Sporadic cases (99.5%), occurring almost exclusively in females:
        1. A de novo mutation in the child with Rett syndrome
        2. Disease-causing mutation inherited from one parent who has somatic or germ line mosaicism
    2. Several reports of familial recurrence support X-linked dominant inheritance with lethality in hemizygous males.
2. The region of interest has been localized to Xq28 by linkage analysis from available familial cases (Sirianni et al. 1998; Webb et al. 1998).
3. Caused by mutations in the *MECP2* (methyl-CpG-binding protein 2) gene (Amir and Zoghbi 2000; Lombroso 2000) in Xq28:
    1. Caused by partial loss of *MECP2* function (Amir et al. 2000).
    2. Result in a loss of function by either disrupting the methylated DNA-binding properties of the protein or interfering with its association with transcriptional corepressors.
    3. *MECP2* mutations account for most cases of typical forms of Rett syndrome (Bienvenu et al. 2000).

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4. Detection of mutations and variants in the MeCP2 gene in Rett syndrome patients (Hampson et al. 2000):
    1. Missense
    2. Protein truncation (most mutations) (Huppke et al. 2000)
    3. Variants
5. *MECP2* mutations in sporadic or atypical cases (Webb and Latif 2001):
    1. Up to 80% of sporadic affected females.
    2. One third of the clinically atypical cases.
    3. MECP2 mutations in sporadic cases of Rett syndrome are almost exclusively of paternal origin (Trappe et al. 2001).
6. *MECP2* mutations in familial cases (lower incidence):
    1. Germ line mosaic mothers.
    2. Asymptomatic carrier mothers due to nonrandom patterns of X-inactivation. The pattern of X-inactivation most likely protects the mutation carriers from expression of the disease by preferential inactivation of the mutant *MECP2* allele.
7. Clinical spectrum of MECP2 mutations (Shahbazian and Zoghbi 2001):
    1. In classic Rett syndrome, genotype–-phenotype correlation studies suggest that X chromosome inactivation patterns have a more prominent effect on clinical severity than the type of mutation.
    2. When the full range of phenotypes associated with MECP2 mutations is considered, however, the mutation type strongly affects disease severity.
8. Deletion of MeCP2 results in a wide and temporally varied range of phenotypes (Feldman et al. 2016).

4. Rett syndrome targets synapses and synaptic plasticity and has been shown to disrupt the balance between glutamate excitatory synapses and GABAergic inhibitory synapses (Johnston et al. 2015). In fact, it can be argued that Rett syndrome is primarily a disorder of synaptic plasticity and that agents that can correct this imbalance may have beneficial effects on brain development.
5. MeCP2 is a multifunctional protein, with involvement in chromatin architecture, regulation of RNA splicing, and a role both as transcriptional repressor or activator (De Felice et al. 2016):
    1. The MeCP2 protein plays a critical role in the complex pathways linking innate and adaptive immune systems.
    2. MECP2 loss-of-function mutations elicit an inflammatory–autoinflammatory response in Rett syndrome patients.
6. Pathogenesis and clinical course of Rett syndrome: systemic subclinical inflammation and oxidative stress are crucial players of a detrimental vicious circle, driving the pathogenesis and clinical course of RTT (Pecorelli et al. 2016).
7. RTT gastrointestinal physiopathology (Strati et al. 2016):
    1. RTT is associated with a dysbiosis of both the bacterial and fungal component of the gut microbiota, suggesting that impairments of MeCP2 functioning favor the establishment of a microbial community adapted to the costive gastrointestinal niche of RTT patients.
    2. The altered production of short chain fatty acids associated with this microbiota might reinforce the constipation status of RTT patients and contribute to RTT gastrointestinal physiopathology.
8. Females with the *MECP2* mutations (Takahashi et al. 2008):
    1. High frequency of MeCP2 gene mutations causative of Rett syndrome in females and provides data concerning the molecular basis for clinical variability (mutation type and position and X-inactivation patterns) (Hoffbuhr et al. 2001).
    2. Regardless of the type of mutation, the XCI pattern is the major determinant of the phenotype in females (Wan et al. 1999).
    3. Exhibit a broad spectrum of clinical presentations ranging from classical Rett

syndrome to asymptomatic carriers due to differences in X chromosome inactivation (XCI) (Singer and Naidu 2001).
4. Correlation between the intrafamilial phenotypic differences observed in RTT families and their respective XCI pattern in blood (Ravin et al. 2011).
5. Mechanisms other than XCI may contribute to the phenotypic heterogeneity associated with *MECP2* mutations.

9. Males with the *MECP2* mutations:
1. MECP2 mutation causes X-linked mental retardation (Orrico et al. 2000) and progressive spasticity in male patients (Meloni et al. 2000).
2. May suffer from severe neonatal encephalopathy (Villard et al. 2000) and die from breathing difficulties before their second year.
3. The almost absence of men with classic Rett syndrome suggests a lethal effect of the *MECP2* mutation in hemizygous-affected men.
4. However, males with Rett syndrome are not always lethal although neurologic impairment is slowly progressive and much more severe in men than in women (Dotti et al. 2002).
5. Somatic mosaicism could explain the occurrence of other X-linked dominant disorders in males, when they would normally be lethal (Clayton-Smith et al. 2000).
6. Affected men have been reported in association with Klinefelter syndrome and somatic mosaicism.
7. Most *MECP2* mutations have originated in the paternal germ line. The paternal X *MECP2* never passed on from father to their sons.
8. The only way for a male to have Rett syndrome is a de novo mutation of a maternal X or inheritance of an *MECP2* gene mutation from his mother.
9. Some reported *MECP2* mutations may actually represent genetic variant rather than true pathogenetic novel mutations in the *MECP2* gene in males.

10. Genotype–phenotype correlations in males with MECP2 mutations (Moretti and Zoghbi 2006; Villard 2007):
1. The first group
1. Boys with Rett syndrome have XXY karyotype or somatic mosaic and carry the same *MECP2* mutations that cause classic Rett syndrome in girls.
2. The affected boys have severe neonatal encephalopathy and usually die in their first year of life.
3. These mutations can also lead to a milder phenotype when they are diluted among normally expressing cells.
2. The second group
1. Has mutations that are not found in females with Rett syndrome.
2. These mutations are usually compatible with life into adulthood.
3. The neurological presentation ranges from severe to mild nonspecific mental retardation.
3. The third group
1. Composed of males having a duplication of the whole *MECP2* gene (and sometimes genes in its vicinity)
2. The primary clinical features associated with this microduplication are nonspecific, but they comprise a severe phenotype.
3. Affected individuals experience infantile hypotonia (Heilstedt et al. 2002), recurrent respiratory infection, severe mental retardation, absence of speech development, seizures, and spasticity.

10. Clinical phenotypes of MeCP2 dysfunction in Rett syndrome and related disorders (Moretti and Zoghbi 2006; Chahrour and Zoghbi 2007):
1. Females (loss-of-function of MeCP2)
1. Classic Rett syndrome
2. Atypical Rett (preserved speech or normal hand use)
3. Infantile encephalopathy

4. Angelman syndrome phenotype
5. Mental retardation with seizures
6. Mild mental retardation
7. Learning disability
8. Autism
9. Normal

2. Males (loss-of-function of MeCP2)
   1. Infantile encephalopathy
   2. Classic Rett syndrome (47, XXY or somatic mosaics)
   3. Mental retardation with motor deficits
   4. Bipolar disorder, mental retardation, and tremors
   5. Juvenile-onset schizophrenia, mental retardation, and tremors
   6. Mental retardation, psychosis, pyramidal signs, and macroorchidism
3. MECP2 gene duplications (overexpression)
   1. Preserved speech variant of Rett syndrome (De Bona et al. 2000)
   2. Severe mental retardation and clinical features of Rett syndrome
   3. Nonspecific X-linked mental retardation

Clinical Features

1. Wide spectrum of clinical features associated with *MECP2* mutation (Auranen et al. 2001)
   1. Male patients with early-onset lethal encephalopathy to adult cases with severe mental retardation
   2. Female patients from asymptomatic or mildly mentally retarded to severe variant of Rett syndrome with congenital onset
2. Normal prenatal and perinatal history
3. Appropriate head circumference
4. Apparently normal psychomotor development until about 6–18 months of life in affected girls
5. Developmental milestones afterward beginning to slow down and regress with loss of skills already achieved
   1. Deterioration of communicative skills
   2. Social withdrawal
   3. Loss of purposeful hand movement
6. Continued deterioration over the next few years
   1. Loss of language
   2. Poor motor function (truncal and gait apraxia/ataxia)
   3. Stereotypic hand movements (hand wringing and flapping)
   4. Deceleration of head growth (acquired microcephaly)
   5. Autistic behavior
7. Period of stabilization
   1. Severe psychomotor dysfunction.
   2. Some patients may make small recoveries in contact and communication skills.
8. Breathing difficulties
   1. Periodic apnea
   2. Hyperventilation
   3. Breath holding
   4. Forced explosion of air/saliva
   5. Bruxism
9. Swallowing difficulties
10. Dystonia and hand and foot deformities as affected girls grow older
11. Later development of scoliosis
12. Osteoporosis at risk for fractures
13. Seizures (epilepsy) in 50% affected females
14. Possible survival into adulthood without further deterioration
15. An increased risk for sudden, unexplained death
    1. Longer corrected QT intervals
    2. T-wave abnormalities
    3. Reduced heart rate
16. Rett syndrome variants (Hagberg and Skjeldal 1994; Hagberg 1995) (<10% of cases)
    1. Patients with a milder clinical course ("forme fruste" phenotype): considered to be the most common variant of nonclassical Rett syndrome
       1. Less dramatic regression
       2. Mild learning disability
       3. Milder mental retardation
       4. Preserved speech
       5. Ability to walk
       6. Some hand use
       7. Usually without seizures

8. No apparent symptoms observed in a few women who demonstrate skewed X chromosome inactivation
2. Patients with a severe phenotype
   1. Lack of normal postnatal developmental period
   2. Congenital hypotonia
   3. Infantile spasms
3. Patients with late regression
4. Male patients with Rett syndrome
   1. Males with XXY (Klinefelter syndrome) (Schwartzman et al. 1998)
   2. Males with somatic mosaicism
   3. Males with XY (normal karyotype)
5. Male Rett syndrome variant: males with idiopathic developmental regression, autistic features, and loss of hand function (Jan et al. 1999)

17. Clinical stages in classic Rett syndrome (Percy 1995; Jedele 2007; Briggs 2013)
    1. Stagnation stage (early infancy to 18 months)
       1. Developmental arrest
       2. Deterioration of eye contact and possible loss of communication
    2. Rapid destructive stage (1–4 years): developmental regression
       1. Developmental deterioration
       2. Loss of acquired skills, including fine motor, babbling of words, and active playing
       3. Loss of purposeful hand use
       4. Stereotyped hand movements
       5. Apparent cognitive impairment
       6. Intermittently "in another world"
       7. Autistic features
       8. Gait ataxia and apraxia
       9. Irregular breathing (hyperventilation)
       10. Seizures in only 15%
    3. Pseudostationary stage (preschool–early school years)
       1. Some communication improvements
       2. "Wake-up" period
       3. Decreased autistic features
       4. Preserved ambulation (A few are never ambulant.)
       5. Prominent gait ataxia and hand apraxia
       6. Slow neuromotor regression
       7. Seizures most frequent and severe
    4. Late motor deterioration stage (5–25 years)
       1. Decreased mobility (loss of ambulation)
       2. Severe debilitation in patients who never walked
       3. Spasticity
       4. Improved emotional contact
       5. Scoliosis
       6. Severe wasting and debilitation leading to "frozen stiffness"
       7. Cachexia and growth retardation
       8. Staring, unfathomable gaze
       9. Complete wheelchair dependency
       10. Seizures may lessen or disappear
18. Wide spectrum of clinical features associated with an *MECP2* mutation
    1. Male patients with early-onset lethal encephalopathy
    2. Adult cases with severe mental retardation
    3. Female cases
       1. Asymptomatic
       2. Mildly mentally retarded
       3. Severe variant of Rett syndrome with congenital onset
19. Clinical findings in males with MECP2 mutation (Imessaoudene et al. 2001; Laccone et al. 2002)
    1. Normal pregnancy/delivery
    2. Developmental delay
    3. Severe mental retardation
    4. Acquired microcephaly
    5. Seizures
    6. Neurological findings
       1. Restless, uncoordinated movements
       2. Hypotonia
       3. Hyperlaxity
       4. Mild distal muscular atrophy
       5. Periodic breathing
       6. Dorsal extension of the hands
       7. Neurogenic muscular atrophy
    7. Purposeful hand skills
    8. Loss of skills
    9. Electroencephalogram: generalized slow waves
    10. Brain MRI: marked brain atrophy

20. Cardinal clinical features of Rett syndrome in relation to pathology (Julu et al. 2008; Smeets et al. 2011)
    1. Decreased dendritic arborization and smaller than normal brain (cortical); severe intellectual disability
    2. Epilepsy (cortical): seizures
    3. Monoaminergic dysfunction (extrapyramidal):
        1. Dystonia
        2. Incoordination of motor activities
        3. Secondary orthopedic deformities and muscle wasting with contractures
    4. Monoaminergic dysfunction (brainstem):
        1. Dyspraxia
        2. Agitation
        3. Sleep disturbances
    5. Immaturity with incompetence of inhibitory neuronal networks (brainstem): Abnormal breathing rhythms and lack of integrative inhibitions are likely causes of sudden deaths.
    6. Dysautonomia (brainstem):
        1. Cold and blue extremities
        2. Sympatho-vagal imbalance
21. Relatively restrictive international diagnostic criteria (The Rett syndrome Diagnostic Criteria Work Group 1988)
    1. Apparently normal prenatal and perinatal period*
    2. Normal head circumference at birth
    3. Apparently normal development through age 6 months*
    4. Deceleration of head growth occurring anytime between ages 3 months and 48 months
    5. Loss of acquired hand skills and purposeful hand use between ages 5 months and 30 months, with subsequent development of stereotyped hand movements
    6. Severe impairment of expressive and receptive language together with severe psychomotor retardation
    7. Development of gait apraxia and truncal ataxia between ages 12 months and 48 months

    * Clinical criteria "a" and "c" may not be applicable to severely affected females; other criteria will not apply to those who are mildly affected and are identified as having mutations in *MECP2*.
22. Modified diagnostic criteria (Percy 1995; Clarke in 1996)
    1. Necessary criteria
        1. Normal prenatal and perinatal development
        2. Loss of acquired skills such as communication and speech
        3. Normal head circumference at birth with acquired microcephaly
        4. Deceleration of head growth
        5. Marked developmental delay
        6. Loss of acquired hand skills
        7. Loss of communication skills (words and interpersonal)
        8. Autistic features
        9. Gait apraxia
        10. Stereotypic handwringing or handwashing
    2. Supportive criteria
        1. Seizures
        2. Abnormal EEG
        3. Awake breathing dysfunction
            1. Apnea
            2. Hyperventilation
            3. Forced air or saliva expulsion
            4. Air swallowing
            5. Breath holding
        4. Growth retardation
        5. Bruxism
        6. Cold feet
        7. Scoliosis
        8. Vasomotor instability
        9. Gait dyspraxia
        10. Spasticity with muscle wasting
        11. Unprovoked laughing or screaming
        12. Reduced or altered pain response
        13. "Eye pointing"
23. Revised diagnostic criteria for classical and variant Rett syndrome (Ellaway and Christodoulou 1999; Hagberg et al. 2002; Williamson and Christodoulou 2006)
    1. Classical Rett syndrome
        1. Necessary criteria
            1. Normal prenatal and perinatal history

2. Normal psychomotor development for the first 6 months
3. Normal head circumference at birth
4. Postnatal deceleration of head growth in most individuals
5. Loss of purposeful hand skills between 6 months and 2.5 years
6. Hand stereotypes
7. Evolving social withdrawal, communication dysfunction, loss of acquired speech, and cognitive impairment
8. Impairment or deterioration of locomotion

2. Supportive criteria
   1. Breathing disturbances during waking hours
   2. Bruxism
   3. Impairment of sleeping pattern from early infancy
   4. Abnormal muscle tone associated with muscle wasting and dystonia
   5. Peripheral vasomotor disturbances
   6. Progressive kyphosis or scoliosis
   7. Growth retardation
   8. Hypotrophic small and cold feet and/or hands
3. Exclusion criteria
   1. Evidence of a storage disorder including organomegaly
   2. Cataract, retinopathy, or optic atrophy
   3. History of perinatal or postnatal brain damage
   4. Confirmed inborn error of metabolism or neurodegenerative disorder
   5. Acquired neurological disorder due to severe head trauma or infection

3. Variant Rett syndrome
   1. Inclusion criteria
      1. At least three of the six main criteria
      2. At least 5 of the 11 supportive criteria
   2. Main criteria
      1. Reduction or absence of hand skills
      2. Loss or reduction of speech (including babble)
      3. Hand stereotypes
      4. Loss or reduction of communication skills
      5. Deceleration of head growth from early childhood
      6. Regression followed by recovery of interaction
   3. Supportive criteria
      1. Breathing irregularities
      2. Abdominal bloating or air swallowing
      3. Bruxism
      4. Abnormal locomotion
      5. Kyphosis or scoliosis
      6. Lower limb amyotrophy
      7. Cold, discolored, and usually hypotrophic feet
      8. Nighttime screaming and other sleep disturbances
      9. Inexplicable episodes of screaming or laughing
      10. Apparently diminished sensitivity to pain
      11. Intense eye contact and/or eye pointing

24. Differential diagnosis (Christodoulou and Ho 2012)
    1. Angelman syndrome (Please see the chapter on "► Angelman Syndrome")
    2. Pathogenic variants in *CDKL5*, a gene also located on the X chromosome and encoding cyclin-dependent-like kinase 5, have been identified in individuals with a Rett syndrome-like phenotype.
    3. Pathogenic variants in *FOXG1* are associated with the congenital form of Rett syndrome (Ariani et al. 2008; Bahi-Buisson et al. 2010; Mencarelli et al. 2010). The gene was first implicated in Rett syndrome by identification of microdeletions at its genetic locus on 14q12 (Papa et al. 2008; Jacob et al. 2009).
    4. Cerebral palsy (please see the chapter on "Cerebral Palsy")
    5. Autism (please see the chapter on "► Autism")

Diagnostic Investigations

1. Mutational analyses of *MECP2* gene (Buyse et al. 2000):
   1. Sequence analysis and mutation scanning.
   2. Mutations detected in 35–90% of patients (detected in almost every patient with classical Rett syndrome).
   3. Wide spectrum of mutations of the *MECP2* gene (Obata et al. 2000):
      1. Missense
      2. Nonsense
      3. Frameshift and stop
   4. Mutations extending to phenotypes that are not easily recognized as Rett syndrome.
   5. No significant correlation exists between the clinical course and mutation type.
   6. *MECP2* mutations have been identified in patients previously diagnosed with the following conditions:
      1. Autism
      2. Mild learning disability
      3. Clinically suspected but molecularly unconfirmed Angelman syndrome
      4. Mental retardation with spasticity or tremor
   7. Clinical predictors that facilitate a clinician's decision to order genetic testing for Rett syndrome (Knight et al. 2016):
      1. Loss of hand skills resulted in the highest odds of having a positive genetic test.
      2. Gait abnormalities and stereotypic hand movements were also strong predictors of MECP2þ testing.
      3. Many individuals with language delay had genetic testing; however, this is the least specific of the major criteria.
      4. These findings have implications for which patients should have genetic testing.
2. X chromosome inactivation pattern: not tested routinely
3. EEG: not specific
4. CT and MRI
   1. Cortical atrophy predominantly in the frontal area
   2. No abnormalities in the white matter, basal ganglia, thalamus, or hippocampus
   3. Narrowing of the brain stem in some patients
5. Photon emission CT
   1. Lower cerebral blood flow in the prefrontal and temporoparietal association regions with sparing of the sensorimotor regions
   2. The flow distribution in Rett patients
      1. Similar to that observed in infants of a few months of age
      2. Suggesting a neurodevelopmental abnormality rather than a neurodegenerative process

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib
      1. 50% risk to sibs of inheriting *MECP2* allele from the carrier mother.
      2. Low risk to sibs (<1/300) (Killian 1986) when a mutation present in the proband is not identified in a parent, provided germ line mosaicism is not present in either parent (Amir et al. 1999; Mari et al. 2005).
   2. Patient's offspring
      1. Unlikely to have offspring due to mental retardation and other handicaps
      2. Reproduction reported in mildly affected females
         1. Each offspring of a carrier female with 50% risk of inheriting the disease-causing mutation.
         2. Daughters who inherit the mutation are at high risk of developing classic Rett syndrome although skewed X chromosome inactivation may result in a milder phenotype.
         3. Sons who inherit the mutation may suffer a severe neonatal encephalopathy or severe mental retardation in those who survive beyond the first year of age.
      3. Healthy sisters of a girl with Rett syndrome

1. Possibility of being carriers of the *MECP2* mutation but with little or no symptoms because of favorable skewed X chromosome inactivation
2. At risk of transmitting the disease-causing *MECP2* mutation to their own children

4. No male with an *MECP2* mutation known to reproduce

2. Prenatal diagnosis (Christodoulou and Ho 2012):
   1. Amniocentesis or chorionic villus sampling available to pregnancies at risk for women with a known *MECP2* mutation identified in a family member
   2. Appropriate to offer prenatal diagnosis to couples who have had a child with Rett syndrome or mental retardation due to an *MECP2* mutation, whether or not the disease-causing mutation has been identified in a parent since germ line mosaicism cannot be excluded in either parent
   3. A male fetus with the mutation
      1. May suffer from a severe neonatal encephalopathy
      2. May survive with a severe mental retardation syndrome
   4. A female fetus with the mutation
      1. Difficult to predict the phenotype in a female fetus with an *MECP2* mutation which can range from apparently normal to severely affected
      2. At high risk of developing classic Rett syndrome although skewed X chromosome inactivation may result in a milder phenotype
3. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the pathogenic variant has been identified (Christodoulou and Ho 2012).
4. Management (Budden 1997; Naidu 1997):
   1. No treatment is known to improve the neurologic outcome of Rett patients.
   2. Supportive and symptomatic therapies:
      1. The most important aspects are high caloric intake to overcome the energy expenditure from increased motor activity (Naidu 1997).
      2. Feeding and swallowing difficulties may warrant a gastrostomy.
      3. Constipation beginning early in life is easily relieved with mineral oil and stool softeners.
      4. Anticonvulsants for seizures.
      5. Chloral hydrate for agitation.
      6. Carbidopa and levodopa for rigidity.
      7. Melatonin for sleep disturbances.
      8. Management of gastroesophageal reflux:
         1. Antireflux agents
         2. Smaller and thickened feedings
         3. Positioning
   3. Occupational and physical therapies:
      1. Maintain function
      2. Prevent scoliosis and deformities
   4. Augmentative communication.
   5. Facilitate communication.
   6. Maintain hand function and ambulation.
   7. Decreasing repetitive purposeless hand movements can be achieved by the use of various arm restraints, such as soft elbow splints, and are occasionally helpful in training specific hand skills such as self-feeding. These methods are also helpful in decreasing agitation and self-injurious behavior (Ellaway and Christodoulou 1999).
   8. Prevent deformities.
   9. Therapeutic horseback riding, swimming, and music therapy.
   10. During adulthood, continuation of multidisciplinary services and programs is necessary to optimize health and wellbeing (Anderson et al. 2014).
   11. Several clinical studies are under way to attempt to normalize synaptic abnormalities in Rett syndrome (RTT) (Johnston et al. 2015):
      1. Studies by Naidu et al. with dextromethorphan, a clinically approved competitive *N*-methyl-D-aspartate (NMDA) receptor blocker: A randomized unblinded trial of dextromethorphan showed improvement in receptive language in girls with RTT.
      2. Preclinical studies suggest that low-dose ketamine, a noncompetitive NMDA

blocker, might be useful for improving the connectivity of brain circuits affected in RTT and improving function.
3. Human recombinant IGF-1 has also shown benefit in mice with Mecp2 deficiency, and a preliminary study in girls with RTT showed that it was well tolerated and may have some benefits.

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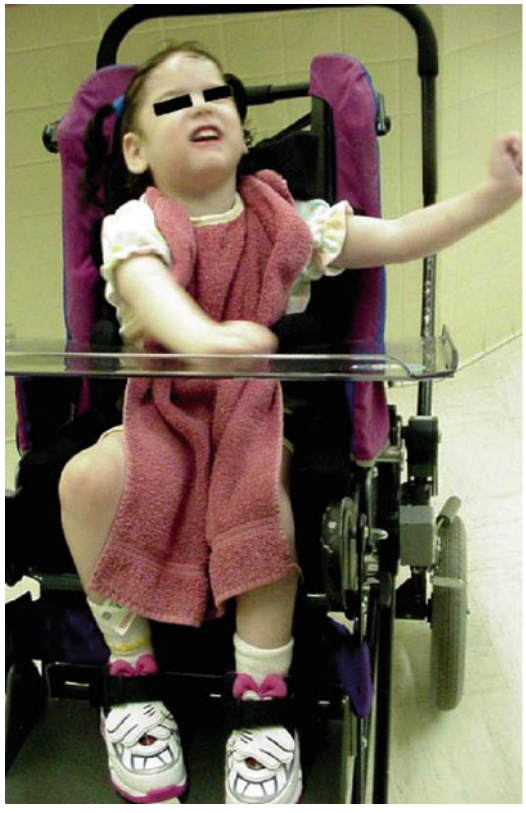

Fig. 1 A girl with Rett syndrome

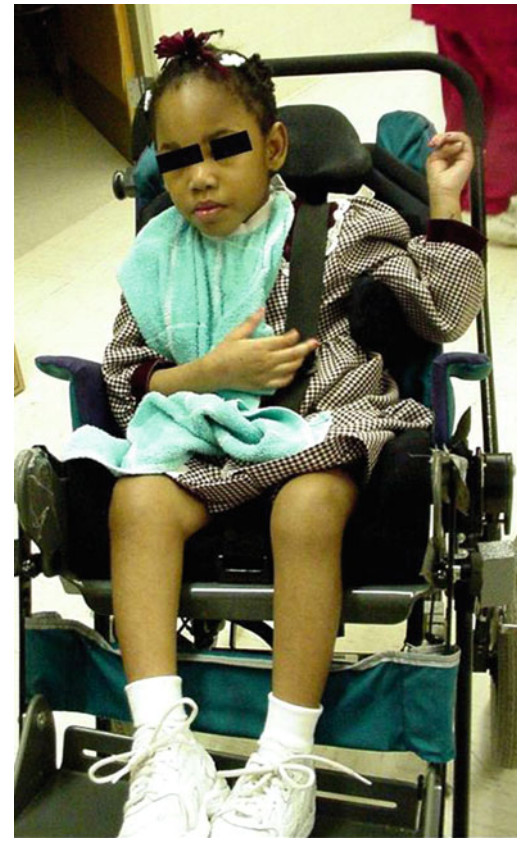

Fig. 2 A girl with Rett syndrome who has *MECP2* mutation (R106W)

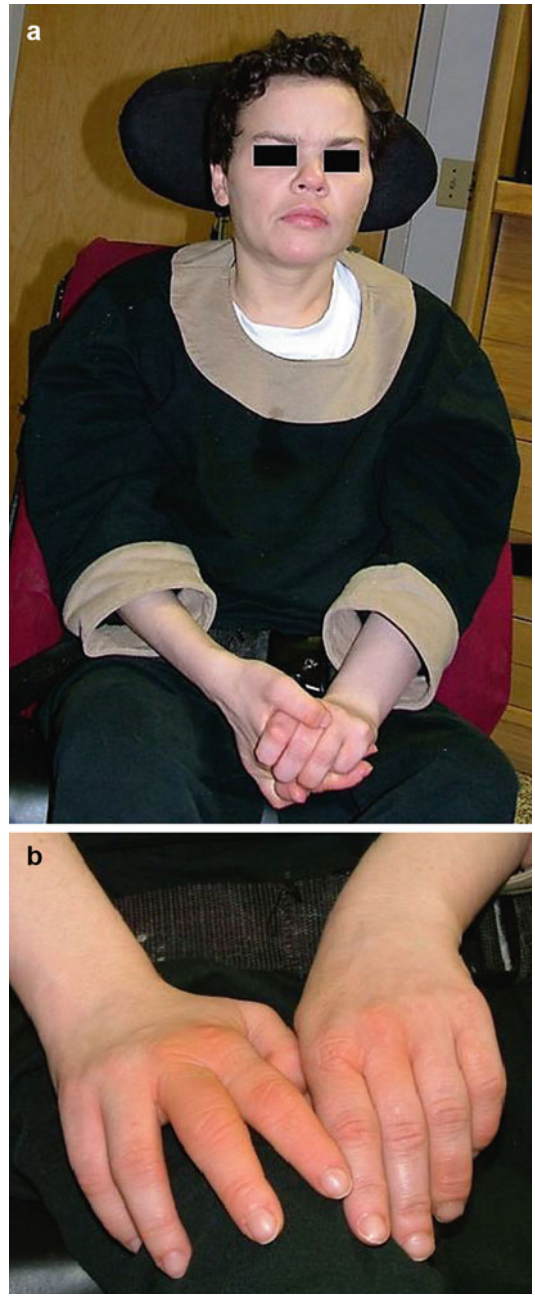

Fig. 3 (**a**, **b**) A 33-year-old female (**a**) with Rett syndrome showing severe psychomotor retardation and hand wringing so severe that the part of the hand and fingers are red, rough, and swollen from constant irritation by stereotypic hand movement (**b**). She was normal developmentally until about 18 months of age when she started to have handwashing/wringing, tiptoe walking, fell easily, and lost the skills she already attained. Shortly after, she started to lose eye contact with people and has seizures. DNA sequence analysis identify a nucleotide change of 763 C > T in one copy of the *MECP2* gene which predicts an amino acid change of arginine to a premature translation stop at codon 255 (R255X). This nonsense mutation was previously identified in multiple Rett syndrome patients as a disease-causing *MECP2* mutation

Rickets

Contents

Normal bone mineralization requires adequate supplies of calcium and phosphate and normal vitamin D metabolism (Norman 1982). Defective supply or function of any of these factors can cause rickets and osteomalacia (Pitt 1991). Nutritional rickets is a major public health problem in many countries of the world (Prentice 2013).

Synonyms and Related Disorders

Cutaneous skeletal hypophosphatemia syndrome; Familial hypophosphatemic rickets; Hereditary pseudo-vitamin D deficiency rickets; Nutritional rickets; Vitamin-deficiency rickets; Vitamin D-dependent rickets

Genetics/Basic Defects

1. Classification of rickets (Mughal 2011; Pai and Shaw 2011; Shore and Chesney 2013b)
    1. Calcipenic rickets
        1. Rickets due to dietary calcium deficiency or interruption in the supply, metabolism, or utilization of vitamin D
        2. Nutritional vitamin D deficiency
        3. Vitamin D deficiency due to:
            1. Malabsorption
            2. Liver disease
            3. Renal insufficiency
        4. Impaired hepatic 25-hydroxylation
        5. Impair renal 1α-hydroxylation of 25 (OH)D
        6. End-organ resistance to $1,25(OH)_2D$
    2. Phosphogenic (hypophosphatemic) rickets (DiMeglio and Econs 2001; Baroncelli et al. 2012)
        1. Primary
            1. X-dominant hypophosphatemic rickets (*PHEX* gene mutation)
            2. Autosomal dominant hypophosphatemic rickets (*FGF23* mutation)
            3. Autosomal recessive hypophosphatemic rickets type 1 (*DMP1* mutation)
            4. Autosomal recessive hypophosphatemic rickets type 2 (*ENPP1* mutation)
            5. Hereditary hypophosphatemic rickets with hypercalcinuria (*SLC34A3* gene mutation)
            6. X-linked recessive hypophosphatemic rickets (*CLCN5* mutation)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_203

7. Hypophosphatemic rickets and hyperparathyroidism (a translocation causing increased α-Klotho level) (Brownstein et al. 2008)
   2. Secondary
      1. Fibrous dysplasia: McCune-Albright syndrome
      2. Tumor-induced (oncogenic) osteomalacia
      3. Linear nevus sebaceous syndrome
      4. Ifosfamide nephrotoxicity
      5. Fanconi syndrome
      6. Low dietary phosphate intake
2. Major regulators of mineral homeostasis (Shore and Chesney 2013a)
   1. Parathyroid hormone (PTH) (Kruse 1995)
      1. Bone resorption to mobilize calcium and phosphate: increased by low Ca++ concentration via parathyroid calcium-sensing receptor
      2. Upregulates 1-OHase to promote calcitriol synthesis: decreased by calcitriol
      3. Increases calcium reabsorption in distal tubule decreased by FGF-23
      4. Decreases phosphate reabsorption in proximal tubule
   2. Calcitriol
      1. Increases gut absorption of Ca and phosphate: increased by PTH
      2. Permissive for PTH effect on bone resorption: decreased by FGF-23
   3. FGF-23
      1. Increases phosphate excretion by decreasing tubular reabsorption: increased by calcitriol
      2. Downregulates 1-OHase to decrease calcitriol synthesis: increased by high dietary or circulating phosphate, although no phosphate-sensing receptor found
3. Causes of rickets by age of onset
   1. Younger than 6 months of age
      1. The fetus is protected by the calcium trans-placental pump, but in severe maternal chronic osteomalacia such as with morbid exhaustion of calcium and in maternal malabsorption (Begum et al. 1968), neglected renal failure, prematurity, or inherited diseases, rickets might show up clinically at birth (Elidrissy 2016).
      2. Hypophosphatasia (Currarino et al. 1957).
      3. Prematurity.
      4. Primary hyperparathyroidism.
      5. Maternal factors.
         1. Vitamin D deficiency (Mancrieff and Fadahunsi 1974)
         2. Poorly controlled hyperparathyroidism
         3. Poorly controlled renal insufficiency (Levin et al. 1992)
   2. Older than 6 months of age
      1. Nutritional rickets in children (Felman et al. 1990)
         1. Inadequate levels (deficiency) of vitamin D due to either inadequate oral intake or insufficient exposure to sunlight (Bishop1999).
         2. With resultant decreased calcium absorption in the small intestine.
         3. Thereby decreasing the available calcium for epiphyseal cartilage and skeletal mineralization.
         4. Secondary hyperparathyroidism due to limited calcium availability and attendant renal phosphate losses contributes to the bone and growth plate pathophysiology that lead to the clinical manifestations of rickets.
      2. Liver disease (impaired 25-vitamin D formation)
         1. Chronic liver diseases (extrahepatic biliary atresia, total parenteral nutrition, tyrosinemia)
         2. Anticonvulsant therapy
      3. Malabsorption
         1. Celiac disease
         2. Inflammatory bowel disease
         3. Pancreatic insufficiency
      4. Renal tubular insufficiency (hypophosphatemia)
         1. Vitamin D-resistant rickets
         2. Vitamin D-dependent rickets
         3. Fanconi syndrome

4. Lowe syndrome
5. Cystine storage disease

5. Chronic renal disease (renal osteodystrophy)
1. Pyelonephritis
2. Polycystic kidney disease
3. Chronic glomerulonephritis
4. Renal tubular acidosis

4. Hypophosphatemic disorders (Goldsweig and Carpenter 2015)
1. Fibroblast growth factor-23 (FGF23) (Hardcastle and Dittmer 2015) regulates phosphate reabsorption in the kidney and therefore plays an essential role in phosphate balance in humans.
2. There is a host of defects that ultimately lead to excess FGF23 levels and thereby cause renal phosphate wasting and hypophosphatemic rickets:
1. X-linked hypophosphatemia (XLH), the best characterized of these abnormalities
2. Autosomal dominant hypophosphatemic rickets (ADHR)
3. Autosomal recessive hypophosphatemic rickets (ARHR)
4. Tumor-induced osteomalacia (TIO)
5. Other rarer FGF23-mediated conditions
1. Osteoglophonic dysplasia (OGD)
2. Epidermal nevus syndrome (ENS)
3. McCune-Albright syndrome (MAS) (please see the chapter on "McCune-Albright Syndrome")
4. Neurofibromatosis 1 (please see the chapter on "Neurofibromatosis 1")
5. A nonlethal variant of Raine syndrome:

5. Vitamin D deficiency rickets: caused by low endogenous vitamin D
1. Selected pediatric populations at high risk for vitamin D deficiency
1. Dietary factors (breast-fed infants with marginal calcium stores due to low levels of vitamin D in breast milk)
2. Skin pigmentation (African American children due to dark skin absorbing ultraviolet radiation less available for vitamin D production) (Kreiter et al. 2000)
3. Sunscreen application
4. Insufficient sun exposure (far northern latitudes, during the winter months, cultural traditions)
5. Latitude (Singleton et al. 2015)
2. Other predisposing factors
1. Severe liver failure
2. Nephrotic syndrome
3. Severe malnutrition
4. Gastrointestinal diseases leading to malabsorption, including impaired fat absorption or enterohepatic recirculation

6. Vitamin D-dependent rickets: caused by reduced activity of 25(OH)1-alphahydroxylase
1. Vitamin D-dependent rickets type I (1α-hydroxylase deficiency) (Miller 2016)
1. Autosomal recessive disorder.
2. Commonly found in the French Canadian population.
3. The gene locus mapped to chromosome 12q14.
4. Caused by mutation in the vitamin D 1-alpha-hydroxylase gene.
5. Impaired 1-alpha-hydroxylation in the renal proximal tubule that converts 25 (OH)D to $1,25(OH)_2D$.
6. Novel pathogenic mutations of the *CYP27B1* gene were reported patients with vitamin D-dependent rickets type 1A (Babiker et al. 2014; Demir et al. 2015).
7. Mutations in *CYP2R1* are responsible for an atypical form of vitamin D-deficiency rickets, which has been classified as vitamin D-dependent rickets type 1B (Thacher and Levine 2016).
8. The disease formerly known as "hereditary pseudo-vitamin D deficiency rickets" (PDDR), "vitamin D-dependent rickets," or "vitamin D-dependent rickets type I" is now more properly called vitamin D 1-alpha-hydroxylase deficiency, as it is known to be caused by mutations in CYP27B1, which converts 25OHD to $1,25(OH)_2D$ (Miller and Portale 2000).
2. Vitamin D-dependent rickets type II (receptor mutation): also known as hereditary

vitamin D-resistant rickets (Malloy et al. 1999)
1. Autosomal recessive inheritance
2. Caused by mutations in the vitamin D receptor (VDR) that result in end-organ resistance to active vitamin D (1,25-dihydroxyvitamin D) [1,25-$(OH)_2D_3$]
3. Major defect caused by the mutant VDR: a decrease of intestinal calcium and phosphate absorption which leads to decreased bone mineralization and rickets
4. The major biochemical distinction between type I and type II
    1. Low circulating 1,25-$(OH)_2D_3$ levels in patients with type I
    2. High circulating 1,25-$(OH)_2D_3$ levels in patients with type II

7. Familial hypophosphatemic rickets
    1. A heterogeneous disease with an incidence of 1 in 20,000 newborns
    2. Caused by defect in reabsorption of phosphate in the proximal tubule, resulting in hypophosphatemia, defective bone mineralization, normocalcemic rickets, and short stature
    3. Types of hypophosphatemia
        1. Dominant X-linked hypophosphatemic rickets (also called vitamin D-resistant rickets)
            1. The gene locus: mapped to Xp22.1.
            2. The gene responsible: phosphate-regulating (*PHEX*) gene with homologies to endopeptidases in the X chromosome (the HYP Consortium (1995; Chandran et al. 2010).
            3. Complete penetrance.
            4. This is the most common form of metabolic rickets.
        2. Autosomal dominant hypophosphatemic rickets
            1. The gene locus: mapped to 12p13
            2. Caused by mutations in *FGF23*
            3. Incomplete penetrance
        3. Autosomal recessive hypophosphatemic rickets (Farrow et al. 2009; Levy-Litan et al. 2010; Lorenz-Depiereux et al. 2010)
            1. Caused by mutations in dentin matrix protein-1 (*DMP1*) gene, which is associated with elevated fibroblast growth factor 23 (FGF23), or ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) gene.
            2. Surprisingly, *ENPP1* loss-of-function mutations have previously been described in generalized arterial calcification of infancy, suggesting an as yet elusive mechanism that balances arterial calcification with bone mineralization.
        4. Hereditary hypophosphatemic rickets with hypercalcinuria (Pettifor 2008)
            1. Caused by *SLC34A3* mutations
            2. Gene product: inactivating mutation in NaPi-IIc (renal Na-P_i cotransporter)
            3. Elevated 1,25$(OH)_2D$

8. Cutaneous skeletal hypophosphatemia syndrome (CSHS) (Lim et al. 2016).
    1. A multilineage somatic mosaic *RAS*opathy.
    2. Identical RAS mutations in the affected skin and bone.
    3. Features epidermal or melanocytic nevi and hypophosphatemic rickets with elevated levels of a serum phosphatonin, fibroblast growth factor (FGF)-23 (Lim et al. 2014).
    4. Patients often require phosphate and calcitriol supplementation to maintain mineral homeostasis.

Clinical Features

1. Rickets versus osteomalacia
    1. Rickets: occurs only before fusion of the epiphyses.
    2. Osteomalacia: occurs in adults deficient in calcium, phosphate, or vitamin D.
2. Signs of rickets in osseous tissues (Wharton and Bishop 2003)
    1. Craniotabes in newborn baby and young infant
        1. Softening of skull bones
        2. May be present but not pathognomonic

2. Frontal bossing in early infancy
    1. Expansion of cranial bones relative to facial bones
    2. Also possibly due to hydrocephalus ("rickets hydrocephalus")
3. Fontanelle
    1. Delayed closure
    2. Occasional intracranial hypertension
4. Wrists: an apparent bracelet of the bone around the wrist (specificity 81%)
5. Rickety rosary: swollen costochondral junctions of ribs (specificity 64%)
6. Skeletal deformities
    1. Particularly, "bow legs" once the child is walking.
    2. Genu valgum generally not due to rickets.
    3. Spinal curvature most likely due to nonrickets cause.
    4. Narrowed pelvic outlet used to cause obstructed labor.
    5. The "double malleoli" sign (Kumar et al. 2015): The knobbed ankle of the rachitic child (anterior view) takes appearance of two distinct medial prominences resembling a second malleoli, one atop of the other.
7. Brown tumor: rare fibrous-cystic osteitis associated with the secondary hyperparathyroidism
8. Limb pain
    1. Bone pain and pseudoparalysis uncommon
    2. Osteomalacia and the subperiosteal hematoma of scurvy: more likely causes of pain
9. Teeth
    1. Delayed eruption of teeth
    2. Enamel hypoplasia: greater susceptibility to caries in the first dentition

3. Nonosseous effect of vitamin D deficiency (Wharton and Bishop 2003)
    1. Symptomatic hypocalcemia with convulsions: particularly in young infants less than 6 months of age born to mothers with untreated osteomalacia, many of whom are subclinical cases.
    2. Myopathy.
        1. Proximal myopathy in infants and adolescents
        2. Heart failure simulating cardiomyopathy with severe hypocalcemia
        3. Responding to treatment for rickets and inotropes
    3. Myelofibrosis.
        1. With pancytopenia or microcytic hypochromic anemia
        2. Returning to normal when treated with vitamin D
    4. Possible link between early vitamin D deficiency and other disorders in later life.
        1. Type I diabetes
        2. Multiple sclerosis
        3. Schizophrenia
        4. Hear disease
    5. Intrauterine and infant growth: vitamin D supplement in the last trimester of pregnancy improves growth in utero and during infancy in some studies.
4. Vitamin D deficiency rickets (Joiner et al. 2000; Elder and Bishop 2014)
    1. History
        1. Dark skin color
        2. Reduced skin exposure
        3. No vitamin D supplementation during pregnancy
        4. Prolonged exclusive breastfeeding
        5. No vitamin D supplementation of infant
        6. Use of foods high in phytates
        7. Iron deficiency
        8. Not clinically apparent before 6 months of age because of prenatal stores of vitamin D imparted by the mother
    2. Skeletal features
        1. Slowing linear growth
        2. Metaphyseal swelling at long-bone ends
        3. Rickety rosary
        4. Bowing deformity of long bones
        5. Frontal bossing
        6. Craniotabes
        7. Persistent anterior fontanelle
        8. Harrison's sulci
        9. Development of secondary hyperparathyroidism due to increasing severity of vitamin D deficiency, progressing to frank osteomalacia and fractures

3. Nonskeletal features
    1. Hypocalcemic convulsions
    2. Hypocalcemic cardiac failure
    3. Hypotonia
    4. Delayed motor milestones
    5. Carpopedal spasm
    6. Enamel hypoplasia
    7. Delayed dentition
    8. Failure to thrive
    9. Fractious, irritable child
    10. Bone pain
5. Vitamin D-dependent rickets
    1. Vitamin D-dependent rickets type I (hereditary pseudo-vitamin D deficiency rickets)
        1. Clinical presentation within the first few months of life
        2. First clinical sign: acute or chronic hypocalcemia because the major physiologic role of 1,25-dihydroxyvitamin D is to promote intestinal calcium absorption
        3. Hypocalcemic seizures as early as 4 weeks of age or usually before 2 years of age
        4. Growth retardation
        5. Bowing of the extremities
        6. Bone pain secondary to rickets and osteomalacia
        7. Enamel hypoplasia and oligodontia
        8. Hypocalcemia accompanied by secondary hyperparathyroidism resulting in hypophosphatemia and occasional aminoaciduria
    2. Vitamin D-dependent rickets type II (hereditary vitamin D-resistant rickets)
        1. Onset of disease: infancy or childhood.
        2. Major clinical findings: hypocalcemia and rickets due to defective intestinal calcium absorption lead to impaired mineralization of newly forming bone and preosseous cartilage.
        3. Rickets.
            1. Often severe
            2. Usually exhibits within months of birth
        4. Bone pain.
        5. Muscle weakness.
        6. Hypotonia.
        7. Occasional convulsions from hypocalcemia.
        8. Often growth retarded.
        9. Enamel hypoplasia, oligodontia, and severe dental caries.
        10. Hypocalcemia accompanied by secondary hyperparathyroidism results in hypophosphatemia and occasional aminoaciduria.
        11. Pneumonia secondary to severe rickets of the chest wall and poor respiratory effort causes death in some infants.
        12. Alopecia (Al-Khenaizan and Vitale 2003)
            1. Sparse body hair in many patients
            2. Alopecia totalis observed in some kindreds, including eyebrows and in some cases eyelashes
6. Hereditary hypophosphatemic rickets
    1. X-linked dominant hypophosphatemic rickets
        1. Characterized by renal phosphate wasting with hypophosphatemia.
        2. Disease severity is similar in males and females but differs among individuals (some patients with isolated hypophosphatemia; others with disabling severe bone disease).
        3. The disease may persist into adulthood.
        4. Short stature.
        5. Rickets with resultant lower-extremity deformities.
        6. Bone pain.
        7. Enthesopathy (calcification of tendons, ligaments, and joint capsules).
        8. Deficient calcification of teeth (Sarat et al. 2016).
            1. Delayed eruption
            2. Spontaneous periapical infections
            3. Exfoliation
            4. Dental abscesses
        9. Cranial abnormalities (e.g., craniosynostosis) (Murthy 2009) and spinal stenosis in some severely affected individuals.
        10. X-linked hypophosphatemic rickets has been associated with craniosynostosis, the sagittal suture being the most

commonly involved. Rachitic patients with scaphocephaly should be screened for craniosynostosis (Jaszczuk et al. 2016).

11. Secondary craniosynostosis develops postnatally due to metabolic or mechanical factors. The most common metabolic cause is hypophosphatemic rickets, which has a variety of etiologies. Head shape changes occur later and with a more heterogeneous presentation compared with that of primary craniosynostosis. Cranial vault remodeling (CVR) may be required to prevent or relieve elevated intracranial pressure and abnormalities of the cranial vault (Vega et al. 2016).

2. Autosomal dominant hypophosphatemic rickets
    1. Isolated renal phosphate wasting
    2. Short stature
    3. Impressive windswept deformity (valgus on one side and varus on the other side)
    4. Marked tendency for fracture with or without trauma
    5. Delayed onset of disease in some patients
    6. Patients who present as adults: osteomalacia with bone pain, weakness, and fractures
3. Autosomal recessive hypophosphatemic rickets: severe disease course (Stamp and Baker 1976; Farrow et al. 2009)
    1. Marked hypophosphatemia
    2. Persistent osteomalacia upon bone biopsy
    3. Increased bone density by dual-energy X-ray absorptiometry
    4. Stunted growth
    5. Nerve deafness
    6. Facial and dental abnormalities
    7. Learning disabilities

7. Cutis nevi in cutaneous skeletal hypophosphatemia syndrome (Ovejero et al. 2016)
    1. A giant congenital melanocytic nevus composed of nevomelanocytes (neural crest origin).
    2. Hair follicles may be enlarged and infiltrated by these cells, giving the observed hairy appearance.
    3. Phakomatosis pigmentokeratotica characterized by speckled lentiginous nevi, a subtype of melanocytic nevi (neural crest origin), and nevus sebaceous, a subtype of epidermal nevus (epidermal origin).
    4. Nevus sebaceous: seen as a round waxy alopecic scalp plaque containing small speckled lentiginous nevi.
    5. Epidermal nevus: characterized by hyperplasia of elements of epidermal origin, e.g., sebaceous glands or keratinocytes.
    6. Superimposed café au lait macules are frequently present in these patients.

Diagnostic Investigations

1. Classification of rickets by biochemical profile (Prentice 2013).
    1. Calciopenic: Typically, calciopenic rickets is associated with an elevated plasma parathyroid hormone concentration (PTH) in response to low plasma calcium, which results in internalization of phosphate transporters in the kidneys and decreased renal phosphate reabsorption.
    2. Phosphopenic
        1. Phosphopenic rickets is associated with a chronically low plasma phosphate with normal PTH and results from increased production or gain of function of FGF23, a phosphaturic hormone, or from renal disorders that compromise phosphate reabsorption.
        2. In both cases the result is urinary phosphate loss and hypophosphatemia, leading to reduced apoptosis of hypertrophic chondrocytes in the growth plate and rickets.
    3. Inhibited mineralization
        1. The third category, inhibition of mineralization, refers to rickets where the mineralization process in the growth plate is directly affected and typically the plasma

concentrations of calcium and phosphate are normal.
2. There are a variety of underlying causes responsible for the various forms of rickets, including genetic disorders, such as autosomal dominant hypophosphatemic rickets (ADHR) and X-linked hypophosphatemic rickets (XLH), tumors, organ malfunction, drugs, and exposure to toxic agents such as aluminum and fluoride.

2. A number of biochemical markers of deranged mineral or vitamin D metabolism have been considered as possible screening tools for nutritional rickets in communities (Pettifor 2015).
   1. 25(OH)D as a marker of vitamin D status
   2. Serum calcium, phosphorus, parathyroid hormone, and alkaline phosphatase as markers of bone mineral homeostasis
3. Vitamin D deficiency rickets.
   1. Decreased levels of 25-OH vitamin D (best screening test for vitamin D stores in otherwise healthy individuals)
   2. Normal or increased levels of 1,25 $(OH)_2$ vitamin D
   3. Increased levels of parathyroid hormone
   4. Decreased levels of calcium (hypocalcemia)
   5. Decreased levels of phosphate (hypophosphatemia)
4. Vitamin D-resistant rickets
   1. Renal tubular phosphate leakage and subsequent hypophosphatemia in all affected individuals
   2. Normal levels of 25-OH vitamin D
   3. Normal or decreased levels of 1,25 $(OH)_2$ vitamin D
   4. Normal or increased levels of parathyroid hormone
   5. Normal levels of calcium
   6. Decreased phosphate (hypophosphatemia)
5. Vitamin D-dependent rickets.
   1. Elevated or normal levels of 25-OH vitamin D
   2. Low levels of 1,25 $(OH)_2$ vitamin D in type I and elevated levels in type II
   3. Normal or increased levels of parathyroid hormone
   4. Normal or decreased levels of calcium
   5. Decreased levels of phosphorous (hypophosphatemia)
   6. Elevated serum alkaline phosphatase activity
6. Radiographic findings (Pitt 1981, 1991; Pai and Shaw 2011)
   1. Cupping, fraying, and widening of the metaphyses: a requirement for diagnosis of rickets
   2. Rachitic rosary (enlargement of the wrists, knees, and costochondral beadings)
   3. Flaring of ribs at diaphragm level (Harrison's groove)
   4. Bowing of the lower extremities in the newly ambulating child
   5. Widening and irregularity of all the physes
   6. Osteopenia (decreased mineralization of the bone matrix) (Schneider 1984) with blurred or nonapparent cortical outlines of the epiphyseal ossification centers
   7. Multiple fractures in various stages of healing
   8. Deformities caused by softening of the bone or poor muscle tone
      1. Femoral bowing
      2. Tibial bowing
      3. Genu valgum (knock knees)
   9. Genu valgum or varum
   10. Lordosis/kyphosis/scoliosis
   11. Pelvis
      1. Coxa valga
      2. Protrusio acetabuli
   12. Thorax: hourglass shape
   13. Skull
      1. Postural molding
      2. Frontal bossing
      3. Craniotabes
      4. Delayed closure of anterior fontanel
   14. Dental abnormalities
   15. The zone of provisional calcification appearing as a dense metaphyseal band due to calcium deposit in response to vitamin D therapy
      1. Seen as early as 2–3 weeks after initiation of therapy in children with nutritional rickets

2. Seen after 2–3 months in children with renal rickets
3. Persistence of deformities caused by bone softening despite successful treatment

16. X-linked dominant hypophosphatemia
    1. The rachitic changes, though less dramatic than in vitamin D deficiency rickets, are more severe in the knees than the wrists.
    2. The modeling defects manifest as short, squat long bones with coarse trabeculation of the axial skeleton.

7. Radiological features of cutaneous skeletal hypophosphatemia syndrome (Lim et al. 2016)
    1. Stretches of dysplastic bone with mixed sclerotic and lytic changes in the femurs
    2. Multiple transverse defects in the shaft of the humerus representing pseudofractures (Looser zones or Milkman lines), which is a sign of osteomalacic bone (arrows) in the setting of dysplastic bone, consistent with the mosaic nature of CSHS
8. Histological findings
    1. Primary metabolic abnormality at the zone of provisional calcification
    2. Diminished calcification of cartilage columns in the metaphysis
    3. Continued osteoid production by osteoblasts, but ossification of the osteoid tissue is impaired because of insufficient calcium deposition
    4. Widened, irregularly calcified physis resulting from resorption of osteoid and calcium because of impaired osteoclast function
    5. Metaphyseal broadening or "cupping" likely caused by stress at sites of ligament attachment
    6. Splaying of cartilage cells peripherally
    7. Microfractures of the primary spongiosa by herniation of cartilage into this area
    8. Tumor-associated FGF-23-induced hypophosphatemic rickets in children: In contrast to biochemical screening for increased circulating FGF-23 levels, immunohistochemical confirmation of FGF-23 production in resected tumor tissue can be regarded as being well established (Burckhardt et al. 2015)
9. Molecular genetic diagnosis
    1. X-linked dominant hypophosphatemic rickets (*PHEX* gene mutations)
        1. Sequencing of entire coding region
        2. Deletion/duplication analysis
    2. Autosomal dominant hypophosphatemic rickets (*FGF23* gene mutations)
        1. Sequencing of entire coding region
        2. Mutation scanning
        3. Targeted mutation analysis
        4. Deletion/duplication analysis
    3. Hypophosphatemic rickets, autosomal recessive 1 (*DMP1* gene mutations)
        1. Sequencing of the entire coding region
        2. Deletion/duplication analysis
    4. Hypophosphatemic rickets, autosomal recessive 2 (*ENPP1* gene mutations): sequencing of the entire coding region
    5. Vitamin D-dependent rickets, type I (*CYP27B1* gene mutations)
        1. Sequencing of the entire coding region
        2. Targeted mutation analysis
        3. Deletion/duplication analysis
    6. Vitamin D-dependent rickets, type II (VDR gene mutations): sequencing of the entire coding region
    7. Hereditary hypophosphatemic rickets with hypercalcinuria (*SLC34A3* gene mutations): sequencing of the entire coding region

Genetic Counseling

1. Recurrence risk: depends on the etiology
    1. Vitamin D deficiency rickets: recurrence risk high if conditions leading to vitamin D deficiency exist
    2. Autosomal recessive inheritance
        1. Patient's sib: 25%
        2. Patient's offspring: not increased unless the spouse is a carrier or affected
    3. Autosomal dominant inheritance
        1. Patient's sib: not increased unless a parent is affected

2. Patient's offspring: 50%
4. X-linked dominant inheritance
   1. Patient's sib: not increased unless a parent is affected
   2. Patient's offspring
      1. Affected female: 50% of daughters and 50% of sons will be affected.
      2. Affected male: All daughters will be affected and all sons normal.

2. Prenatal diagnosis
   1. Fetal radiography, particularly in mothers with osteomalacia
      1. Poorly mineralized fetal bones
      2. Thin cortices of the limb bones and penciled outlines of the vertebral bodies
      3. Cupped tibial/radial metaphysis with indistinct border to the epiphyseal aspect
   2. Fetal echocardiography
      1. Atrial flutter with heart failure reported in a fetus affected with X-linked dominant hypophosphatemic rickets (Vintzileos et al. 1985).
      2. Causal relationship in this case remained unknown.
   3. Amniotic fluid cells from a mother of a child with vitamin D-dependent rickets, type II (VDDR-II), were unable to bind [3H]1,25-(OH)2D3, and the hormone failed to stimulate 24-hydroxylase activity. VDDR-II in this fetus was confirmed after termination of pregnancy by the total inability of 1,25-(OH)2D3 to stimulate 24-hydroxylase activity in tissue explants and cell cultures prepared from the fetus's kidney and skin (Weisman et al. 1990).
   4. Prenatal diagnosis by molecular analysis of cultured fetal cells obtained from CVS and amniocentesis in pregnant women from high-risk families to look for disease-causing mutation, previously identified in an affected individual
      1. X-linked dominant hypophosphatemic rickets
      2. Autosomal dominant hypophosphatemic rickets
      3. Autosomal recessive hypophosphatemic rickets, I
      4. Vitamin D-dependent rickets type I and type II
      5. Hereditary hypophosphatemic rickets with hypercalcinuria

3. Management (Smith 1972; Carpenter 1997)
   1. Hypocalcemia and "simple rickets" (Wharton and Bishop 2003)
      1. Hypocalcemia (early infancy)
         1. IV calcium gluconate to control continuing seizures.
         2. Oral calcium daily.
         3. Oral calciferol daily.
         4. Look for evidence of rickets in the baby (radiographs of the knees and wrists).
         5. Look for maternal osteomalacia (elevated maternal alkaline phosphatase).
         6. Slowly withdraw treatment when the plasma calcium is normal.
         7. Continue prophylactic vitamin D thereafter.
      2. Rickets without hypocalcemia (early infancy): oral calciferol daily for 2–4 months
      3. Older infants, toddlers, and adolescents
         1. Oral calciferol.
         2. Add oral calcium if dietary deficiency may be a factor.
         3. Phosphorus not needed in simple rickets since phosphorus is abundant in the diet.
         4. Necessary to supplement phosphorus for very preterm babies and in the phosphate-wasting causes of rickets.
   2. Prevention and treatment of nutritional rickets (Shaw 2015)
      1. Traditionally with vitamin D2 or D3, often given as a daily oral dose for several weeks until biochemical and radiological evidence of healing.
      2. However, other treatment regimens with single or intermittent high doses have also proved to be effective.
      3. It is now recognized that oral calcium either as dietary intake or supplements should be routinely used in conjunction with vitamin D for treatment.

3. Vitamin D deficiency rickets
    1. Increase dietary intake of vitamin D
        1. The new recommended adequate intake of vitamin D by the National Academy of Sciences to prevent vitamin D deficiency in normal infants, children, and adolescents is 200 IU per day (Gartner and Greer 2003).
        2. An intake of at least 200 IU per day of vitamin D will prevent physical signs of vitamin D deficiency and maintain serum 25-hydroxy-vitamin D at or above 27.5 nmol/L.
    2. Increased sun exposure
    3. Prevent other predisposing factors
4. Vitamin D-resistant rickets
    1. Increase dietary intake of vitamin D
    2. Increased sun exposure
    3. Prevent other predisposing factors
5. Vitamin D-dependent rickets: lifelong treatment with 1-alpha-hydroxyvitamin D or 1,25-dihydroxyvitamin D
6. Dominant X-linked hypophosphatemic rickets: treat bone lesions and impaired longitudinal growth
    1. Without treatment, clinical manifestations begin in the first year of life, and affected children suffer progressive growth failure and bony deformities, such as tibial bowing and frontal bossing (Quinlan et al. 2012).
    2. However, treatment with vitamin D and phosphate resulted in only a partial growth improvement in most cases and was frequently complicated by hypercalcinuria, hypercalcemia, nephrocalcinosis, or hyperparathyroidism (Cho et al. 2005).
    3. Early initiated vitamin D and phosphate treatment are not sufficient to correct hypophosphatemic rickets caused by severe loss-of-function mutations (Cheon et al. 2014).
    4. Medical treatment remains the main pillar of therapy in affected children (Glorieux et al. 1972).
        1. Vitamin D supplement
        2. Oral phosphate supplement: risks of stimulating secondary hyperparathyroidism (Schmitt and Mehls 2004)
5. Dental treatment options (Sabandal et al. 2015).
    1. Frequent dental examination
    2. Besides vitamin D analogs and phosphate supplements that improve tooth mineralization, rigorous oral hygiene, active endodontic treatment of root abscesses, and preventive protection of teeth surfaces are recommended (Linglart et al. 2014).
    3. Application of topical fluoride varnish and sealing of pits and fissures to prevent microbial invasion that may result in pulpitis and further endodontic complications.
6. Surgery can be safely performed in XL vitamin D-resistant hypophosphatemic rickets, independent of age or bone maturation (Fucentese et al. 2008).
7. Cranial vault expansion for craniostenosis in XL hypophosphatemic rickets patients (Jaszczuk et al. 2016).
8. Contemporary medical and surgical management of X-linked hypophosphatemic rickets (Sharkey et al. 2015).
    1. Despite medical management, progressive bone deformities develop in some children.
    2. Surgical treatment of these deformities can be done before or after skeletal maturity, although growth plate-respecting surgery is necessary in the presence of open growth plates.
    3. In younger children, milder deformities may correct with guided-growth treatment.
    4. Skeletally mature persons may benefit from the placement of intramedullary rods for osteotomy fixation because the rods can span the bone and provide long-term support.

9. Surgical measures are usually reserved for the treatment of severe bowing, tibial torsion, or pathological fractures. Osteotomy with plating and multiple osteotomies and intramedullary fixation are standard methods for operative management (Pavone et al. 2015).
10. CSHS: Oral phosphate and calcitriol can improve rachitic symptoms and help heal dysplastic bone by enhancing mineralization (Lim et al. 2016).

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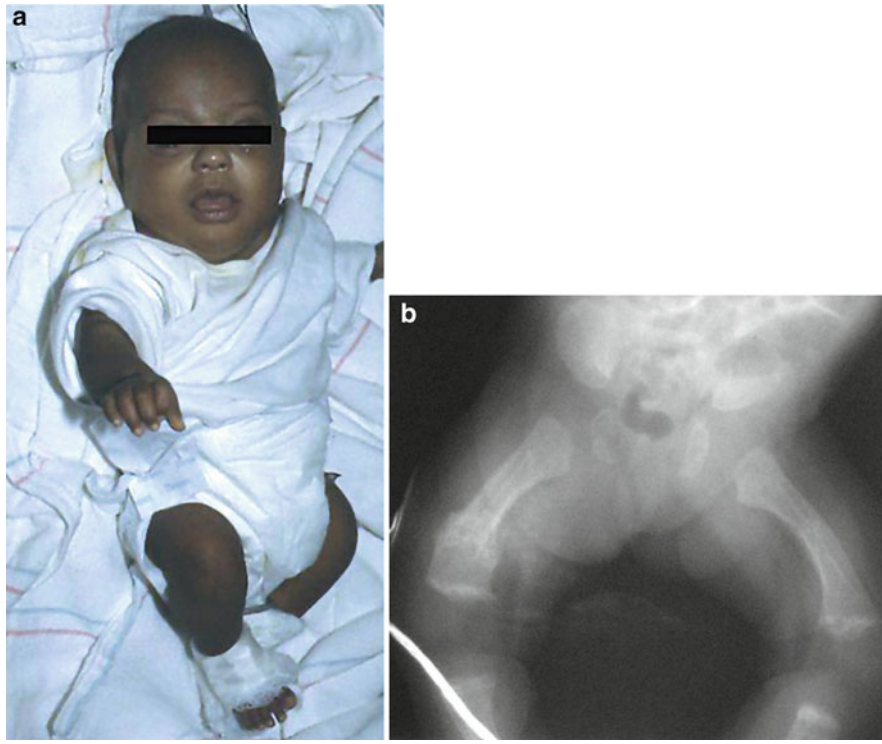

Fig. 1 (**a**, **b**) An infant with healing nutritional rickets (**a**). The radiograph (**b**) shows femoral bowing and a healing fracture with callus formation in the right femur

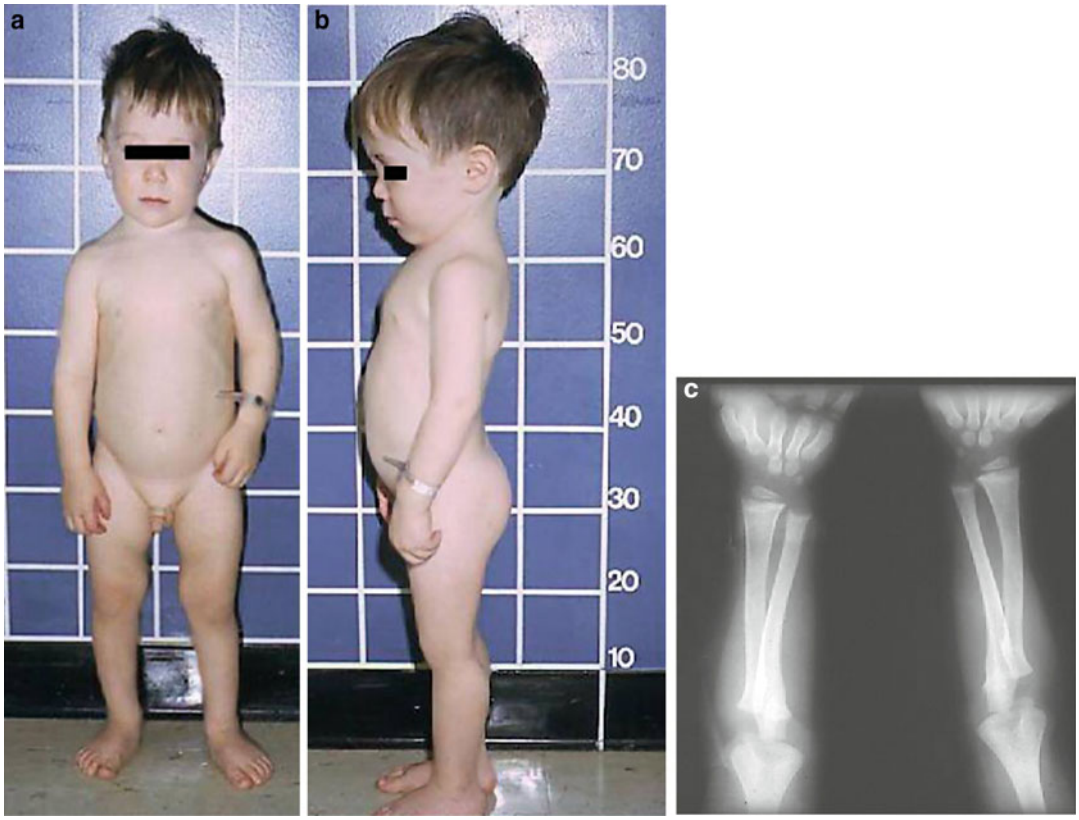

Fig. 2 (**a**–**c**) A boy with vitamin D-resistant rickets showing short stature (**a**, **b**). The radiograph (**c**) shows widening, cupping, and fraying of the distal radius and ulna

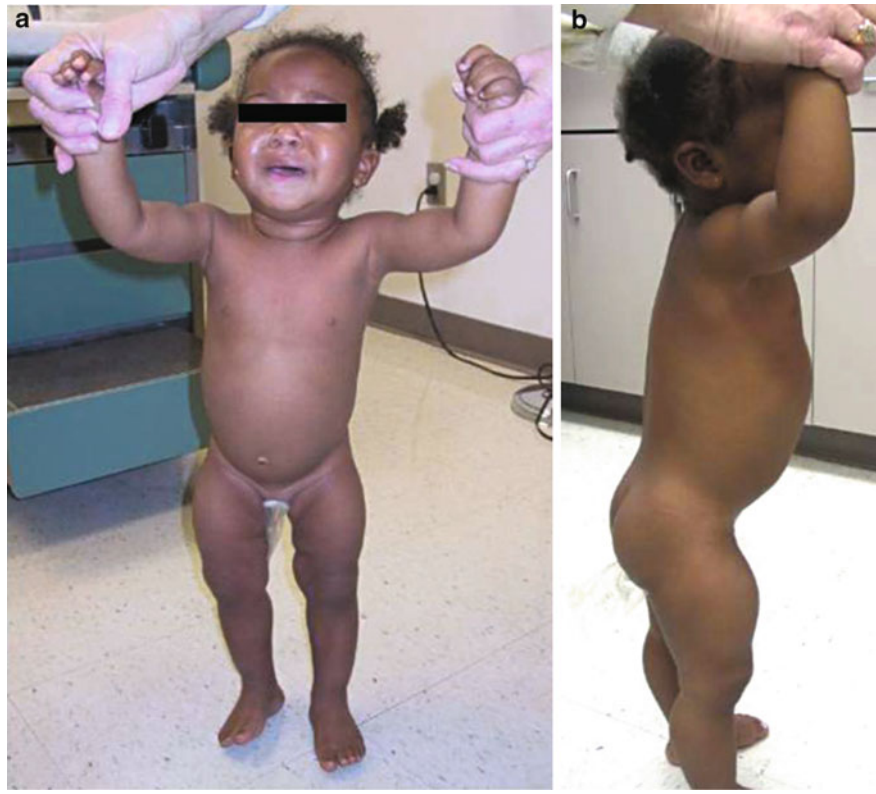

Fig. 3 (**a**, **b**) Another boy with vitamin D-resistant rickets

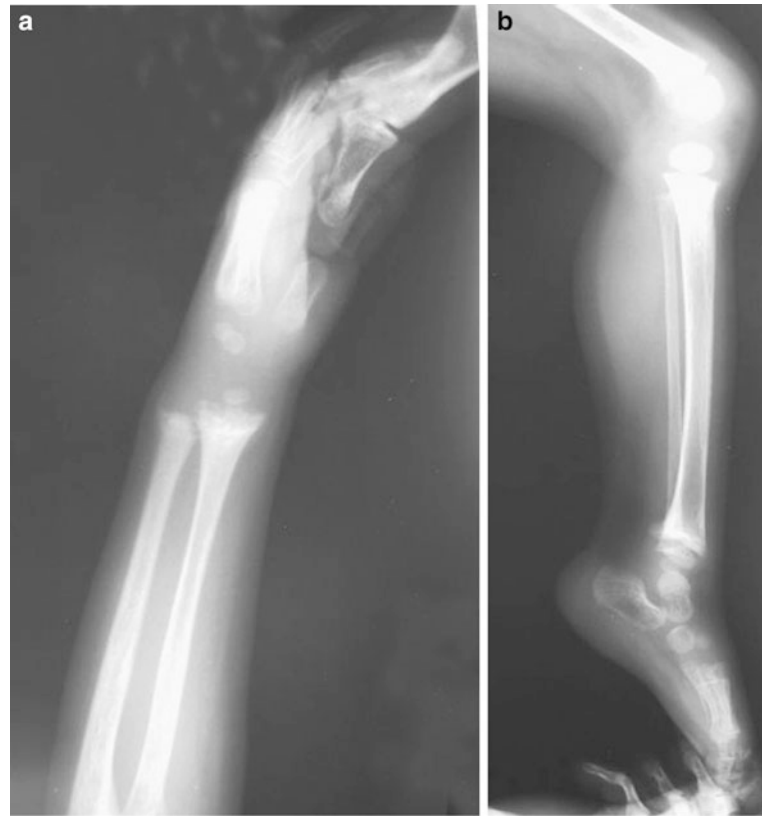

Fig. 4 (**a**, **b**) Radiograph from a patient with renal rickets shows widening, cupping, and fraying of the distal radius and ulna

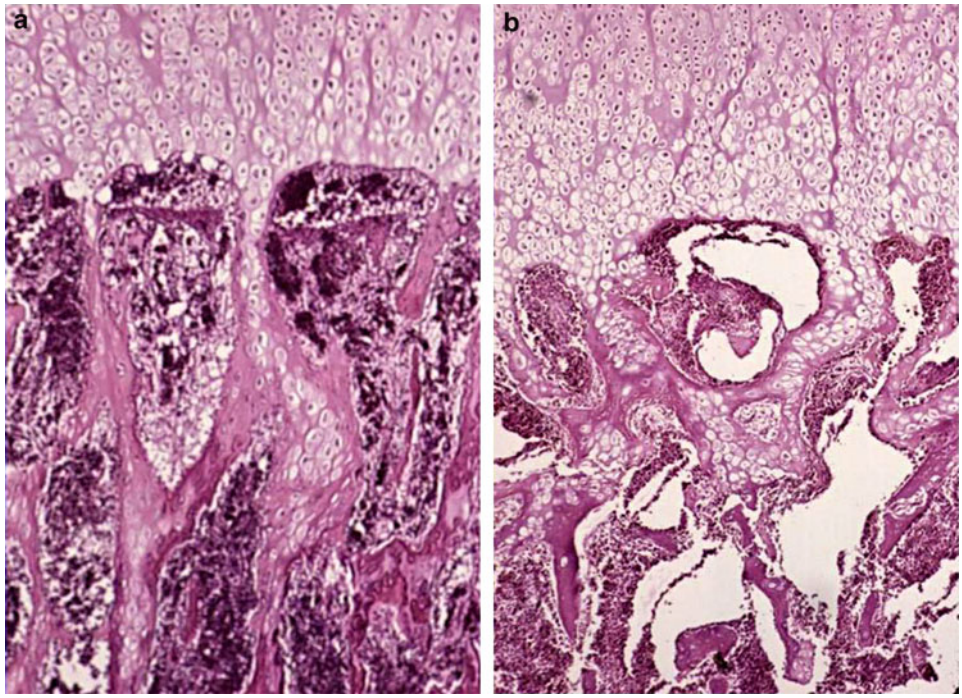

Fig. 5 (**a**, **b**) Photomicrograph of the humerus (*left*) and the rib (*right*) of a female neonate who lived 43 min. Broad cartilage columns with many large chondrocytes are present in the metaphysis. They have broad osteoid seams and are poorly ossified. The abnormal area corresponds to the radiographic metaphyseal irregular lucency. The findings are similar to those of hypophosphatasia, though the changes are milder. The cause of congenital rickets in this case is unknown. The mother did not have history of malabsorption, vitamin D intake deficiency, renal failure, or preeclampsia

Fig. 6 Three sisters with hypophosphatemic rickets showing short stature and bowed legs. They have an affected father

Fig. 7 Two sisters and a brother with hypophosphatemic rickets showing short stature. The brother had severe short stature and bowed legs. The oldest sister had surgeries on her legs to correct the lower leg deformities. The middle sister was mildly affected. Their mother was affected

Rigid Spine Syndrome

Contents

The peculiar phenotype caused by the combination of muscle wasting and prominent spinal rigidity was first proposed by Dubowitz (1965, 1973) and termed "rigid spine syndrome." Rigid spine syndrome (RSS) is also a heterogenous disease with a broad spectrum of skeletal and muscular disorders and a prominent feature in the X-linked, autosomal dominant, and/or autosomal recessive forms of Emery–Dreifuss muscular dystrophy (Emery 1987), nemaline (Topaloglu et al. 1994), and other congenital myopathies (Reichmann et al. 1997).

Synonyms and Related Disorders

Congenital muscular dystrophy with spinal rigidity; Emery–Dreifuss muscular dystrophy, nemaline and other congenital myopathies; Selenoprotein N1-related myopathy

Genetics/Basic Defects

1. *SEPN1* gene mutations resulting in rigid spine congenital muscular dystrophy were first identified by Moghadaszadeh et al. in (Moghadaszadeh et al. 2001).
2. Several different forms of autosomal recessive muscle disorders caused by mutations in the *SEPN1* gene (Rederstorff et al. 2007).
    1. Different forms.
        1. Congenital muscular dystrophy with spinal rigidity (RSMD1) (Moghadaszadeh et al. 2001; Okamoto et al. 2006; Flanigan et al. 2000)
        2. Multiminicore myopathy (MmD) (Ferreiro et al. 2002)
        3. Desmin-related myopathy with Mallory body-like inclusions (MB-DRM) (Ferreiro et al. 2004)
        4. Congenital fiber-type disproportion myopathy (CFTD) (Clarke et al. 2006)
    2. Share identical clinical features, despite distinctly different histopathological descriptions of these different disorders.
        1. Early weakness of axial muscles
        2. Development of spinal rigidity and scoliosis
        3. Severe respiratory insufficiency
3. These phenotypes are now grouped under the generic term of *SEPN1*-related myopathy (Ferreiro et al. 2002).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. *SEPN1* gene mutations.
    1. *SEPN1* gene, mapped on chromosome 1p35-36 (Moghadaszadeh et al. 1998), codes for selenoprotein N, an endoplasmic reticulum glycoprotein.
    2. Numerous mutations scattered all over the *SEPN1* gene (Deniziak et al. 2007).
    3. Most mutations are nonsense mutations and deletions, likely to induce a loss of function.
4. Aggresome–autophagy involvement in a sarcopenic patient with rigid spine syndrome and a p.C150R mutation in four-and-a-half LIM domain 1 (*FHL1*) gene (Shalaby et al. 2008; Sabatelli et al. 2015).
5. Recessive skeletal muscle α-actin gene (*ACTA1*) variant causes congenital muscular dystrophy with rigid spine (O'Grady et al. 2015).

Clinical Features

1. SEPN1-related myopathies.
    1. Mutations in *SEPN1* have been associated with three autosomal recessive congenital myopathies, including rigid spine muscular dystrophy, multiminicore disease, and desmin-related myopathy with Mallory body-like inclusions. These disorders constitute the SEPN1-related myopathies (SEPN-RM) (Tajsharghi et al. 2005).
    2. Characterized by an early onset of hypotonia and weakness, with predominant axial muscle impairment leading to life-threatening respiratory failure and scoliosis. A variable degree of spinal rigidity was observed in most of the patients (Petit et al. 2003).
2. Early spine rigidity: a predominant feature (limitation in flexion of dorsolumbar and cervical spine due to contracture of spinal extensors) (Van Munster et al. 1986).
3. The origin of spine stiffness in rigid spine syndrome is not well understood (Sastre-Garriga et al. 2001).
    1. Shortening of paraspinal ligaments or shortening of muscle fibers due to myofibrillar disorganization has been invoked as possible origins of stiffness (Lotz and Stübgen 1993).
    2. Weakness of neck flexors can make this group of muscles incapable of counteracting extensor strength, finally causing spinal rigidity and cervical lordosis.
4. Diffuse and mild to severe muscle wasting with failure to thrive.
5. Muscle weakness/axial hypotonia.
    1. Diffuse, more prominent in the neck and trunk
    2. Facial weakness
    3. Finger extensors and trunk flexors weakness
6. Contractures.
    1. Limitation in mouth opening
    2. Joint contractures (knees, ankles, elbows, and/or hips)
7. Lumbar scoliosis.
8. Delay of gross motor milestones evident, though ambulation is eventually achieved and preserved in most patients.
9. Nasal speech common due to palatal weakness.
10. Impaired respiratory function.
    1. Respiratory failure due to skeletal abnormalities and diaphragmatic weakness.
    2. Nocturnal hypoventilation may be an early feature and a cause of mortality (Morita et al. 1990; Ras et al. 1994).
    3. May require mechanical ventilation by teens.
11. Rare reports of various cardiac involvement (Stübgen 2008a).
    1. Complete heart block.
    2. Interventricular septum hypertrophy.
    3. Left atrial and ventricular hypertrophy.
    4. Cardiomyopathy may occur concomitantly.
12. Differentiating features between myopathic rigid spine and rigid spinal muscular dystrophy (Koul et al. 2014).
    1. Myopathic rigid spine
        1. Neck stiffness (rigidity): part of myopathy and late onset
        2. Muscle weakness: proximal
        3. Respiratory involvement: late

4. Muscle contractures: peripheral and common
5. Imaging of spine: negative
6. Creatine kinase: high
7. Muscle biopsy: typical of underlying disease
8. Cardiac involvement: early
9. Electromyogram: typical and more proximal
10. Genetics: underlying disease
11. Inheritance: autosomal dominant, autosomal recessive, X-linked recessive

2. Rigid spinal muscular dystrophy
    1. Neck stiffness (rigidity): early onset and severe
    2. Muscle weakness: axial
    3. Respiratory involvement: early
    4. Muscle contractures: minimal and mainly spine
    5. Imaging of spine: positive and typical
    6. Creatine kinase: normal
    7. Muscle biopsy: nonspecific
    8. Cardiac involvement: late
    9. Electromyogram: axial muscles
    10. Genetics: *SEPN1* gene
    11. Inheritance: autosomal recessive

13. Differential diagnosis of spine rigidity associated with various neuromuscular and movement disorders (Sponholz et al. 2006).
    1. Classic form of multiminicore disease
    2. Desmin-related myopathy with Mallory body-like inclusions
    3. Emery–Dreifuss muscular dystrophy
    4. Bethlem myopathy
    5. Ullrich congenital muscular dystrophy
    6. Dysferlinopathy: an autosomal recessive neuromuscular disorder caused by a deficiency of functional dysferlin protein due to mutations in the dysferlin gene (Bashir et al. 1998; Liu et al. 1998; Nagashima et al. 2004)
    7. Other congenital myopathies
    8. Mitochondrial myopathies
    9. Metabolic diseases (e.g., lysosomal storage disorders)
    10. Dystonias
    11. Ankylosing spondylitis

Diagnostic Investigations

1. CK serum levels: normal or only mildly elevated (Lisi and Cohn 2007).
2. Muscle biopsy/histology (Lotz and Stübgen 1993): nonspecific myopathic changes.
    1. Autophagic vacuoles: a salient histological feature.
    2. Vacuoles containing capillaries.
    3. Muscle spindle swelling.
    4. Type I fiber predominance.
    5. Fiber diameter variability.
    6. Atrophy and internalization of nuclei.
    7. Marked fibrosis.
    8. Some specimen contains minicores typical of classical minicore myopathies (Ferreiro et al. 2002).
    9. Consistent with nemaline myopathy in two siblings with familial rigid spine syndrome (Topaloglu et al. 1994).
3. Electromyogram: myopathic pattern in spinal muscles.
4. There was evidence of minor upper alimentary tract dysfunction in patients with the "vacuolar variant" of RSS. The myopathy that underlies this syndrome likely caused dysfunction of striated muscle of the pharyngeal constrictors and upper esophageal sphincter (Stübgen 2008b).
5. Computed tomography of the muscles: severe involvement of the paraspinal musculature (Vanneste et al. 1988).
6. MRI imaging of muscles: range from mild isolated involvement of the sartorius muscle to a more striking involvement of the sartorius compared with the other thigh muscles in patients with an overall more diffuse involvement. No involvement or only minimal nonselective involvement of calf muscles (Mercuri et al. 2010).

7. MRI of the brain: normal
8. Antibodies directed against the 70-kDa SEPN1 show the absence of the protein in fibroblasts of patients with nonsense mutations.
9. Screening for mutations in the *SEPN1* gene is required to establish the diagnosis of rigid spine muscular dystrophy.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25% affected, given the parents are carriers
    2. Patient's offspring
        1. When the spouse is not a carrier, all offspring obligate heterozygotes.
        2. When the spouse is a carrier, 50% of offspring affected and 50% of offspring carriers.
2. Prenatal diagnosis
    1. Not reported to date.
    2. Possible for pregnancies at increased risk if the disease-causing gene mutation has been identified in the family.
3. Management (Jungbluth 2007).
    1. No curative treatment currently available.
    2. Regular physiotherapy.
        1. Promote endurance
        2. Preserve muscle function
        3. Prevention of contractures, especially Achilles tendon
    3. Swimming and riding for promoting truncal stability.
    4. Management of scoliosis.
        1. Conservative approaches often unsuccessful due to the progressive nature of the deformity
        2. Eventually need to be managed surgically
    5. Mobilization following surgery ought to be early in order to avoid the detrimental effects of prolonged immobilization on muscle strength.
    6. Appropriate rehabilitative measures to promote independent ambulation.
    7. Management of severe respiratory impairment; mechanical ventilation may eventually be needed.
    8. Botulinum toxin may have an important part to play in preventing development of contractures and avoiding stiffness, not only in a symptomatic way but also in a curative manner (Sastre-Garriga et al. 2001).
    9. Echocardiography for cardiomyopathy.
    10. Therapeutic perspectives (Reed 2009).
        1. Recently, Rederstorff et al. (2007) reported a patient with a homozygous point mutation at the selenocysteine (Sec) codon (c.G1385A) that converted the normal codon UGA to UAA, therefore preventing synthesis of a full-length active SePN protein.
        2. Lescure et al. (2008) subsequently "engineered a mutant tRNASec gene carrying a point mutation in the anticodon, thereby restoring the base complementarity with the SEPN1-mutated codon; in patient-derived primary fibroblasts, the corrector tRNASec gene allowed read through of the UAA stop codon, thus enabling synthesis of the full-length SePN protein" (Rederstorff et al. 2007).
        3. This is the first attempt of a therapeutic strategy for rigid spine CMD and other SEPN-related disorders, using a mutation-specific approach.

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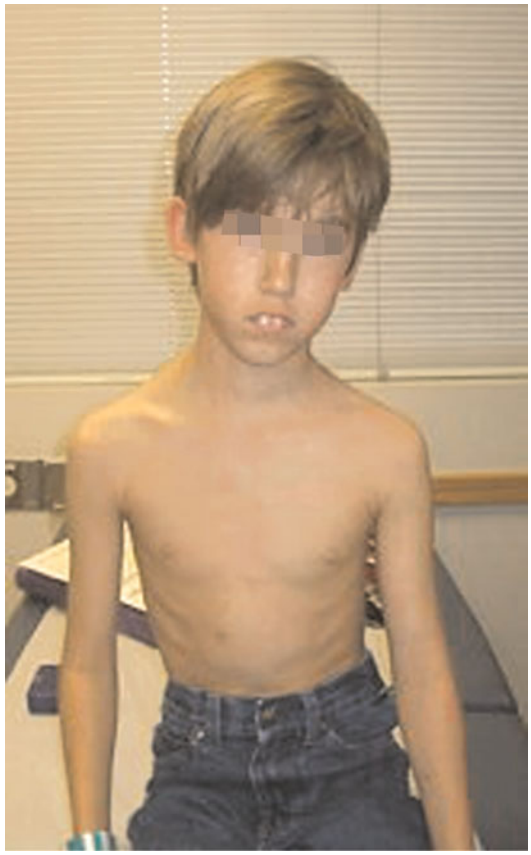

Fig. 1 This 8-year-and-6-month-old boy was evaluated for poor weight gain, hypotonia, and muscle weakness. On examination, he was noted to be very hypotonic with poor head control, inability to flex the spine or the neck and limited rotation of the neck, mild scoliosis, and chest wall asymmetry. Metabolic panel revealed a minimally elevated AST (40 μ/L), a minimally elevated CPK (362 μ/L), and a mildly elevated aldolase (7.8 μ/L). The radiographs of the spine showed straight lateral view of the spine without normal cervical and thoracic curvatures with minimal scoliosis. Because of the radiographs, rigid spine muscular dystrophy, a selenoprotein N1-related myopathy, was suspected. The *SEPN1* mutation analysis revealed that the patient is heterozygous for a mutation in exon 1 of the *SEPN1* (c.1A > G) and a mutation in exon 7 of the *SEPN1* gene (c.943 G > A) which are both known to be pathogenic. The results are consistent with a diagnosis of SEPN1-related myopathy, an autosomal recessive myopathy. Note the myopathic face

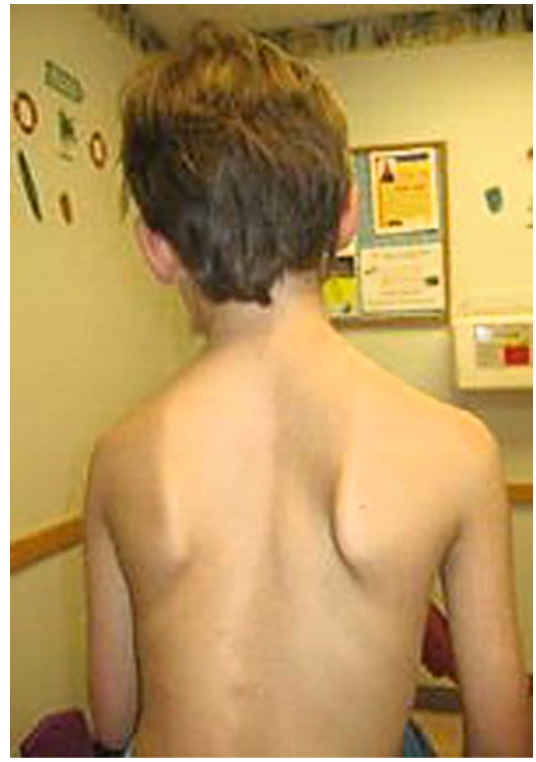

Fig. 2 Note the stiff neck and spine with minimal scoliosis

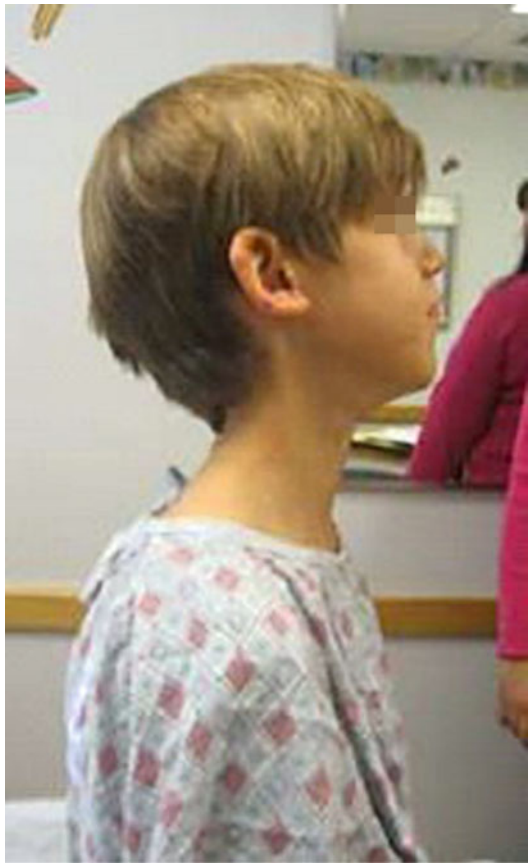

Fig. 3 Note his rigid neck that cannot bend

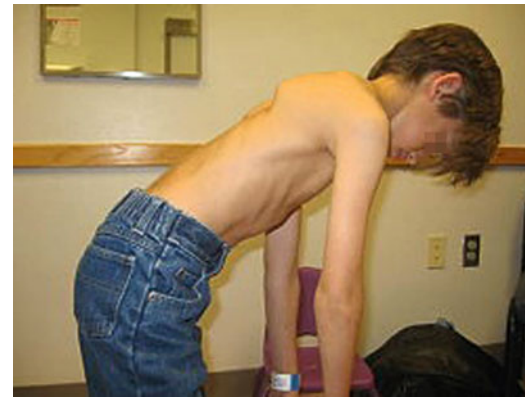

Fig. 4 Note difficulty in bending his neck and spine

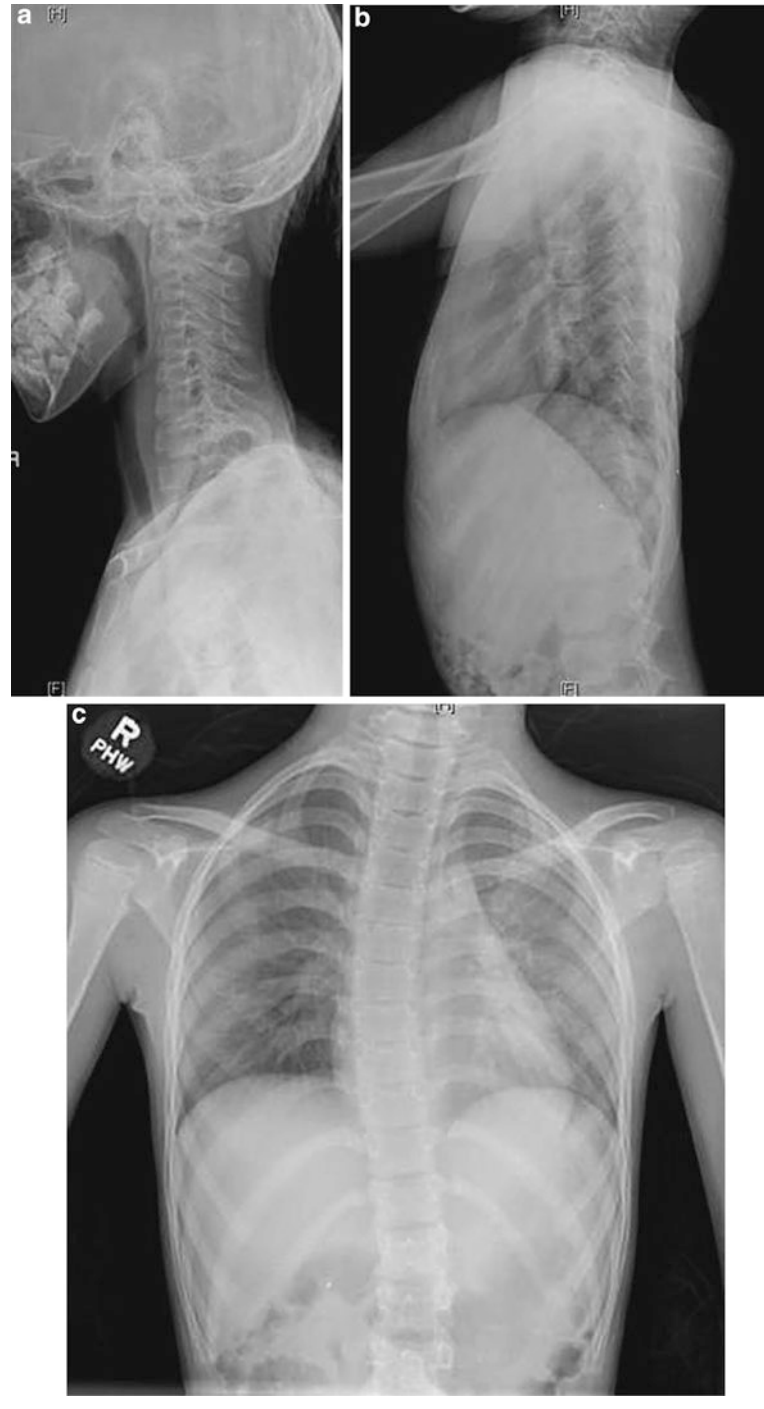

Fig. 5 (**a**–**c**) Radiographs of the spine showed stiff spinal column (lateral views) (**a**, **b**) and mild scoliosis (AP view) (**c**)

Roberts Syndrome

Contents

Roberts syndrome is a rare hereditary disorder characterized by symmetrical reduction of all limbs and a unique cytogenetic abnormality of premature centromere separation, which disrupts the process of chromatid pairing.

Synonyms and Related Disorders

Cohesinopathies (Barbero 2013); Roberts-SC phocomelia syndrome; Roberts tetraphocomelia syndrome; Tetraphocomelia syndromes (Roberts syndrome and SC phocomelia (Herrmann and Opitz 1977)/pseudothalidomide syndrome (Lenz et al. 1974))

Genetics/Basic Defects

1. Autosomal recessive disorder: affected siblings with the Roberts tetraphocomelia syndrome (Qazi et al. 1979; Fryns et al. 1987; Holmes-Siedle et al. 1990).
2. Associated with unique cytogenetic abnormality: premature centromere separation:
   1. Disrupts the process of chromatid pairing and disjoining of sister chromatids (German 1979)
   2. Responsible for the development of multiple structural anomalies observed in Roberts syndrome
3. Caused by mutations in *establishment of cohesion 1 homologue 2* (*ESCO2*) on 8p21.1, a human homologue of yeast *ECO1* that is essential for the establishment of sister chromatid cohesion (Vega et al. 2005).
4. Loss of ESCO2 acetyltransferase activity was recently implicated in the molecular mechanism of Roberts syndrome (Gordillo et al. 2008; Vega et al. 2010).
5. Roberts syndrome and SC phocomelia: a single genetic entity (Römke et al. 1987).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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6. Roberts syndrome and pseudothalidomide syndrome are the same condition and emphasize that normal intelligence and positive social-personal adjustment are possible, even with all of the stigmata of Roberts syndrome (Holden et al. 1992; Hwang et al. 2002).
7. A deficit in acetylated cohesin leads to nucleolar dysfunction in Roberts syndrome (Xu et al. 2014).

Clinical Features

1. Highly variable clinical features (Sinha et al. 1994)
2. Craniofacial malformations: marked variability (Vega et al. 2010; Afifi et al. 2016):
    1. Bilateral cleft lip and cleft palate in severe cases (Roberts 1919)
    2. No clefting of the lip or palate in some cases
    3. Hypertelorism secondary to widely spaced orbits
    4. Ophthalmic manifestations:
        1. Exophthalmos due to shallow orbits
        2. Microphthalmia
        3. Peter anomaly
        4. Cloudy cornea
        5. Cataracts
    5. Wide nasal bridge
    6. Hypoplastic nasal alae
    7. Hemangiomata of the lip, nose, face, or forehead
    8. Micrognathia
    9. Dark scalp hair that becomes thin and silvery blond
3. Limb defects:
    1. Phenotype varies from a complete absence of arms and legs with rudimentary digits to mild growth reduction in the limbs.
    2. Limb reduction defects tend to be symmetric and more severely involved in the upper extremities than the lower extremities.
    3. The presence of phocomelia:
        1. Tetraphocomelia: a prominent characteristic of the syndrome
        2. Two deficient limbs in 11% of cases
        3. No phocomelia in 2% of cases
    4. Often reduced number of fingers (oligodactyly)
    5. Radial aplasia or dysplasia common
    6. Lack of first metacarpal, thumb, or first phalanx
    7. Report of a mild form of this syndrome, who presented with an asymmetrical reduction of the right upper limb (Concolino et al. 1996)
    8. Tetra-amelia with lung hypoplasia and facial clefts (Roberts-SC syndrome) (Ragavan et al. 2010)
4. Other associated anomalies:
    1. CNS anomalies:
        1. Mental retardation
        2. Microcephaly
        3. Hydrocephalus
        4. Absent olfactory lobes
        5. Calcification of the basal ganglia
        6. Encephalocele
        7. Cranial nerve paralysis (Parry et al. 1986)
        8. Seizures
    2. Congenital heart defects:
        1. Atrial septal defect
        2. Patent ductus arteriosus
        3. Pulmonic stenosis
        4. Valvular aortic stenosis (Dogan et al. 2014)
        5. AV canal defect
    3. Renal anomalies:
        1. Polycystic kidneys
        2. Dysplastic kidneys
        3. Horseshoe kidney
        4. Hydronephrosis
        5. Renal agenesis
    4. Gastrointestinal obstruction
    5. Splenogonadal fusion
    6. Cryptorchidism
    7. Enlarged phallus
    8. Failure to thrive
    9. Neoplasms:
        1. Sarcoma botryoides
        2. Malignant melanoma
5. Adult patients (Goh et al. 2010):
    1. The characteristic clinical features of RBS/SC phocomelia were present in the majority of adult patients:

1. Limb anomalies (9/10)
2. Craniofacial anomalies (8/10)
3. Growth retardation (10/10)
4. Mental retardation/learning difficulties (7/10)

2. Clinically apparent limb anomaly may not be an obligate feature for the diagnosis of this condition and that careful measurements may be required to detect subclinical limb shortening.

6. Prognosis:
   1. Severe cases:
      1. Often resulting in spontaneous abortions or stillbirths.
      2. Few cases survive past one month of life.
   2. Phenotypically milder cases:
      1. Requiring minimal to full time care depending on the degree of mental retardation
      2. May require surgical interventions to correct craniofacial and limb anomalies
7. Differential diagnosis (Gordillo et al. 2013):
   1. SC phocomelia (Herrmann et al. 1969):
      1. Clinical characteristics:
         1. Tetraphocomelia
         2. Scanty silvery blond hair
         3. Microcephaly
         4. Mild mental retardation
         5. Facial hemangioma
         6. Cloudy cornea
         7. Hypoplastic nasal alae and ears
      2. Originally thought to differ from Roberts syndrome by:
         1. Usual absence of midfacial clefting
         2. Prolonged survival
         3. Lesser degree of mental and physical retardation
         4. Relatively milder degree of phocomelia
      3. Now considered to be the same entity as Roberts syndrome (Roberts-SC phocomelia syndrome) based on the following observations (Schüle et al. 2005):
         1. The presence of severely and mildly affected individuals in the same sibship raised the suspicion that the two disorders are allelic, representing spectrum of severity.
         2. Furthermore, both are characterized by heterochromatin repulsion (HR) or premature centromere separation in mitotic cells (Judge 1973; Freeman et al. 1974a, b; Tomkins et al. 1979).
         3. Somatic cell complementation studies revealed that cells positive for HR (HR+) from individuals with Roberts syndrome and from those with SC do not complement each other, further supporting the notion that the same gene is affected in the two disorders (McDaniel et al. 2000).
   2. Thrombocytopenia-absent radius (TAR) syndrome (Urban et al. 1998) (see the chapter on "Thrombocytopenia-Absent Radius Syndrome"):
      1. Absent radii with thumbs present
      2. Hypomegakaryocytic thrombocytopenia
      3. Absent cleft palate
   3. Baller-Gerold syndrome:
      1. Autosomal recessive disorder
      2. Craniosynostosis (brachycephaly)
      3. Ocular proptosis
      4. Bulging forehead
      5. Radial ray defect (oligodactyly)
      6. Aplasia or hypoplasia of the thumb and/or aplasia or hypoplasia of the radius
      7. Growth retardation
      8. Poikiloderma
      9. Caused by mutations in *RECQL4*
   4. Fanconi anemia (see the chapter on "Thrombocytopenia-Absent Radius Syndrome")
   5. Tetra-amelia, X-linked (Zimmer tetraphocomelia):
      1. Tetra-amelia
      2. Facial clefts
      3. Absence of ears and nose
      4. Anal atresia
      5. Absence of frontal bones
      6. Pulmonary hypoplasia with adenomatoid malformation
      7. Absence of thyroid

8. Dysplastic kidneys, gallbladder, spleen, uterus, and ovaries
9. Imperforate vagina

6. Tetra-amelia, autosomal recessive:
   1. Caused by mutations in the WNT3
   2. Amelia
   3. Severe lung hypoplasia and aplasia of the peripheral pulmonary vessels
   4. Cleft lip/palate
   5. Hypoplasia of the pelvis
   6. Malformed uterus
   7. Atresia of the urethra, vagina, and anus
   8. Diaphragmatic defect
   9. Agenesis of the kidney, spleen, and adrenal glands
7. Splenogonadal fusion with limb defects and micrognathia (de Ravel et al. 1997):
   1. Autosomal recessive inheritance
   2. Abnormal fusion between the spleen and the gonad or the remnants of the mesonephros
   3. Tetramelia
   4. Mild mandibular and oral abnormalities (micrognathia, multiple unerupted teeth, crowding of the upper incisors, and deep, narrow, V-shaped palate without cleft)
8. DK phocomelia syndrome:
   1. Autosomal recessive inheritance
   2. Phocomelia
   3. Absence of radius and digits
   4. Thrombocytopenia
   5. Encephalocele
   6. Cleft palate and absence of radius and digits
   7. Anal atresia
   8. Abnormal lobation of the lungs
   9. Diaphragmatic agenesis
9. Holt-Oram syndrome (see the chapter)
10. Thalidomide embryopathy (see the chapter on "Dysmelia"):
    1. Abnormalities of the long bones of the extremities:
       1. Upper limb bones are affected in an order of frequency starting with the thumb, followed by the radius, the humerus, the ulna, and finally the fingers on the ulnar side of the hand.
       2. In extreme cases, the radius, ulna, and humerus are lacking; the hand bud arises from the shoulders.
       3. Legs may be affected but less severely.
    2. The second major group of defects involves the ears (anotia, microtia, accessory auricles) and the eyes (coloboma of the iris, anophthalmia, microphthalmia).
    3. Internal defects commonly involve the heart, kidneys, and urinary, alimentary, and genital tracts.
11. Cornelia de Lange syndrome (Skibbens et al. 2013) (please see the chapter on "De Lange Syndrome"):
    1. Roberts syndrome (RBS) and Cornelia de Lange syndrome (CdLS) are severe developmental maladies that present with nearly an identical suite of multi-spectrum birth defects.
    2. Not surprisingly, RBS and CdLS arise from mutations within a single pathway involving cohesion.
    3. Sister chromatid tethering reactions that comprise cohesion are required for high-fidelity chromosome segregation, but cohesin tethers also regulate gene transcription, promote DNA repair, and impact DNA replication.
    4. Currently, RBS is thought to arise from elevated levels of apoptosis, mitotic failure, and limited progenitor cell proliferation, while CdLS is thought to arise, instead, from transcription dysregulation.
    5. RBS cells, like CdLS cells, show hypersensitivity to DNA-damaging agents such as mitomycin C, camptothecin, and etoposide, suggesting a role of *ESCO2* in cohesin-mediated DNA repair and genome stability maintenance (van der Lelij et al. 2009; Cucco and Musio 2016).
12. Mosaic variegated aneuploidy syndrome:
    1. Autosomal recessive inheritance.
    2. Caused by mutations in *BUB1B* which encodes BUBR1, a key protein in the

mitotic spindle checkpoint, which have been found in individuals with this disease.
3. Severe microcephaly.
4. Growth deficiency.
5. Mental retardation.
6. Childhood cancer predisposition.
7. Associated with constitutional mosaicism for chromosomal gains and losses.
8. Cytogenetic findings include premature centromere division, in which mitotic cells show split centromeres and splayed chromatids in all or most chromosomes (Plaja et al. 2001).

Diagnostic Investigations

1. Cytogenetics:
    1. Distinctive abnormality of the constitutive heterochromatin (the RS effect): premature centromere separation (PCS):
        1. Detected in:
            1. Fibroblasts and lymphocytes in neonates
            2. Chorionic villi and amniocytes in the fetus
        2. Consists of "puffing" or "repulsion" of the constitutive heterochromatin:
            1. Chromosome puffing most obvious at the large heterochromatic regions of chromosomes 1, 9, and 16
            2. Chromosome repulsion most evident at the short arms of the acrocentrics and the distal long arm of the Y chromosome (Louie and German 1981; Mann et al. 1982)
        3. A "railroad-track" or "tram-track" appearance of the sister chromatids due to the absence of a constriction at the centromere in several other chromosomes (Van Den Berg and Francke 1993; Lopez-Allen et al. 1996):
            1. This phenomenon, called heterochromatin repulsion, is observed in cells of different tissue origin with several chromosomes in each metaphase showing a visible abnormality.
            2. Most evident in chromosomes containing the largest amount of heterochromatin.
    2. There are other cytogenetic features that are equally characteristic of Roberts syndrome (Jabs et al. 1989, 1991):
        1. Aneuploidy with random chromosome loss
        2. Micronuclei and/or nuclear lobulations of 8–24% of interphase cells
    3. Sporadic aneuploidy was noted with the pattern of aneuploidy different in each patient. The possible relationship between centromere "splaying" and aneuploidy is yet to be determined.
    4. Normal karyotypes lacking any microdeletion or chromosomal rearrangement from either leukocytes or fibroblasts in about a fifth of all cases.
    5. Roberts syndrome variant with normal cell division (Keppen et al. 1991).
    6. Phenomenon of centromeric heterochromatin separation (as occasionally revealed by C-bands in normal subjects) in obligate heterozygotes and possible heterozygotes for RS: indicative of the possibility to screen for heterozygotes (Maserati et al. 1991).
2. Radiography for phocomelia evaluation:
    1. Absence of the radius and fibula: the most common skeletal abnormalities in the upper and lower limbs
    2. Absent, short, deformed, and/or hypoplastic ulna and tibia: the second most common bone defects
    3. Absent, short, deformed, or hypoplastic humerus and femur: the third and least common abnormalities
3. Echocardiography for congenital heart defect.
4. Renal ultrasound for renal anomalies.
5. MRI of the brain for CNS anomalies.
6. In situ hybridization on human embryos showed ESCO2 expression in the brain, face, limb, kidney and gonads, which corresponds to the structures affected in Roberts syndrome (Vega et al. 2010).
7. Molecular genetic testing: sequence analysis of the *ESCO2* gene available clinically.

Genetic Counseling

1. Recurrence risk according to autosomal recessive inheritance (Gordillo et al. 2013):
   1. Patient's sib: 25%
   2. Patient's offspring:
      1. Not increased (not surviving to reproduction in severe cases).
      2. The offspring of an individual with RBS are obligate heterozygotes (carriers) for a disease-causing mutation in *ESCO2*.
2. Prenatal diagnosis (Schulz et al. 2008):
   1. First trimester prenatal evaluation for RS in an at-risk pregnancy: cytogenetic analysis and transvaginal ultrasound (Otaño et al. 1996)
   2. Ultrasonography (Paladini et al. 1996):
      1. Intrauterine growth retardation
      2. Bilateral phocomelia (tetraphocomelia in majority of cases) of varying degree (Robins et al. 1989)
      3. Cleft lip and palate
      4. Associate anomalies:
         1. Hydrocephalus
         2. Congenital heart defects
         3. Renal anomalies
         4. Pulmonary hypoplasia (Sherer et al. 1991)
   3. Three-dimensional (3D) sonography (Dulnuan et al. 2011): can reveal additional abnormalities such as:
      1. Bilateral hypoplastic and proximal implantation of the thumb
      2. Exophthalmic eyes
      3. Suspected cleft lip
      4. Shortened upper extremities
      5. Contracted legs
   4. DNA from fetal cells obtained from amniocentesis or CVS:
      1. Confirmed by characteristic disjunction of centromeres (premature centromere separation in metaphases) (Tomkins 1989; Stioui et al. 1992; Benzacken et al. 1996)
      2. Molecular diagnosis of *ESCO2* gene mutations (Gordillo et al. 2013)
3. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the disease-causing mutations have been identified (Gordillo et al. 2013).
4. Management:
   1. Aggressive medical intervention for those with normal intelligence and no internal anomaly (Karabulut et al. 2001)
   2. Special education
   3. Cornea grafting
   4. Corrective surgery:
      1. Cleft lip/palate
      2. Limb defects
   5. Prosthetic devices:
      1. For underdeveloped or missing limbs
      2. Used to increase independence

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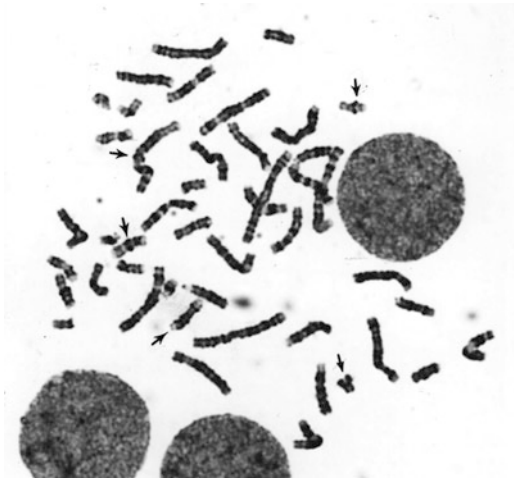

Fig. 1 The G-banded metaphase spread from fibroblast culture of a male infant with Roberts syndrome showing characteristic heterochromatin separation: puffing of the centromeric heterochromatin of some chromosomes and splaying of the Yqh region (arrows). The patient had profound psychomotor retardation, corneal clouding, and tetraphocomelia

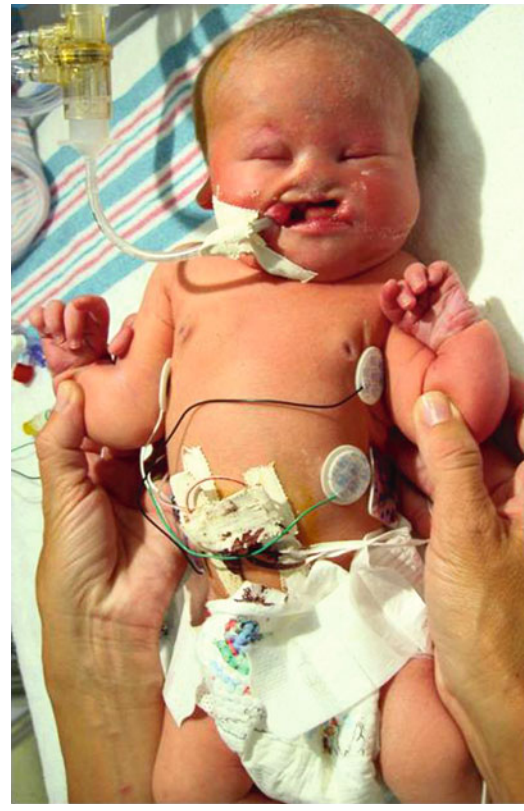

Fig. 2 A newborn with Roberts syndrome variant showing bilateral cleft lip and cleft palate, phocomelia, and club hands with an appendage-like thumb on the right and a missing thumb on the left. The infant also had intrauterine growth retardation, hydrocephalus, cloudy cornea, AV canal heart defect, and normal lower extremities. Cytogenetic studies revealed no premature centromere separation. The mother took Diflucan during pregnancy and the teratogenic etiology was a possibility

Robinow Syndrome

Contents

In *1969*, Robinow et al. (1969) described a new dwarfing syndrome characterized by mesomelic shortening of extremities, hemivertebrae, genital hypoplasia, and "fetal facies" (Wadlington et al. 1973). The incidence is estimated to be approximately 1 in 500,000.

Synonyms and Related Disorders

Acral dysostosis with facial and genital abnormalities; Costovertebral segmentation defect with mesomelia; Fetal face syndrome; Robinow dwarfism

Genetics/Basic Defects

1. Genetic heterogeneity (Robinow 1993)
2. Autosomal recessive (AR) form
    1. Affected siblings from consanguineous parents (Teebi 1990; Schorderet et al. 1992).
    2. Phenotype tends to be more severe than the autosomal dominant form.
    3. Caused by different homozygous (and compound heterozygous) missense, nonsense, and frameshift mutations of the *ROR2* gene (Tufan et al. 2005).
    4. *ROR2* gene:
        1. Mapped to chromosome 9q22 (Afzal et al. 2000a).
        2. Encoding an orphan receptor tyrosine kinase 2 with orthologues in mouse and other species.
        3. Mutation of the gene encoding the ROR2 tyrosine kinase causes autosomal recessive Robinow syndrome (van Bokhoven et al. 2000).
        4. Allelic to dominant brachydactyly type B (characterized by terminal deficiency of fingers and toes) (Afzal et al. 2000b; Patton and Afzal 2002; Afzal and Jeffery 2003).
3. Autosomal dominant (AD) form (Person et al. 2010):
    1. Caused by missense mutations in *WNT5A*, which result in amino acid substitutions of highly conserved cysteines and are associated with autosomal dominant Robinow syndrome.
    2. One mutation has been found in all living affected members of the original family described by Meinhard Robinow and another in a second unrelated patient.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Targeted sequencing identified five unrelated individuals harboring heterozygous, de novo frameshift variants in *DVL3*, including two splice acceptor mutations and three 1 bp deletions. Similar to the variants observed in *DVL1*-mediated Robinow syndrome, all variants in *DVL3* result in a −1 frameshift, indicating that these highly specific alterations might be a common cause of dominant Robinow syndrome (White et al. 2016).
4. Mutations in *DVL1* cause an osteosclerotic form of Robinow syndrome (Bunn et al. 2015).

Clinical Features

1. Characteristic craniofacial appearance (Butler and Wadlington 1987)
    1. Early childhood
        1. Frontal bossing
        2. Midfacial hypoplasia
        3. Occasional midline capillary hemangioma
        4. Eyes
            1. Marked hypertelorism
            2. Prominent eyes giving the appearance of exophthalmos (pseudoexophthalmos)
        5. A short upturned nose with anteverted nares
        6. Mouth (Soman and Lingappa 2015)
            1. Long philtrum.
            2. Small chin.
            3. "Tented" upper lip having an inverted-V appearance with tethering in the center.
            4. Midline clefting of the lower lip.
            5. Gum hypertrophy at birth.
            6. Dental crowding/irregular teeth.
            7. "Tongue tie" (ankyloglossia) resembling a bifid tongue when the tongue tie is marked.
            8. Malocclusion in the form of crowding and irregular teeth may be seen in primary and secondary dentition.
        7. Ears
            1. Low set
            2. Simple
            3. Deformed pinna
        8. Resemblance to a fetal face
            1. Relatively small face.
            2. Laterally displaced eyes.
            3. Forward-pointing alae nasi.
            4. "Fetal facies" becomes less prominent over time.
            5. Facial features of autosomal dominant RS (with WNT5A mutation) in Chinese ethnic background are not different from those in other ethnicities (Xiong et al. 2016).
    2. Adulthood
        1. Loss of fetal facial proportions
        2. Absent midfacial hypoplasia
        3. Persistent hypertelorism with a broad nasal root and broad forehead
2. Short stature
    1. Reduced birth length
    2. Not a universal finding with some reports of normal growth
3. Limb abnormalities
    1. Mesomelic or acromesomelic limb shortening
    2. Shortening of the forearms more striking than the shortening of the legs
    3. Occasional Madelung deformity
    4. Hands/feet
        1. Brachydactyly with shortening of the distal phalanx and nail hypoplasia or dystrophy
        2. Thumbs
            1. Displaced
            2. Occasionally bifid
            3. Partial cutaneous syndactyly
            4. Ectrodactyly (especially patients reported from Turkey)
4. Other skeletal abnormalities
    1. Chest deformities
    2. Kyphoscoliosis
    3. Vertebral anomalies
    4. Rib defects
    5. Pectus excavatum

6. Acrodysostosis
7. Delayed bone age

5. Genital hypoplasia
    1. Genital abnormalities: may be present at birth causing concern regarding gender assignment
        1. Males
            1. Micropenis
            2. Normal scrotum and testes
        2. Females
            1. Reduced clitoral size
            2. Hypoplasia of the labia minor
            3. Associated vaginal atresia and hematocolpos
        3. Onset of puberty normal in both sexes
        4. Several reports of both male and female patients having normal children
6. Congenital heart defects (15%) (Webber et al. 1990; Atalay et al. 1993; Al-Ata et al. 1998)
    1. Severe pulmonary stenosis or atresia (the most common cardiac abnormalities)
    2. Atrial septal defect
    3. Ventricular septal defect
    4. Coarctation of the aorta
    5. Bicuspid aortic valve
    6. Tetralogy of Fallot
    7. Tricuspid atresia
    8. Double-outlet right ventricle
    9. Patent ductus arteriosus
7. Renal abnormalities
    1. Hydronephrosis (relatively common)
    2. Cystic dysplasia of the kidney (Wiens et al. 1990)
8. Developmental delay but intelligence is usually normal
9. Dermatoglyphics
    1. Absent interphalangeal creases
    2. Bilateral transverse creases
    3. Hypothenar whorl pattern
10. Clinical characteristics of recessive Robinow syndrome: Tend to be more severe with fusions of vertebrae and ribs, hemivertebrae, radial head dislocation, severe mesomelic brachymelia than the dominant form (Patton and Afzal 2002). Parental consanguinity, multiple affected sibs, or other similarly affected family members in addition to increased mortality rate among affected patients favored the AR inheritance pattern of RS (Aglan et al. 2015).
    1. Short stature
    2. Mesomelic and acromelic brachymelia
    3. Thick abnormally modeled radius and ulna
    4. Characteristic face
        1. Hypertelorism
        2. Wide palpebral fissures
        3. Broad-based nose with everted nares
        4. Large mouth
        5. Gum hypertrophy
        6. Irregular and crowded teeth
    5. Costovertebral anomalies
    6. Endocrine dysfunction
        1. Empty sella
        2. Partial insensitivity of Leydig cells to HCG
        3. Low basal testosterone in prepubertal boys
        4. Defective sex-steroid feedback mechanism
    7. Micropenis in males
11. Clinical characterization of autosomal dominant and recessive variants of Robinow syndrome, based on inheritance pattern in familial cases and presence of rib fusions as diagnostic of the recessive variant (Mazzeu et al. 2007):
    1. Clinical signs present in more than 75% of patients with either form and therefore the most important for the characterization of this syndrome:
        1. Hypertelorism
        2. Nasal features (large nasal bridge, short upturned nose, and anteverted nares)
        3. Midfacial hypoplasia
        4. Mesomelic limb shortening
        5. Brachydactyly
        6. Clinodactyly
        7. Micropenis
        8. Short stature
    2. The craniofacial dysmorphology of RS was more severe in ARRS (Beiraghi et al. 2011).
        1. Nasal anomalies were the most frequent craniofacial features in both ADRS and ARRS.

2. In contrast, intraoral features such as wide retromolar ridge, alveolar ridge deformation, malocclusion, dental crowding, and hypodontia were more severe in patients with ADRS.
3. Overall, facial characteristics appeared less pronounced in adult subjects compared to younger subjects.
4. Craniofacial and intraoral findings are highly variable in RS, with abnormalities of the intraoral structures being more prominent in the ADRS form.
5. The difference in the alveolar ridge deformation pattern and severity of other intraoral characteristics could enhance the differential diagnosis of the two forms of this syndrome.
    1. Hemivertebrae and scoliosis were present in more than 75% of patients with the recessive form but in less than 25% of patients with the dominant form.
    2. Umbilical hernia (32.3%) and supernumerary teeth (10.3%) were found exclusively in patients with the dominant form.
2. Differential diagnosis of mesomelic dwarfism (Giedion et al. 1976)
    1. With Madelung deformity: dyschondrosteosis (please see the chapter on "► Dyschondrosteosis")
    2. With malformations of long bones depending on various distribution/severity patterns and types of transmission
        1. Ulnofibular
            1. With mild triangular deformity
            2. With extreme variety: boomerang bone disease
        2. Radiotibial with "normal" fibula
        3. Ulno-fibular-mandibular (Langer type, homozygous dyschondrosteosis)
        4. Ulno-radio-fibular-tarsal with square, triangular, or rhomboid tibia
        5. Ulno-radio-tibial with absent fibula
    3. With associated malformations of spine
        1. Robinow syndrome
        2. Wegmann syndrome
        3. Campallia and Martinelli syndrome
        4. "Spondylo-epiphyso-metaphyseal" dysplasia
    4. With acrodysplasia
        1. Acromesomelic dwarfism
        2. Ellis-van Creveld syndrome (please see the chapter on "► Ellis-van Creveld Syndrome")
        3. Grebe achondrogenesis

Diagnostic Investigations

1. Partial primary hypogonadism in pubertal boys, with persistence of micropenis (Lee et al. 1982)
    1. Normal pubertal virilization with persistence of micropenis
    2. Elevated basal serum follicle-stimulating hormone levels and a hyperresponse of serum-luteinizing hormone to gonadorelin hydrochloride (Factrel) stimulation among postpubertal male patients, suggesting partial primary hypogonadism
    3. Normal 5 alpha-reductase and androgen receptor activity in genital skin fibroblasts
    4. Normal to borderline adult height.
2. Radiography
    1. Skull
        1. Macrocephaly
        2. Prominent forehead
        3. Hypertelorism
        4. Hypoplastic mandible
        5. Dental anomalies
    2. Spine/ribs: widespread fusion of thoracic vertebrae with frequent hemivertebrae and fusion of the ribs, resembling Jarcho-Levin syndrome (spondylocostal dysostosis) in severe cases (autosomal recessive form)

1. Hemivertebrae and vertebral fusions
2. Fusion of ribs
3. Shortened interpeduncular distance

3. Extremities (long bones): mesomelic shortening
   1. Upper extremities
   2. Lower extremities
   3. Ulna shorter than radius
   4. Luxation of the radius
4. Hands and feet
   1. Brachymesophalangism of fifth digits
   2. Clinodactyly of the fifth digits
   3. Shortening of other phalanges
   4. Brachymetacarpism
   5. Fusion of carpal bones
   6. Bifid terminal phalanges (splitting of one or more distal phalanges)
   7. Fusion of phalanges
   8. Retarded bone age
5. Axial and appendicular osteosclerosis: may represent a distinctive sub-phenotype of Robinow syndrome (Bunn et al. 2014)
   1. Marked generalized osteosclerosis affecting the skull, axial and appendicular skeleton.
   2. The calvaria were thickened and sclerotic with the skull base most affected.
   3. The frontal sinuses were hypoplastic.
   4. There was undertubulation of the long bones with pronounced cortical thickening.
   5. The ulnae were bowed bilaterally.

3. Computed tomography scan and magnetic resonance imaging (Altunkas et al. 2016)
   1. Rib fusions
   2. Multilevel block vertebrae
   3. Butterfly vertebra
   4. Posterior fusion defects in vertebrae
   5. Diastematomyelia in the spinal cord
4. A single butterfly vertebra is more frequent in the dominant form, whereas hemivertebrae, vertebral fusions, and narrow interpedicular distance are more frequent in the recessive form (Kanatupra et al. 1999).
5. Spondylothoracic dysplasia is formed as a result of posterior fusion of cervical-thoracic-lumbar vertebrae with hypoplastic-dysplastic asymmetric rib changes (Bain et al. 1986).
6. Renal ultrasound for renal anomalies.
7. Echocardiography for congenital heart disease.
8. Growth hormone assay for possible growth hormone deficiency.
9. DNA mutation analysis: available on clinical basis.
   1. *ROR2* gene is the gene responsible for autosomal recessive *ROR2*-related Robinow syndrome.
   2. Sequence analysis of *ROR2* gene detects 65–100% of affected individuals.

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal dominant inheritance: not increased unless a parent is affected
      2. Autosomal recessive inheritance: 25%
   2. Patient's offspring
      1. Autosomal dominant inheritance: 50%
      2. Autosomal recessive inheritance: not increased unless the spouse is a carrier
2. Prenatal diagnosis
   1. Ultrasonography
      1. First-trimester ultrasonography: shortening of extremities and increased nuchal translucency thickness in a family at risk (Percin et al. 2001)
      2. Possible by measuring the length of the long bones and the ulna/humerus ratio for the fetus at risk (Loverro et al. 1990)
      3. Characteristic US craniofacial findings: hypertelorism with prominent eyes that give the impression of exophthalmos, low-set ears, micrognathia, and cleft palate (Castro et al. 2014)
   2. Prenatal diagnosis: also possible for pregnancies at increased risk for ROR2-related Robinow syndrome by sequencing of entire coding region of *ROR2* gene on fetal DNA obtained by amniocentesis or CVS, provided the disease-causing alleles have been previously identified in the proband.

3. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variants in the family (Bacino 2011; Roifman et al. 2015).

3. Management
   1. Anticipate difficult intubation because of midfacial hypoplasia.
   2. Orthopedic care for vertebral anomalies and hip dislocation.
   3. Orthodontics for dental malalignment.
   4. Surgery for cleft lip and palate, inguinal hernia, and undescended testes.
   5. Growth hormone therapy if associated with growth hormone deficiency (Kawai et al. 1997; Castells et al. 1999).
   6. HCG and/or testosterone therapy during infancy may improve the severe micropenis in these patients (Soliman et al. 1998).
   7. Psychologic support.

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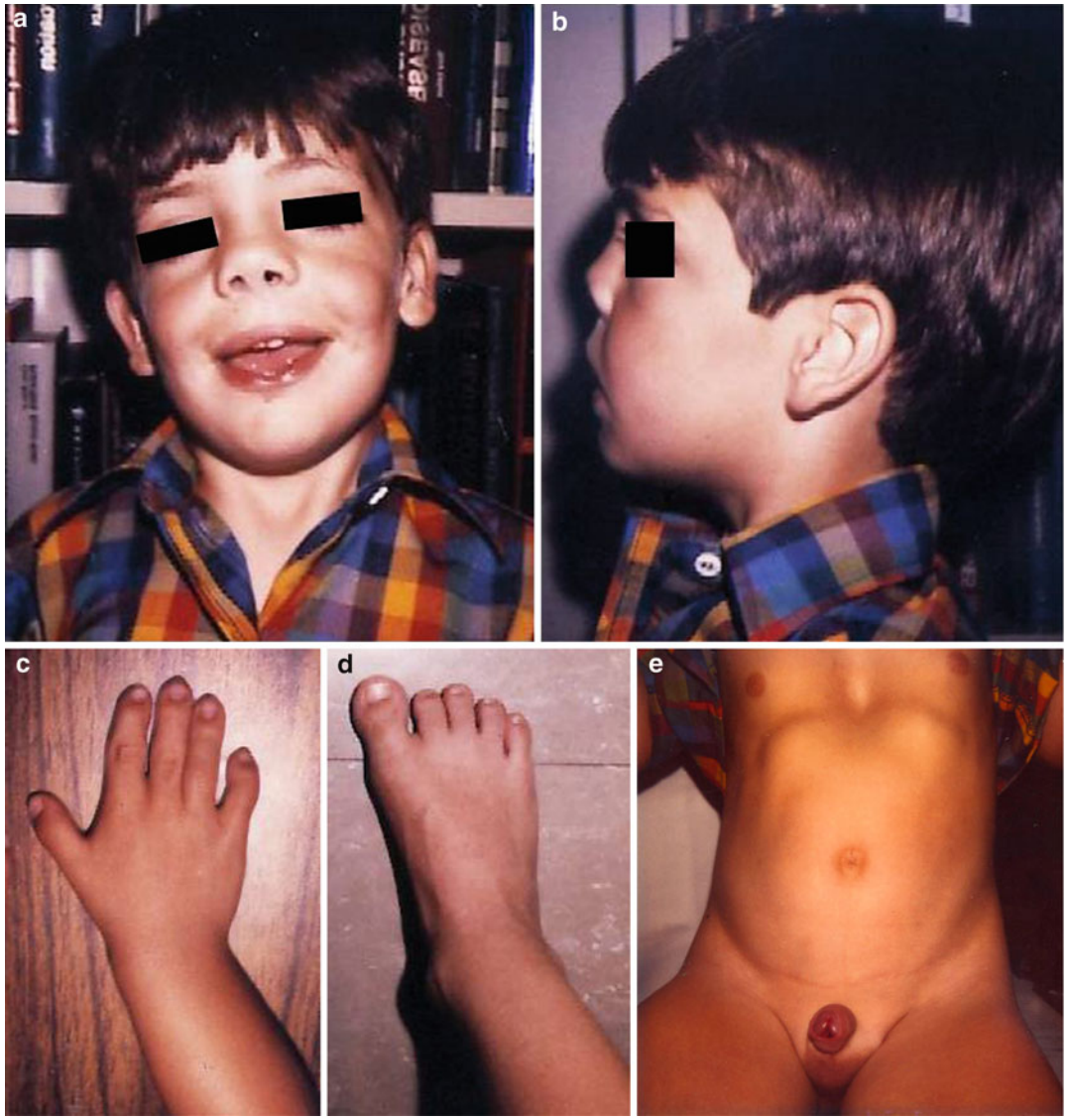

Fig. 1 (**a**–**e**) A child with Robinow syndrome showing prominent forehead, ocular hypertelorism, short upturned nose (**a**, **b**), pectus excavatum, penile hypoplasia (**e**), and acromesomelic shortening of the limbs (**c**, **d**)

Rubinstein-Taybi Syndrome

Contents

In *1963*, Rubinstein and Taybi (1963) described a new syndrome characterized by broad thumbs and toes, facial abnormalities, and mental retardation. The prevalence of Rubinstein-Taybi syndrome (RTS) is estimated to be 1 in 100,000–1 in 125,000 live births in the Netherlands.

Synonyms and Related Disorders

Broad thumb-hallux syndrome (Rubinstein 1990); broad thumbs and great toes, characteristic facies, and mental retardation; Rubinstein syndrome

Genetics/Basic Defects

1. Inheritance: autosomal dominant.
2. Most cases are sporadic (~99%); familial cases are extremely rare (Hennekam et al. 1989; Bartsch et al. 2010).
3. Caused by deletions or heteroallelic mutations of *CREBBP*, the gene for cAMP-responsive element-binding (CREB) protein, which resides on chromosome 16p13.3 (Lacombe et al. 1992; Hennekam et al. 1993; Giles et al. 1997). CREBBP is a large nuclear protein involved in transcription regulation, chromatin remodeling, and the integration of several different signal transduction pathways. The following mutations of *CREBBP* were reported in patients with Rubinstein-Taybi syndrome (Bartsch et al. 2002; Coupry et al. 2002):
    1. Chromosomal translocations (t(2;16)(p13.3;p13.3)) (Imaizumi and Kuroki 1991)/inversions
    2. Deletions at the microscopic and submicroscopic levels (Masuno et al. 1994; Wallerstein et al. 1997; Taine et al. 1998)
    3. Molecular mutations
4. Mutations in the *CREBBP* gene are responsible for:
    1. Rubinstein-Taybi syndrome (Petrij et al. 1995)
    2. t(8;16)-associated acute myeloid leukemia
5. Also rarely caused by mutations in *EP300* gene (located on 22q13.2)
    1. Individuals reported with mutations in *EP300* have a milder skeletal phenotype, lacking typical broadening and angulation of the thumb and hallux (Bartholdi et al. 2007).

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2. As more of the EP300 protein is preserved, particularly the HAT domain, the milder the phenotype (Sellars et al. 2016).
3. EP300 mutations might account for a higher frequency of RTS patients than previously thought. The clinical presentation of EP300-mutated patients is milder than that of CREBB-mutated patients (Negri et al. 2015).

6. RTS caused by mutations in *CREBBP* has been referred to as RTS type 1 (RTS1), whereas mutations in *EP300* cause RTS type 2 (RTS2) (Hamilton et al. 2016).
7. No clear phenotypic differences are observed between patients in whom microdeletions or truncating mutations were found.
8. Variable expression and somatic mosaicism contribute to the phenotypic variability of RTS. Somatic mosaicism may be more frequent in RTS than previously assumed (Bartsch et al. 2010).
9. Different chromosomal anomalies have been identified in some patients with this syndrome (Imaizumi et al. 1993; Cantani and Gagliesi 1998).

Clinical Features

1. Characteristic craniofacial features.
    1. Typical facial phenotype may not be obvious until late childhood (Allanson 1990; Hennekam 1993).
    2. Microcephaly (35–94%).
    3. Prominent forehead.
    4. Down-slanting palpebral fissures.
    5. Apparent ocular hypertelorism.
    6. High-arched or heavy eyebrows.
    7. Long eyelashes.
    8. Epicanthal folds.
    9. Prominent nose with columella (lower margin of the nasal septum) below the alae nasi.
    10. Malpositioned ears with dysplastic helices.
    11. Grimacing smile.
    12. Hypoplastic maxilla.
    13. Oral features (Hennekam and Van Doorne 1990)
        1. Thin upper lip
        2. Small oral opening
        3. Pouting lower lip
        4. Retro/micrognathia
        5. Apparently higher arched, narrow palate
        6. Cleft uvula
        7. Cleft palate
        8. Rarely, cleft upper lip
2. Skeletal abnormalities.
    1. Broad thumbs and broad hallux: the hallmarks for the Rubinstein-Taybi syndrome (da Silva et al. 2014)
    2. Thumbs
        1. Broad terminal phalanges
        2. Severe radial angulation deformity ("hitchhiker thumbs") with abnormal shape of the proximal phalanx, which prevents opposition and functional gripping strength (Wood and Rubinstein 1987)
    3. Great toes
        1. Broad terminal phalanges
        2. Angulation deformity with abnormal shape of the proximal phalanx or first metatarsal
        3. Duplicated proximal phalanx
        4. Duplicated distal phalanx
    4. Short stature (78%)
    5. Fifth finger clinodactyly
    6. Overlapping toes
    7. Broad terminal phalanges of other fingers
    8. Pelvic anomalies
        1. Flat acetabular angles
        2. Flaring of the ilia
        3. Notch in the ischia
    9. Stiff gait
    10. Lax ligaments
    11. Hyperextensible joints
    12. Vertebral anomalies
        1. Spina bifida
        2. Kyphosis
        3. Lordosis
        4. Scoliosis
    13. Sternal or rib anomalies
        1. Premature fusion

2. Simian sternum
3. Pectus excavatum or carinatum
4. Forked ribs
5. Cervical ribs
6. Fusion of the first and second ribs

3. History of maternal polyhydramnios (30%) (Hennekam 2006).
4. Hypotonia.
5. Growth retardation.
6. Developmental delay.
7. Variable mental retardation.
   1. Severe in some patients
   2. Moderate degree in many patients
   3. Mild in some patients
8. Behavioral/psychiatric disorders (Levitas and Reid 1998; Hellings et al. 2002).
   1. Childhood (Gotts and Liemohn 1977)
      1. More emotional and excitable
      2. Nightmares and engaged in self-stimulation
      3. Greater difficulty getting over anger (pouted)
      4. Friendly and more readily accepted social contacts
      5. Short attention span
      6. Experience more difficulty in planning motor acts and in executing locomotor and oculomotor skills
      7. Impulsiveness
      8. Clinically nonsignificant stereotype
      9. Withdrawal
      10. Expressive speech skill difficulty and "maladaptive behavior" (Stevens et al. 1990)
      11. Repetitive motions
      12. Resistance to change
      13. Distractibility
      14. Aggressive outbursts
      15. Difficulty in sleeping
   2. Adulthood
      1. Mood disorders
      2. Chronic motor tic disorder
      3. Obsessive compulsive disorder
      4. Depressive disorder
      5. Bipolar disorder
      6. Tourette disorder
      7. Trichotillomania
      8. Pervasive developmental disorder
      9. Self-injurious behaviors
      10. Autistic features
      11. Preference of being alone (between manic episodes)
9. Seizures (27–28%).
10. Ophthalmologic problems: very frequent in RST, ~80% of cases having extraocular or intraocular features (Brei et al. 1995; Van Genderen et al. 2000).
    1. Strabismus (60–71%) with subsequent risk of amblyopia.
    2. Refractive errors (41–56%).
    3. Lacrimal duct obstructions (38–47%).
    4. Ptosis (29–32%).
    5. Coloboma (9–11%).
    6. Duane retraction syndrome (8%).
    7. Ghost vessels.
    8. Peters anomaly.
    9. Optic nerve hypoplasia.
    10. Cataracts.
    11. Corneal opacities.
    12. Congenital glaucoma: the most serious one that requires early diagnosis and treatment is glaucoma.
    13. Retinal abnormalities.
11. Dental manifestations (67%).
    1. Talon cusps of secondary dentition
    2. Crowding and malpositioned teeth
    3. Anterior and posterior crossbites secondary to a narrow palate or jaw size discrepancy
    4. Natal teeth
    5. Gingivitis
    6. Hypodontia/hyperdontia
    7. Increased rate of carries
12. Hearing loss.
13. Respiratory problems.
    1. Neonatal respiratory problems
    2. Upper airway infections
14. Upper airway obstruction during sleep due to:
    1. Hypotonia
    2. Anatomy of the oropharynx and airway
       1. Small nasal passages
       2. Retrognathia
       3. Micrognathia
       4. Hypertrophy of the tonsils and adenoids
       5. Obesity

15. Gastrointestinal problems.
    1. Significant gastroesophageal reflux
    2. Feeding difficulties
    3. Constipation
16. Congenital heart disease (24–38%) (Stevens and Bhakta 1995).
    1. ASD
    2. VSD
    3. PDA
    4. Coarctation of the aorta
    5. Pulmonary stenosis
    6. Bicuspid aortic valve
    7. Pseudotruncus
    8. Aortic stenosis
    9. Hypoplastic left heart syndrome (Bartsch et al. 1999)
    10. Complex congenital heart defects
    11. Dextrocardia
    12. Vascular rings
    13. Conduction problems
17. Renal anomalies (52%).
    1. Hydronephrosis
    2. Duplications
    3. Vesicoureteral reflux
    4. Urinary tract infections
    5. Renal stones
    6. Nephrotic syndrome
    7. Neurogenic bladder
18. Cutaneous manifestations (Selmanowitz and Stiller 1981).
    1. Tendency of keloid and hypertrophic scar formation
    2. Ingrown toenails
    3. Toenail paronychia (44%)
    4. Fingernail paronychia (9%)
    5. Pilomatrixomas
    6. Capillary hemangioma
        1. Forehead
        2. Nape of the neck
        3. Back
    7. Supernumerary nipples
    8. Hirsutism
    9. Transverse palmar creases
    10. Deep plantar crease between the first and second toes
19. Orthopedic problems.
    1. Hypotonia
    2. Lax ligaments
    3. Tight heel cords
    4. Elbow abnormalities
    5. Legg-Perthes disease (3%)
    6. Dislocated patella (2.5%)
    7. Congenital hip dislocation (1.4%)
    8. Slipped capital femoral epiphysis (0.6%)
    9. Congenital or acquired scoliosis, kyphosis, and lordosis
    10. An increased risk of associated thickened filum terminale, tethering of the cord, and lipoma
    11. An increased risk of fractures
20. Polysplenia (Bartsch et al. 1999).
21. A germ cell tumor occurring in a pediatric patient with RTS (Butler et al. 2016): a palpable right-sided abdominal mass and an elevated alpha-fetoprotein. Histology revealed a malignant germ cell neoplasm arising within the undescended testis.
22. An increased risk of having benign and malignant tumors as well as leukemia and lymphoma (Miller and Rubinstein 1995).
    1. Oligodendroglioma
    2. Medulloblastoma
    3. Neuroblastoma
    4. Meningioma
    5. Pheochromocytoma
    6. Nasopharyngeal rhabdomyosarcoma
    7. Leiomyosarcoma
    8. Seminoma
    9. Embryonal carcinoma
    10. Odontoma
    11. Choristoma
    12. Dermoid cyst
    13. Pilomatrixomas (Rokunohe et al. 2016)

Diagnostic Investigations

1. Developmental evaluation
2. Echocardiography for cardiac defects
3. Ophthalmologic examination
4. Renal ultrasound
5. Voiding cystourethrogram
6. Hearing evaluation
7. EEG (Giacobbe et al. 2016)
    1. Normal (24%)
    2. Interictal abnormalities (76%)

1. Spikewave and polyspikewave generalized and spike
2. Spikewave in fronto-central and/or temporal regions
3. Monomorphic activity (33%)

8. Radiography
   1. Hands
      1. Broad thumbs (Hennekam et al. 1990b)
      2. Broad first distal phalanx
      3. Broad first ray
      4. Duplicated first distal phalanx
      5. Delta-shaped proximal phalanges of the thumbs
      6. Mushroom-shaped distal phalanges
      7. Angulation of the distal phalanges
      8. Thin tubular bones
      9. Delayed bone age (74%)
   2. Feet
      1. Broad halluces (Hennekam et al. 1990b).
      2. Broad first distal phalanx.
      3. Broad first ray.
      4. Duplicated first distal phalanx.
      5. Duplicated first proximal and distal phalanges.
      6. Delta-shaped first proximal phalanx. A duplicated longitudinal bracketed epiphysis ("kissing delta" phalanx) always involves the proximal phalanx of the great toe (Wood and Rubinstein 1999).
      7. Angulation deformity of the hallux.
      8. Mushroom-shaped distal phalanges.
      9. Very small distal phalanges.
      10. Thin tubular bones.
      11. Protruding calcaneus.
      12. Synostosis of cuneiform ossicles.
      13. Proximally split fifth metatarsal bone.
   3. Limbs
      1. Thin tubular bones
      2. Fractures
      3. Patella luxations
   4. Spine
      1. Cervical hyperkyphosis
      2. Lumbar hyperlordosis
      3. Scoliosis
      4. Spina bifida occulta: cervical or lumbosacral
      5. Spondylolisthesis
      6. Irregular thoracic endplates
   5. Skull
      1. Microcephaly
      2. Absent sinus frontalis
      3. Deviated nasal septum
      4. Steep skull base
      5. Abnormally shaped sella turcica
      6. Foramina parietal permagna
      7. Prominent digital marking
   6. Thorax
      1. Narrow thoracic aperture
      2. 11 ribs
      3. Fusion of ribs
      4. High diaphragm
   7. Pelvis
      1. Small iliac wings
      2. Flaring iliac wings
      3. Irregularly formed acetabulum
      4. Symphysiolysis
9. MRI (Giacobbe et al. 2016)
   1. Corpus callosum dysmorphism (from mild to severe) (74%)
   2. White matter hyperintensity (63%)
10. Diagnosis of Rubinstein-Taybi syndrome
    1. Made primarily by clinical examination
    2. Confirmed by the presence of microdeletion
11. Cytogenetic analysis: chromosome abnormalities observed in about 10% of patients (Breuning et al. 1993; Blough et al. 2000; Petrij et al. 2000b)
    1. FISH analysis with RT1 probe (McGaughran et al. 1996) and cosmids from the *CBP* region to detect chromosome 16p13.3 microdeletion (Petrij et al. 2000a)
    2. Chromosome abnormalities
       1. t(2;16)(p13.3;p13.3)
       2. t(7;16)(q34;p13.3) (Tommerup et al. 1992)
       3. Inv(16)(p13.3q13)
12. Clinical testing of *CREBBP* gene: available clinically
    1. Fluorescent in situ hybridization (FISH) probes.
       1. Specific for chromosome region 16p13.3

2. Containing regions of the cyclic AMP-responsive element-binding protein gene (*CBP* gene)
3. Microdeletions identified in approximately 10% of patients by five cosmid probes containing almost the entire gene

2. Sequence analysis/mutation scanning available clinically detects *CREBBP* mutation in another 30–50% of affected individuals.
3. Deletion/duplication analysis using array CGH or quantitative multiplex fluorescent-PVR.
4. Whole exome sequencing can be successfully applied as a tool for clinical differentiation of overlapping RST phenotypes (Kamenarova et al. 2016).

13. Clinical testing of *EP300* gene: available clinically
    1. *EP300* mutations available clinically can identify approximately 3% of affected individuals.
    2. Deletion/duplication analysis.

Genetic Counseling

1. Recurrence risk (Berry 1987; Hennekam et al. 1990a; Baxter and Beer 1992).
    1. Patient's sib: Accumulating data suggest a recurrence risk of approximately 0.5–1.0% for parents of a child with RTS due to gonadal mosaicism, exceeding the so far empiric estimated risk of 0.1% for siblings (Chiang et al. 2009; Bartsch et al. 2010)
    2. Patient's offspring: as high as 50%, particularly in individuals with deletions.
    3. Germline mosaicism (Tajir et al. 2013).
        1. Chiang et al. reported a family with two affected siblings with the same CREBBP mutation. This mutation was not found in the blood and saliva DNA samples from the parents, suggesting the mechanism of germline mosaicism (Chiang et al. 2009).
        2. The second report of the recurrence of RSTS with CREBBP mutation in non-twin siblings whose parents are unaffected. It confirms that germ cell mosaicism is a cause of familial recurrence of RSTS with impact on genetic counseling.
        3. Many clinical geneticists and genetic counselors give a recurrence risk of about 1% for RSTS in a family with an obvious sporadic case of RSTS in a child (similar to the situation in many other diseases that occur mostly or exclusively as a consequence of de novo mutation events) (van Belzen et al. 2011).
2. Prenatal diagnosis.
    1. 3D ultrasonography (Bedeschi et al. 2014)
        1. Broad thumb
        2. Facial anomalies: broad nasal bridge and tip with columella extending below the nasal alae, long philtrum
    2. Possible for fetuses at risk on fetal cells obtained by amniocentesis or chorionic villus sampling, provided the disease-causing *CREBBP* or *EP300* mutation or deletion in an affected family member is known (Stevens 2014)
3. Preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family (Stevens 2014).
4. Management (Wiley et al. 2003).
    1. Early intervention programs
        1. Physical therapy
        2. Occupational therapy
        3. Speech therapy
    2. Management of gastroesophageal reflux
    3. Prophylaxis for subacute bacterial endocarditis for patients at risk
    4. Requires assistance and training in self-help skills but can become self-sufficient in most self-help areas such as feeding, dressing, and toileting
    5. Special education
    6. Behavioral modification
    7. Syndrome-specific growth charts can be used in managing problems related to growth in RTS individuals (Beets et al. 2014)

8. Surgery to correct a delta phalanx deformity (Wood and Rubinstein 1987)
9. Caution with general anesthesia in children (Stirt 1981; Karahan et al. 2016)
    1. Challenging to intubate due to airway anomalies.
        1. Relatively anterior position of the larynx
        2. Easily collapsible laryngeal wall
    2. Important to intubate due to the high risk of aspiration during induction and emergence.
    3. Presence of skeletal anomalies.
    4. Cardiac arrhythmia may result from use of cardioactive drugs.
        1. Atropine
        2. Neostigmine
        3. Succinylcholine
        4. Suxamethonium
    5. Control of a difficult airway and difficult intubation in terms of anesthesia management is the most important problem in patients with RTS because of their abnormal anatomical structures. Therefore, it is necessary to prepare for difficult ventilation and intubation prior to anesthesia. Because succinylcholine, neostigmine and atropine will increase the risk of arrhythmia, particularly in patients with heart defects, the use of a rocuronium-sugammadex combination may be a good alternative.

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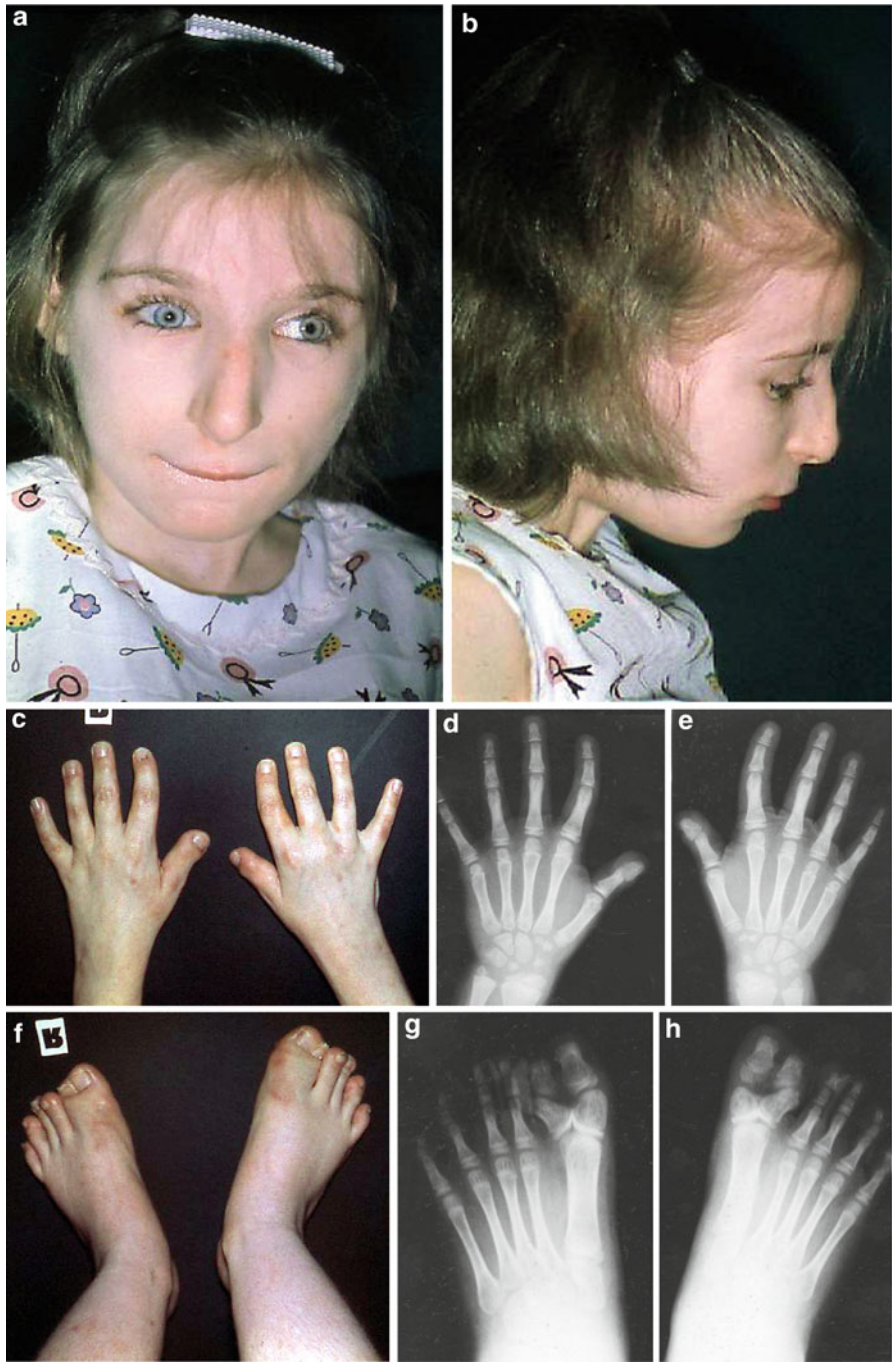

Fig. 1 (continued)

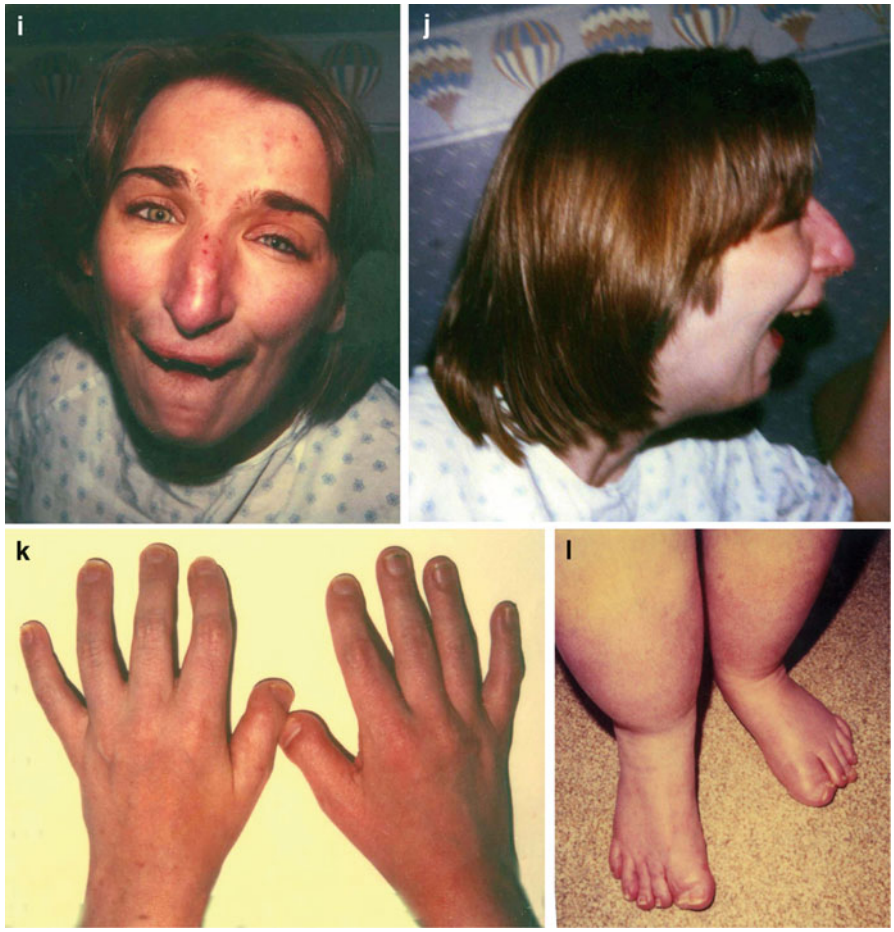

Fig. 1 (**a**–**l**) A patient with Rubinstein-Taybi syndrome at different ages (childhood (**a**–**h**) and adulthood (**i**–**l**)) showing typical facial appearance (prominent beaked nose with the columella below the alae nasi) (**a**, **b**, **i**, **j**), broad thumbs (**c**, **k**), and broad/bifid great toes (**f**, **l**), which are illustrated by radiographs (**d**, **e**, **g**, **h**)

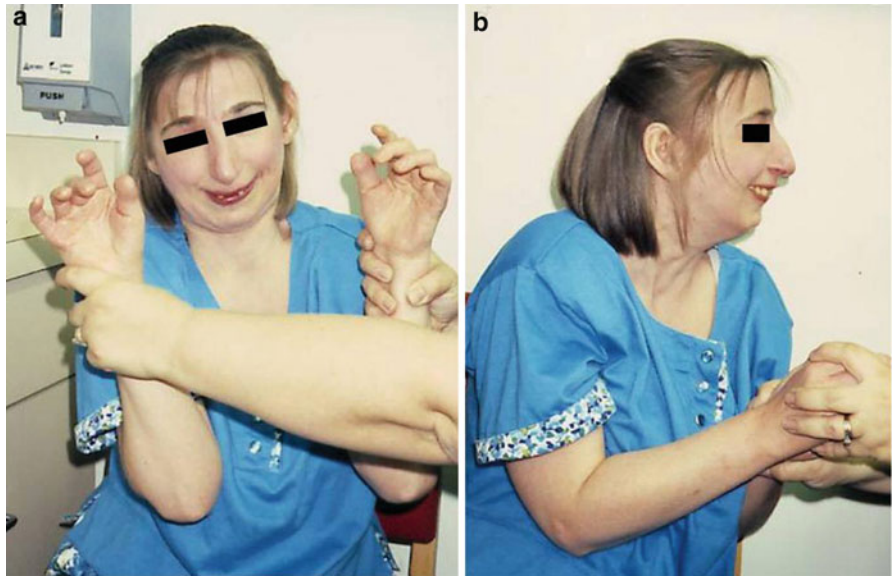

Fig. 2 (**a**, **b**) An adult with Rubinstein-Taybi syndrome showing the characteristic facies and broad thumbs

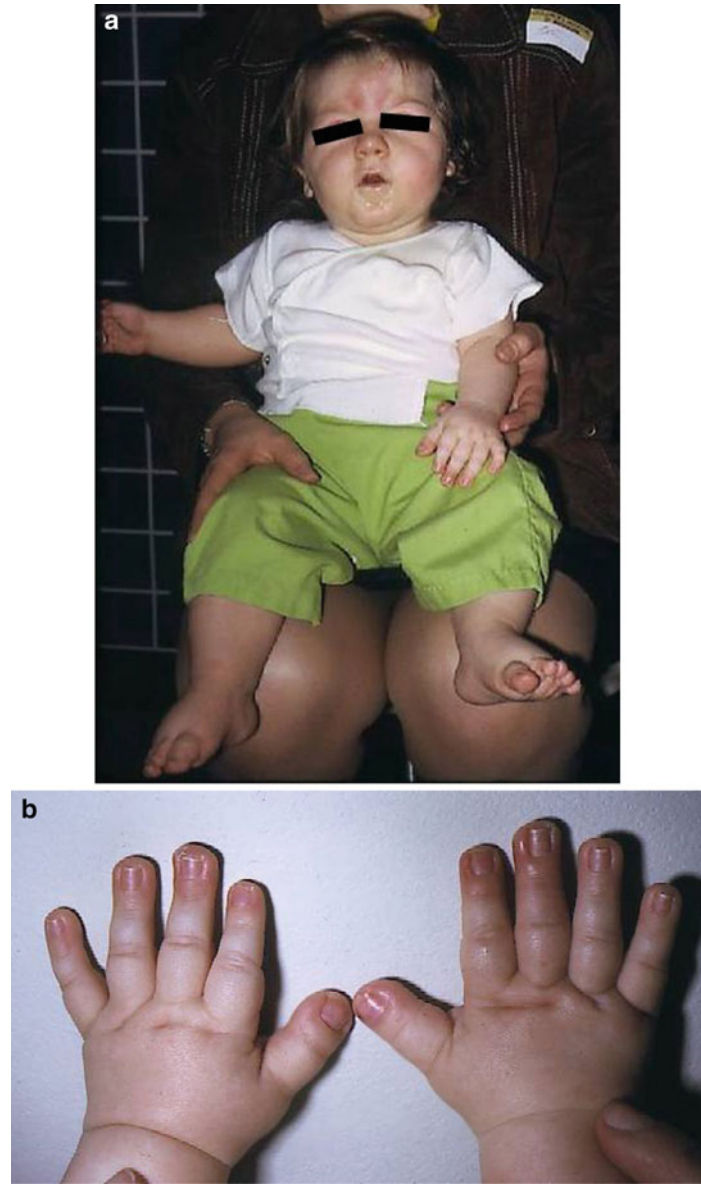

Fig. 3 (**a**, **b**) A young patient with Rubinstein-Taybi syndrome showing characteristic facies (**a**), broad thumbs (**b**), and great toes

Saethre-Chotzen Syndrome

Contents

Saethre (1931) in *1931* and Chotzen (1932) in *1932* separately described a group of patients with cranial vault dysmorphology ("acrocephaly"), skull asymmetry, and incomplete simple syndactyly of the index and middle fingers and the third and fourth toes.

Saethre-Chotzen syndrome (SCS) is one of the more common forms of syndromic craniosynostosis. Its prevalence was estimated to range from 1:25,000 to 1:50,000, approximately the same prevalence as Crouzon syndrome.

Synonyms and Related Disorders

Acrocephalosyndactyly, Type III; Acrocephaly, skull asymmetry, and mild syndactyly; Chotzen syndrome

Genetics/Basic Defects

1. An autosomal dominant disorder with high penetrance and wide variable expressivity (Foo et al. 2009). TWIST1 deletions and intragenic mutations manifest as either mild or severe craniofacial deformities.
2. A variety of mutations, including missense and nonsense mutations (el Ghouzzi et al. 1997), small insertions, duplications, and deletions (Gripp et al. 2000; Chun et al. 2002) on the *TWIST* gene, which was mapped at 7p21, lead to heterogeneous symptoms of the syndrome.
3. Increased risk for developmental delay in Saethre-Chotzen syndrome (SCS) is associated with TWIST deletions (Cai et al. 2003).
4. Strikingly, it was found that all Saethre-Chotzen syndrome patients with large genetic deletions, encompassing the *TWIST* gene and extending onto chromosome 7p, had mental retardation, a rare feature in the syndrome (Johnson et al. 1998; Zackai and Stolle 1998; Chun et al. 2002).
5. A patient with SCS, a large TWIST/7p deletion, and postnatal onset of craniosynostosis (de Heer et al. 2004).
6. A new stop codon mutation in the TWIST1 gene in SCS associated with renal cell carcinoma in childhood (Seifert et al. 2006).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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7. Notable intrafamilial phenotypic variability in a large family with Q28X TWIST mutation (Dollfus et al. 2002).
8. Patients with characteristics of Saethre-Chotzen syndrome but without *TWIST* mutations have been described (de Heer et al. 2005):
    1. Some of these patients harbored the *FGFR3* P250R mutation, nowadays considered to cause a distinct and unique craniosynostosis syndrome, Muenke syndrome (Muenke et al. 1997; Graham et al. 1998).
    2. Germline mutation in the FGFR3 gene in a TWIST1-negative family with Saethre-Chotzen syndrome and breast cancer (Sahlin et al. 2009).

Clinical Features

1. Widely variable phenotype
2. Craniosynostosis (premature fusion of one or more sutures of calvarium) (Paznekas et al. 1998):
    1. Coronal suture (unilateral or bilateral): most commonly affected:
        1. Bilateral (59% of cases)
        2. Unilateral (23% of cases)
    2. Other cranial sutures (21% of cases), such as sagittal, lambdoid, and metopic and even pansynostosis, may be involved:
        1. Can undergo premature fusion
        2. Reports of affected individuals with no evidence of pathologic suture
    3. Often presents with an abnormal skull shape:
        1. Brachycephaly (short, broad skull)
        2. Acrocephaly (tall skull)
    4. A new and unique pattern of sutural fusion "peace sign synostosis" characterized by synostosis of the metopic, bicoronal, and sagittal sutures and associated with abnormalities of the TWIST1 gene known to be associated with Saethre-Chotzen syndrome (Tahiri et al. 2015)
3. Other craniofacial features:
    1. Facial asymmetry (the most conspicuous facial feature), particularly in individuals with unicoronal synostosis
    2. Low frontal hairline
    3. Ptosis of the eyelids: often results from a defective functioning or agenesis of the levator palpebrae muscle
    4. Downslanting of the palpebral fissures
    5. Epicanthal folds
    6. Strabismus
    7. Amblyopia
    8. Midface hypoplasia
    9. A broad nose with depressed nasal bridge
    10. Characteristic appearance of the ears: low-set and rotated ears with small pinna with a prominent superior and/or inferior crus
4. Limb anomalies:
    1. Brachydactyly: most frequent finding
    2. Cutaneous syndactyly of the second and third digits of the hands and feet: highly variable degree but nearly diagnostic in the presence of limb anomalies
    3. Clinodactyly of the fifth fingers
    4. Transverse palmar creases often present
    5. Broad digit I of the feet
    6. Hallux valgus
    7. Duplicated distal phalanx of the hallux
    8. Triangular epiphyses of the hallux
5. Other variable clinical features:
    1. Short stature.
    2. Presence of foramina parietalia permagna (bony defects on both sides of the parietal suture exceeding 1 cm in diameter).
    3. Impressiones digitatae, considered to be an indicator of raised intracranial pressure, often recorded without the presence of increased intracranial pressure.
    4. Conductive, mixed, and profound sensorineural hearing loss (Lee et al. 2002).
    5. Most patients with Saethre-Chotzen syndrome had hearing loss at some point during childhood. This was typically mild and correlated with middle ear abnormality and eustachian tube dysfunction. Usually, the hearing deficit resolved. Early mischaracterization of mixed hearing loss or conductive hearing loss as sensorineural hearing loss was common (Rosen et al. 2011).
    6. Ocular hypertelorism.

7. Occasional blepharophimosis.
8. Lacrimal duct stenosis.
9. Maxillary hypoplasia.
10. High-arched and/or cleft palate.
11. Congenital heart defects.
12. Vertebral fusion.
13. Radioulnar synostosis.
14. Increased risk of cancers (breast (Sahlin et al. 2007), kidney).

6. Intelligence:
   1. More commonly normal intelligence
   2. Significant learning disability usually noted in affected individuals with microdeletion in 7p21 but severe delay or mental retardation is not typical
7. Family history of abnormal skull shape and/or a combination of other physical findings, usually present in SCS; however, craniosynostosis is not an obligatory finding (some affected relatives may not have been diagnosed with a craniosynostosis syndrome).
8. Differential diagnosis (Gallagher et al. 2012):
   1. Muenke syndrome (Kress et al. 2006):
      1. Characterized by "nonsyndromic" coronal craniosynostosis caused by the specific point mutation p.Pro250Arg in *FGFR3* (encoding fibroblast growth factor receptor-3)
      2. Shares features with Saethre-Chotzen syndrome (SCS)
      3. Individuals with *TWIST1* mutations distinguished from those with the *FGFR3* p.Pro250Arg mutations from a recent study of 39 pedigrees (71 affected individuals) ascertained on the basis of coronal synostosis with the following clinical features:
         1. A low frontal hairline
         2. Ptosis
         3. Small ears
         4. Parietal foramina
         5. Interdigital webbing
         6. Hallux valgus or broad great toe with bifid distal phalanx
   2. Isolated unilateral coronal synostosis:
      1. Represents coronal suture fusion with no evidence of other malformations.
      2. Approximately ten times more common than SCS. Coronal synostosis is the second most common form of single-suture fusion after sagittal synostosis.
      3. Facial asymmetry resembling SCS can result from untreated or incompletely treated isolated unilateral coronal synostosis.
   3. Baller-Gerold syndrome (BGS):
      1. Characteristic clinical features:
         1. Coronal craniosynostosis manifesting as abnormal shape of the skull (brachycephaly) with ocular proptosis and bulging forehead
         2. Radial ray defect manifesting as oligodactyly (reduction in number of digits), aplasia or hypoplasia of the thumb, and/or aplasia or hypoplasia of the radius
         3. Growth retardation
         4. Poikiloderma
      2. *RECQL4*: the only gene currently known to be associated with BGS.
      3. Clinical findings overlap with those of Rothmund-Thomson syndrome and Rapadilino syndrome, also caused by mutations in *RECQL4*.

Diagnostic Investigations

1. Diagnosis primarily based on clinical findings
2. Radiographic abnormalities:
   1. Pathognomonic signs for SCS are the triangular shape of the epiphysis and duplicated distal phalanx of the hallux. Calcaneocuboid fusion was detected in Muenke-type mutation (MTM) only. These signs may be helpful in the differentiation of SCS from Muenke-type MTM (Trusen et al. 2003).
   2. Vertebral fusion was present in 9 of the 20 patients (Anderson et al. 1997).
   3. Fusion of both the vertebral bodies and the posterior elements.
   4. C2–3 was the level most commonly involved.

5. Progressive vertebral fusions during childhood.

3. Molecular genetic testing:
   1. Identification of *TWIST* microdeletion by array CGH (Cho et al. 2013).
   2. *TWIST1* mutations: identified in 46–80% of affected individuals using a combination of deletion/duplication analysis and sequence analysis (positive in 46–80% of cases).
   3. Consider testing for *FGFR3* (p. Pro250Arg) mutation if no *TWIST1* mutation is identified in an individual with a presumed diagnosis of Saethre-Chotzen syndrome since clinical findings of Muenke syndrome overlap with Saethre-Chotzen syndrome.
4. Cytogenetic analysis:
   1. A diagnostic approach to identifying submicroscopic 7p21 deletions in Saethre-Chotzen syndrome: Fluorescence in situ hybridization and dosage-sensitive Southern blot analysis (Gripp et al. 2001)
   2. A chromosome translocation or inversion involving 7p21 or ring chromosome 7 reported in occasional patients with atypical findings, including developmental delay

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib:
      1. A 50% risk if a parent is also affected
      2. An apparently low risk if the parents are clinically unaffected and do not have a *TWIST1* mutation:
         1. Spontaneous mutation rate if the proband represents de novo mutation.
         2. Possible parental germ line mosaicism exists although no instances of germ line mosaicism have been reported.
   2. Patient's offspring: a 50% recurrence risk for an affected individual to have an affected offspring
2. Prenatal diagnosis:
   1. Possible for pregnancies at increased risk if the disease-causing mutation has been identified in the family
   2. Prenatal diagnosis of a 7p15-p21 deletion encompassing the TWIST1 gene involved in Saethre-Chotzen syndrome (Spaggiari et al. 2012)
3. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the disease-causing mutation has been identified (Gallagher et al. 2012).
4. Management:
   1. Cranioplasty in the first year of life:
      1. To prevent progressive facial asymmetry in those with asymmetric coronal fusion
      2. To prevent increased intracranial pressure (ICP) in those with multiple sutural synostosis
      3. To prevent developmental delay and impaired vision secondary to increased intracranial pressure
   2. Reoperation for high rate of recurrent elevated intracranial hypertension in TWIST1-confirmed Saethre-Chotzen syndrome (Bartlett and Foo 2009)
   3. Patients with TWIST1-confirmed Saethre-Chotzen syndrome had a reoperation rate of 65% for Whitaker class III and IV surgical outcome, and 59% of these patients required a secondary intracranial procedure for recurrent supraorbital retrusion (Foo et al. 2009).
   4. Midfacial surgery needed for dental malocclusion, swallowing difficulties, and respiratory problems.
   5. Cleft palate surgery usually follows cranioplasty.
   6. Orthodontic treatment and/or orthognathic surgery as needed near the completion of facial growth; developmental intervention.
   7. Routine treatment of hearing loss.
   8. Prevention of secondary complications:
      1. Attention to possible cervical vertebral instability secondary to vertebral anomalies
      2. Periodic ophthalmologic evaluation for chronic papilledema

3. Brain imaging in later life for evidence of increased intracranial pressure
4. Routine evaluation for facial asymmetry, psychomotor development, and hearing loss

9. Variability of the clinical spectrum of craniofacial disorders associated with TWIST1 abnormalities. It is important to note that the Saethre-Chotzen syndrome caused by microdeletion is generally characterized by a mental disability. However, the postoperative psychomotor development of the child considered was within the normal limits (di Rocco et al. 2015).

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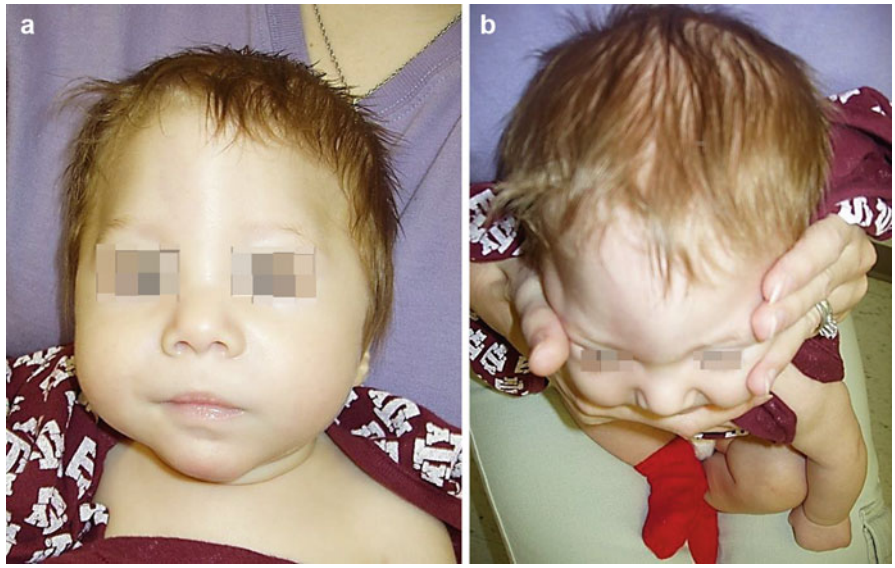

Fig. 1 (**a**, **b**) A 2-month-old boy was evaluated for trigonocephaly (metopic suture premature synostosis)

Fig. 2 His mother was diagnosed to have Saethre-Chotzen syndrome clinically. Preoperatively, she was noted to have marked forehead asymmetry, retrusion of the right side of the supraorbital region, disproportion of the orbits with the right orbit higher, and temporal fossa hollowness. The diagnosis was confirmed molecularly by detection of a *TWIST* gene mutation (c.396-416 dup mutation, i.e., c.417ins21) which has been previously detected in other Saethre-Chotzen syndrome patients

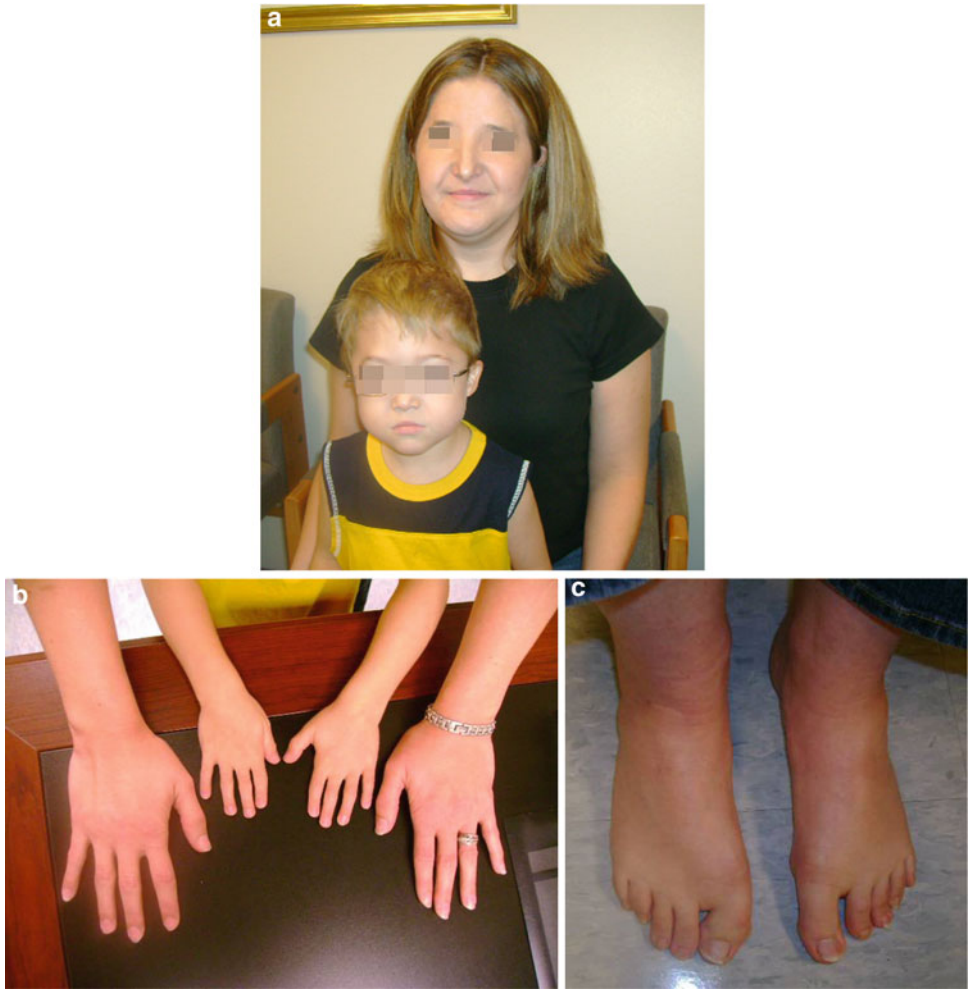

Fig. 3 (**a**–**c**) Follow-up visit of the child and the mother

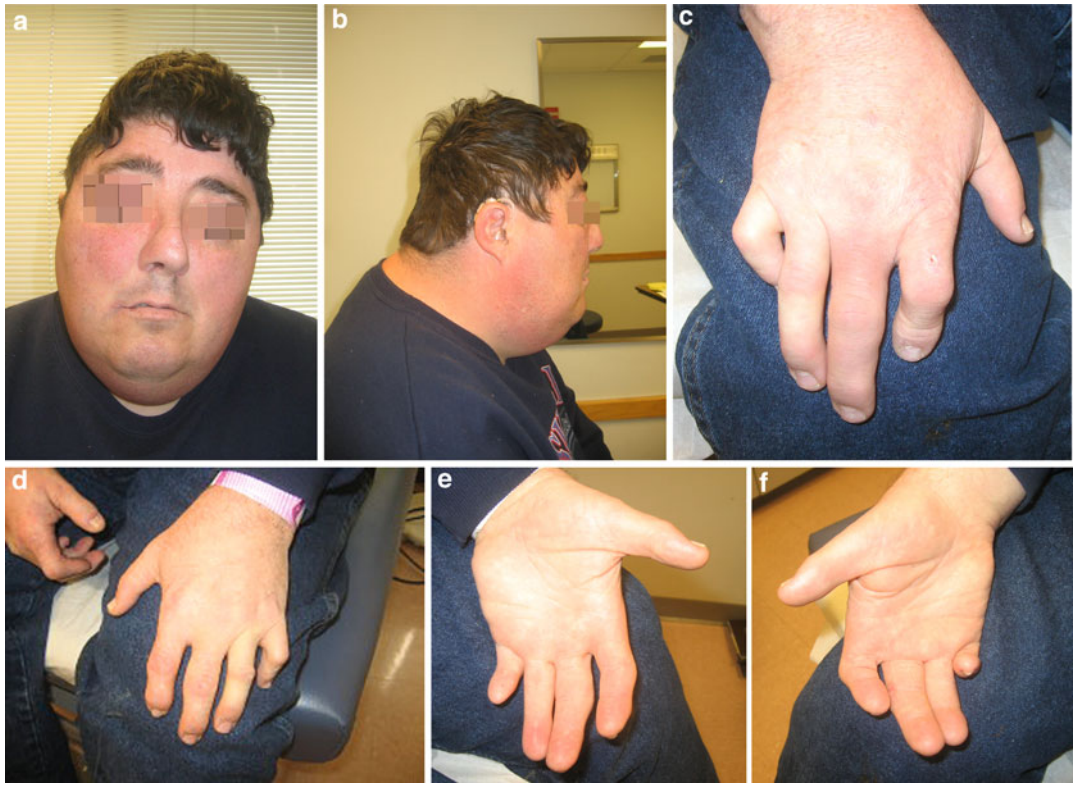

Fig. 4 (**a**–**f**) A 42-year-old man (**a**, **b**) was diagnosed to have Saethre-Chotzen since childhood. He was noted to have a brachycephalic skull with midfacial hypoplasia, a high forehead with a low hairline, a small cranial vault, asymmetric face with a curved nose, marked ptosis, down turned upper lip, underbite, repaired cleft palate, an underbite, low-set ears with prominent crus, cutaneous syndactyly, and contractures at the proximal interphalangeal joints in the second and fifth digits bilaterally (**c**–**f**), a single flexion crease in the fifth digit of both hands with unusual palmar creases, short toes with broad great toes bilaterally, minimal cutaneous syndactyly of toes 2–3 bilaterally, and bilateral hearing aids in place. In addition, he had developmental delay, seizures, heart murmur, and toeing-in requiring braces in childhood, keratoconus requiring corneal transplants, hypertension, and colon polyps and spastic colon. Southern blot analysis of genomic DNA showed complete deletion of one allele of the *TWIST* gene. Such mutations are diagnostic for Saethre-Chotzen syndrome

Sagittal Craniosynostosis Associated with Chromosome Abnormalities with a Brief Review on Craniosynostosis

Contents

Craniosynostosis, defined as the premature closure of >1 cranial suture with an estimated prevalence of 1 in 2,000–3,000 births (Cohen 2000), comprises a heterogeneous group of birth defects, including isolated forms and syndromic cases.

Sagittal craniosynostosis (or synostosis), usually an isolated congenital abnormality in otherwise normal infants, is characterized by scaphocephaly. It is characterized by a scaphocephalic appearance of the cranial vault, with a long, narrow head, widest in the temporal regions and narrowing toward the top of the head, with associated ridging over the fused sagittal suture, giving the appearance of an inverted boat keel (Agrawal et al. 2006). It is the most common form of craniosynostosis with prevalence of 1 in 5,000 children, comprising approximately 50% of all craniosynostosis cases (Lajeunie et al. 1996, 2005). Rarely, when sagittal synostosis is a part of a syndrome, it can be due to a chromosome abnormality associated with multiple congenital abnormalities or due to a single-gene abnormality such as Crouzon or Carpenter syndrome, invariably associated with obvious facial or digital anomalies, with clinically evident closure of multiple sutures.

Genetics/Basic Defects

1. Classification of craniosynostosis based on suture involvement (Kimonis et al. 2007):
    1. Simple (involving one suture) or complex (involving two or more sutures)
    2. Primary (caused by an intrinsic defect in the suture) or secondary (premature closure of normal sutures because of another medical condition such as deficient brain growth)
    3. Isolated (occurring without other anomalies) or syndromic (accompanied by other dysmorphic features or developmental defects)
    4. Frequencies of the various sutures involved:
        1. Sagittal: 40–58%, etiology unknown
        2. Coronal: 20–29%, estimated one-third caused by single-gene mutations
        3. Metopic: 4–10%, etiology unknown
        4. Lambdoidal: 2–4%, etiology unknown
2. Nonsyndromic craniosynostosis (Passos-Bueno et al. 2008; Lattanzi et al. 2012):
    1. Nonsyndromic craniosynostoses are the most frequent craniofacial malformations worldwide. They represent a wide and heterogeneous group of entities, in which the dysmorphism may occur in a single (simple

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forms) or in multiple sutures (complex forms).
2. Simple forms present a higher birth prevalence and are classified according to the involved suture and to the corresponding abnormal cranial shape:
    1. Scaphocephaly (sagittal suture)
    2. Trigonocephaly (metopic suture)
    3. Anterior plagiocephaly (unilateral coronal suture)
    4. Posterior plagiocephaly (unilateral lambdoid suture)
3. Familial recurrence (Hennekam and Van den Boogaard 1990; Lajeunie et al. 1996, 1998, 2005; Cohen and McLean 2000):
    1. Nonsyndromic coronal synostosis (14%)
    2. Nonsyndromic sagittal synostosis (6%)
    3. Nonsyndromic metopic synostosis (3–9%) versus 22% in syndromic metopic synostosis
    4. Pedigrees from familial recurrence: compatible with:
        1. Autosomal dominant inheritance
        2. Autosomal recessive inheritance
        3. X-linked inheritance
4. Genetic etiology:
    1. Poorly understood
    2. *EFNA4*: The only gene that when mutated causes only nonsyndromic craniosynostosis (Merrill et al. 2006)

3. Etiologies of isolated (nonsyndromic) sagittal synostosis:
    1. Suggestions of possible genetic and environmental factors (Johnson et al. 2000; Zeiger et al. 2002; Lajeunie et al. 2005)
    2. Possible intrauterine pressure on the neurocranium on the etiology of craniosynostosis (Johnson et al. 2000; Kirschner et al. 2002)
    3. Preference for (Butzelaar et al. 2009):
        1. Male sex
        2. Twinning
        3. Prematurity
4. Etiologies of syndromic craniosynostosis (Passos-Bueno et al. 2008; Jehee et al. 2008):
    1. To date, well over 180 syndromes are associated with craniosynostosis as a major clinical feature. Mendelian and chromosomal alterations are important causative mechanisms.
    2. Mutations associated with syndromic craniosynostosis:
        1. Mutations in seven genes (*FGFR1*, *FGFR2*, *FGFR3*, *TWIST1*, *EFNB1*, *MSX2*, and *RAB23*): unequivocally associated with Mendelian forms of syndromic craniosynostosis and explain the etiology of about 30% of syndromic cases (Wilkie et al. 2007)
        2. Mutations in four other genes, *FBN1*, *POR*, *TGFBR1*, and *TGFBR2*: also associated with craniosynostosis, but not causing the major clinical feature of the phenotype and/or with an apparently low penetrance (Sood et al. 1996; Flück et al. 2004; Loeys et al. 2005)
5. Chromosome alterations in the etiology of craniosynostosis (Passos-Bueno et al. 2008):
    1. All types of chromosomal abnormalities have already been described in patients with craniosynostosis, including deletions and duplications in almost all human chromosomes.
    2. Approximately 16% of syndromic cases have been associated with chromosomal abnormalities in conventional cytogenetic studies (Cohen 2000):
        1. A high association of craniosynostosis with duplication 13q21-q34
        2. A high association of craniosynostosis with deletion 7p15-p21, 9p21-p24, and 11q23-q25 (Brewer et al. 1998, 1999)
        3. Deletion and/or duplication 1p36 (Gajecka et al. 2005; McDonald-McGinn et al. 2005)
    3. Jehee et al. (2008) screened 45 patients with craniosynostotic disorders with a variety of methods including conventional karyotype, microsatellite segregation analysis, subtelomeric multiplex ligation-dependent probe amplification, and array-based comparative genome hybridization with the following results:
        1. Causative abnormalities were present in 42.2% (19/45) of the samples.

2. 27.8% (10/36) of the patients with normal conventional karyotype carried submicroscopic imbalances.
3. Sagittal synostosis:
    1. Del(1p)
    2. Dup(5)(p15.1-p14.1)
    3. Dup17q
    4. Dup(X)(p11.23)
    5. Association of specific chromosomal 19p microdeletions (19p13.12–13.2) and cranial suture dysmorphology: sagittal craniosynostosis, micrognathia, seizure disorder, hypotonia, and developmental delay (Lyon et al. 2015)
4. Metopic synostosis:
    1. Del(1q)
    2. Del(1q)/dup(15q)
    3. Del(9)(p22.3p24.2)
    4. Del(9q)/dup(17q)
    5. Del(11)(q23.3)
    6. Del(X)(p11.3)
    7. Del(Y)(q11)
    8. Der(9)t(9;4)(p22.3;q34)
    9. Der(9)t(9;?)(p21.3;?)
    10. Dup(3)(p25.2)
    11. Dup(6)(q27)
    12. Dup(15)(q13.2)
    13. Dup(22)(q11.23)
    14. Dup(X)(p22.3)
5. Bilateral coronal synostosis: Dup(3)(q26.33)
6. Bilateral coronal and metopic synostosis: Dup(X)(q22.2)

6. Chromosome abnormalities in children with craniosynostosis (Wilkie et al. 2010):
    1. 47,XX,+mar.ish der(2)(wcp2+)[4]/46,XX[30] (metopic suture)
    2. 46,XY,der(12)t(3;12)(p26.3;p13.33)mat (metopic suture)
    3. 46,XY,der(10)t(3;10)(q2?7;q2?6.1) (R + L squamotemporal sutures)
    4. 46,XY,del(4)(q25q28.2) (sagittal → multiple sutures)
    5. 46,XY,add(4)(q32.3q33) (sagittal suture)
    6. 46,XX,der(7),t(6;7)(p21;q36) (multiple sutures)
    7. 46,XY,t(7;8)(p21;q13) L (coronal suture)
    8. 46,XX,del(9)(p22.1) (metopic suture)
    9. 46,XY,del(11)(q23.3) (metopic suture)
    10. 46,XX,del(17)(q21.31) (sagittal suture)
    11. 47,XX,+21 (sagittal, R coronal sutures)
    12. 46,XX,dup(22)(q11.21q11.23) (sagittal, R coronal sutures)
    13. 46,XY,inv(22)(p1?1.2q13?.1) (metopic, bicoronal sutures)
7. Selected chromosomal aberrations observed in simple craniosynostosis patients (Lattanzi et al. 2012):
    1. 7p21 μdel (karyotype analysis + FISH): coronal suture
    2. 46,XX,del15q15-22.1 (46,XX,del15q15-22.1): (coronal suture)
    3. 47,XY,+mar[14]/46,XY[6] (karyotype analysis + FISH): coronal suture
    4. 46,XY,t(7;8)(p21;q13) (karyotype analysis): coronal suture
    5. 22q11.2 deletion (karyotype analysis) coronal/metopic sutures
    6. 1p36 μdup (FISH + CGH): metopic suture
    7. 46,XY,der(9)t(9;4)(p22.3;q34) (FISH): metopic suture
    8. 11q23.3-qter μdel (FISH): metopic suture
    9. 6p12.3-p21.1 μdup (CGH): metopic
    10. 46,XX, t(5;13)(q33.3;q34) (karyotype analysis + FISH): metopic suture
    11. 46,XX,der(17)t(5;17)(q35.1;p13.3) (karyotype analysis + CGH): metopic suture
    12. 46,XY,inv(22)(p1?1.2q13?.1) (karyotype analysis): metopic/coronal sutures
    13. 46,X,der(Y)t(Y:1)(q12;p36.3) (karyotype analysis + FISH): metopic/sagittal sutures
    14. 46,XX,der(1)t(Y;1)(q12;p36.3) (karyotype analysis + FISH): metopic/sagittal sutures
    15. 7p21.1 μdel (FISH): metopic/sagittal sutures
    16. 46,XX,del(17)(q21.31) (CGH): sagittal suture
    17. 46,XX,dup(22)(q11.21q11.23) (CGH): sagittal/coronal sutures
8. Sagittal synostosis associated with chromosome abnormalities (Figs. 1–5):
    1. Our patient 1: del(4)(q26 → q28.3ter) and del(13)(q21.2 → q21.31) (Fig. 1)

2. Our patient 2: del(13)(q33.1 → qter) and dup(17)(q25.3 → qter) [der(13)(13)(t13;17)(q33.1;q25.3)] (Figs. 3–4)
3. Our patient3: t(4;18)(p12p11.2) (Fig. 5)

9. Multiple craniosynostosis involving sagittal and other sutures associated with chromosome abnormalities:
   1. Sagittal and metopic synostosis (Hiraki et al. 2006): 46,X,der(Y)(t(Y;1)(q12;p36.3) inherited from father [46,X,t(Y;1)(q12;p36.3)]
   2. Sagittal and bilateral lambdoid synostosis (called craniofacial dyssynostosis, "Mercedes Benz" syndrome, or nonsyndromic multisutural synostosis) (Hing et al. 2009):
      1. Case reported by Shiihara et al. (2004), sagittal and metopic suture synostosis:
         1. An unbalanced translocation, 46,XX, der(13)t(5;13)(q33.3;q34)mat resulting in monosomy 13 q34-qter and trisomy 5q33.3-qter.
         2. FISH analysis showed three MSX2 signals indicating the presence of three copies of the MSX2 gene.
      2. Case reported by Cohen (2000): complex rearrangement of chromosome 5, resulting in three paracentric inversions/two insertions and a duplication of 5q35 inclusive of the MSX2 gene region
      3. Case reported by Tagariello et al. (2006):
         1. A de novo-balanced translocation, t(9;11)(q33;p15).
         2. Both breakpoint regions were cloned, and the chromosome 11p15 breakpoint was noted to disrupt the *SOX6* gene between exons 6 and 7. However, the potential role of the *SOX6* gene disruption in BLSS remains undetermined.
      4. Case reported by Hing et al. (2009): an Xp11.2 deletion
   3. Sagittal, metopic, and coronary synostosis (Hiraki et al. 2008): 46,XX,der(15)(q15.2q22.1).
   4. Sagittal, metopic, lambdoid, temporal, and squamosal synostosis (Jehee et al. 2007): De novo interstitial 11q duplication [46,XY,dup(11)(q11-q13.3)(/46,XY] included the duplication of genes FGF3 and FGF4.

Clinical Features

1. Natural history of sagittal synostosis (Chatterjee et al. 2007):
   1. As the condition occurs in utero, diagnosis should be possible at birth with careful attention to the sagittal suture and the deformity that is created.
   2. If uncorrected, sagittal synostosis leads to progression of the scaphocephalic deformity which can be an esthetic problem as well as raised intracranial pressure and speech and language impairment in almost 40% of patients.
2. Clinical features of sagittal synostosis:
   1. Scaphocephaly or dolichocephaly due to growth restriction transverse to the sagittal suture resulting in a biparietally narrowed skull and continuing growth of the calvaria in the ventral-dorsal direction resulting in the elongation of the skull
   2. Variable appearance of the elongation of the skull depending on which portion of the sagittal suture is fused
   3. Ridging of the sagittal suture
   4. Frontal bossing: resulting from premature closure of the anterior portion of the sagittal suture (Jane et al. 2000)
   5. Variants of posterior sagittal synostosis (Jane et al. 2000): Closure of the posterior portion of the sagittal sutures occurs less commonly than anterior closure:
      1. Occipital knob: The occipital bone becomes the site of compensatory overgrowth because it is located distal and perpendicular to the fused suture.
      2. "Golf tee" deformity:
         1. An exaggerated form of the occipital knob, simulating a golf tee
         2. The skull is narrower posteriorly and protrudes more prominently. In addition, the unfused anterior portion of

the sagittal suture may widen the parietal bone anteriorly, accentuating the occipital narrowing.
3. Bathrocephalic deformities: an extreme consequence of premature posterior closure of the sagittal suture:
1. Characterized by the appearance of a podium in the occipital region
2. The posterior portion of the parietal bone slants inferiorly while the occipital bone juts superiorly.
6. Complete sagittal synostosis: the most extreme form of the sagittal synostosis, resulting in both anterior and posterior deformity

3. Sagittal synostosis associated with chromosome abnormalities (our cases):
1. Patient 1 (monosomies 4q and 13q):
1. Sagittal suture synostosis (palpable bonny ridge along the sagittal suture)
2. Ocular hypertelorism
3. Proptotic eyes
4. Micrognathia
2. Patient 2 (translocation 4p and 18p):
1. Sagittal synostosis (scaphocephaly)
2. Tetralogy of Fallot

4. Multiple suture synostoses (including sagittal synostosis) associated with chromosome abnormalities: wide variation of clinical features depending on the gain or loss of the chromosome(s) and chromosome segments involved. Following are some of the examples:
1. Multiple craniosynostoses involving the sagittal and metopic sutures with 1p36.3-pter trisomy (Hiraki et al. 2006):
1. Borderline mental retardation
2. Bitemporal narrowing
3. Sloping forehead
4. Blepharophimosis
5. Blepharoptosis
2. Multiple craniosynostoses involving sagittal and bilateral lambdoid sutures: Premature fusion of the sagittal and both lambdoid sutures results in a characteristic head shape with frontal bossing, turribrachycephaly, biparietal narrowing, occipital concavity, inferior displacement of the ears, and ridging of the sagittal and lambdoid sutures (Hing et al. 2009):
1. Case reported by Shiihara et al. (2004):
1. Sagittal and bilateral lambdoid sutures
2. Developmental delay
3. Atrial septal defect
4. Patent ductus arteriosus
5. Unbalanced translocation, 46,XX,der(13)t(5;13)(q33.3;q34)mat resulting in monosomy 13 q34-qter and trisomy 5q33.3-qter
6. FISH analysis demonstrated three copies of the *MSX2* gene.
2. Case reported by Cohen (2000):
1. Sagittal and bilateral lambdoid sutures.
2. Hypotonia.
3. Ventricular septal defect.
4. Coarctation of the aorta.
5. A complex rearrangement of chromosome 5 resulting in three paracentric inversions/two insertions and a duplication of 5q35 inclusive of the *MSX2* gene region.
6. MSX2 is known to play an important role in cranial bone formation as haploinsufficiency of MSX2 results in parietal skull defects and overexpression causes craniosynostosis.
3. Case reported by Tagariello et al. (2006):
1. Sagittal and bilateral lambdoid sutures.
2. Mild speech delay.
3. A de novo-balanced translocation, t(9;11)(q33;p15).
4. Both breakpoint regions were cloned, and the chromosome 11p15 breakpoint was noted to disrupt the *SOX6* gene between exons 6 and 7.
4. Case reported by Hing et al. (2009):
1. Sagittal and bilateral lambdoid sutures: frontal bossing, brachycephaly, and narrow occiput
2. Hypotonia at birth
3. Progressive apnea
4. Seizures

5. Expired at 4 months of age
6. Xp11.22 deletion: clinical significance unknown

3. Multiple craniosynostoses involving the sagittal, metopic, and coronary sutures:
   1. Cases reported by Hiraki et al. (2008) with a de novo 15q15q22 deletion:
      1. Hypotonia
      2. Profound growth and psychomotor retardation
      3. Craniofacial dysmorphic features (bow-shaped eyebrows, downslanting palpebral fissures, mild blepharophimosis, strabismus, nystagmus, optic nerve atrophy, low-set ears with stenotic bilateral ear canals, bulbous nasal tip, hypoplastic alae nasi, upturned nostrils, high-arched palate, bifid uvula, epiglottic hypoplasia, a thin upper lip, and tucked-in lower lip)
      4. Other anomalies (pectus excavatum, accessory nipples, small hands and feet, long fingers, abducted and proximally placed thumbs, clinodactyly of the fifth fingers, four finger creases, overlapping third and fifth over fourth toes, metatarsus adductus)
4. Sagittal, metopic, lambdoid, temporal, and squamosal synostosis (Jehee et al. 2007): de novo interstitial 11q duplication:
   1. Developmental delay
   2. Marked trigonocephalic, turricephalic, and scaphocephalic-shaped skull
   3. Blue sclerae
   4. Nystagmus
   5. Strabismus
   6. Short neck
   7. Short philtrum
   8. Supernumerary maxillary lateral incisor
   9. PDA
   10. Patent foramen ovale
   11. Seizures
   12. Recurrent infections
   13. Mild brachydactyly of the finger
   14. Clinodactyly of the fifth fingers
   15. Slightly broad thumbs
   16. Shortened distal phalanges
   17. Hypoplastic nails

Diagnostic Investigations

1. Radiographic study to demonstrate sagittal synostosis
2. Three-dimensional computed tomographies to discern the characteristics of sagittal synostosis (David et al. 2009):
   1. Anterior type: characterized by a transverse retrocoronal band.
   2. Central type: Prematurely fused sagittal suture is marked by a prominent heaped-up appearance.
   3. Posterior type: a significantly elongated occiput as the most striking radiographic feature.
   4. Complex type: combined characteristics of anterior, central, and posterior types.
3. Conventional karyotype
4. Microsatellite segregation analysis
5. Subtelomeric multiplex ligation-dependent probe amplification
6. Array-based comparative genome hybridization

Genetic Counseling

1. Recurrence risk (Kimonis et al. 2007; Wilkie et al. 2007):
   1. Patient's sib
      1. "Truly nonsyndromic craniosynostosis": thought to be a multifactorial trait with recurrent risk around 5% for coronal and around 1% for sagittal suture fusion
      2. Autosomal dominant craniosynostosis:
         1. Common in craniosynostosis syndromes with a relatively high proportion of new mutations
         2. Genetic counseling for the parents of a child with an apparently new mutation: difficult by uncertainties over the recurrence risk attributable to occult germ line mosaicism in a parent

3. Negative parental mutation testing: still leaves a small (<1%) risk of recurrence because of potential gonadal mosaicism
3. Craniosynostosis associated with chromosome abnormality: recurrent risk depends on whether a de novo event or a parent is a carrier of the abnormality.

2. Patient's offspring:
1. "Truly nonsyndromic craniosynostosis": thought to be a multifactorial trait with recurrent risk around 5% for coronal and around 1% for sagittal suture fusion.
2. Autosomal dominant craniosynostosis: Mutation carriers have a 50% risk of passing the affected gene to their offspring.
3. Chromosome aneuploidy: depends on the type and complexity of the chromosome rearrangement.

2. Prenatal diagnosis. Craniosynostoses are rarely detected in utero (Fjortoft et al. 2007):
1. Prenatal ultrasonography of the cranial suture:
1. Most craniosynostoses are missed during routine US screening examination.
2. Most of the prenatal diagnoses made have been severe syndromic synostosis elide mainly on cranial deformity and associated abnormalities, in particular limb malformations. Examples include:
1. Pfeiffer syndrome
2. Apert syndrome
3. Saethre-Chotzen syndrome
2. Prenatal MRI imaging of the cranial suture:
1. MRI cannot directly visualize calvarial sutures.
2. Diagnostic when craniosynostosis is suspected by prenatal ultrasound examination.
3. Advantage of MRI: allows detection and provides better assessment of brain abnormalities which may be associated with craniosynostosis.
3. Prenatal 3-dimensional CT: useful as it allows direct visualization of the cranial vault sutures, which is not possible with MRI
4. Prenatal testing strategies:
1. Chorionic villus sampling (typically at 10–14 weeks gestation)
2. Amniocentesis (typically at 16–18 weeks gestation)
3. Prenatal chromosome testing for syndromic craniosynostosis due to chromosome abnormality
4. Molecular genetic testing of syndromic craniosynostosis due to single-gene mutation
5. Preimplantation genetic diagnosis:
1. A valuable option available for those who have been identified as carriers of the mutation but are interested in ensuring that their children are unaffected without making the decision to terminate a pregnancy in the event of a positive prenatal diagnosis.
2. Molecular testing enables the selection of only genetically normal embryos for use in in vitro fertilization.

3. Management (Adamo and Pollack 2009; Jimenez et al. 2008):
1. Goals of surgery in sagittal synostosis:
1. Eliminate the biparietal constriction caused by the fused sagittal suture.
2. Increase the width of the skull.
3. Decrease the anterior-posterior (AP) length of the skull.
2. In cases of mild scaphocephaly:
1. Perform strip or extended craniectomies to remove the sagittal suture using either open or endoscopic techniques
2. Then rely on future cranial vault remodeling with brain growth
3. In cases of more marked scaphocephaly:
1. Extend the craniectomy to follow along the lambdoid sutures.
2. Add bilateral parietal bone wedge osteotomies.
4. The Pi technique (Jane et al. 1978), also widely used:
1. Bilateral parasagittal strip craniectomies with outfracturing of the temporal bones
2. Removal of the vertex bone
3. AP shortening of the calvarial vault, in some instances with bifrontal osteotomies

5. In older children: The bone is more difficult to reshape:
    1. A more extensive calvarial reconstructive procedure is performed with bifrontal, biparietal, and occipital bone removal and reconstruction.
    2. The bones are then angulated to reduce frontal bossing, and the grafts are shortened to reduce the AP dimension of the skull.
6. Surgical procedures used for the treatment of sagittal synostosis:
    1. Strip craniectomy procedure
    2. Total vertex craniectomy
    3. Peninsula craniectomy
    4. Pi procedure
    5. Modified Pi procedure
    6. Clamshell procedure
    7. Distraction-contraction procedure
    8. Foreshortening and lateral expansion
    9. Spiral osteotomy technique
    10. Parietal bone fixation technique
    11. Reversal exchange technique
    12. Sprint-assisted cranioplasty
    13. Marchac transposition
    14. Modified Marchac transposition
    15. Endoscopic craniectomy
    16. Microscopic craniectomies
7. Cranial reconstruction for nonsyndromic sagittal craniosynostosis improved cranial index equally in all patients but increased head circumference and intracranial volume significantly more in patients who underwent surgical reconstruction at age 6 months or older (Bergquist et al. 2016).

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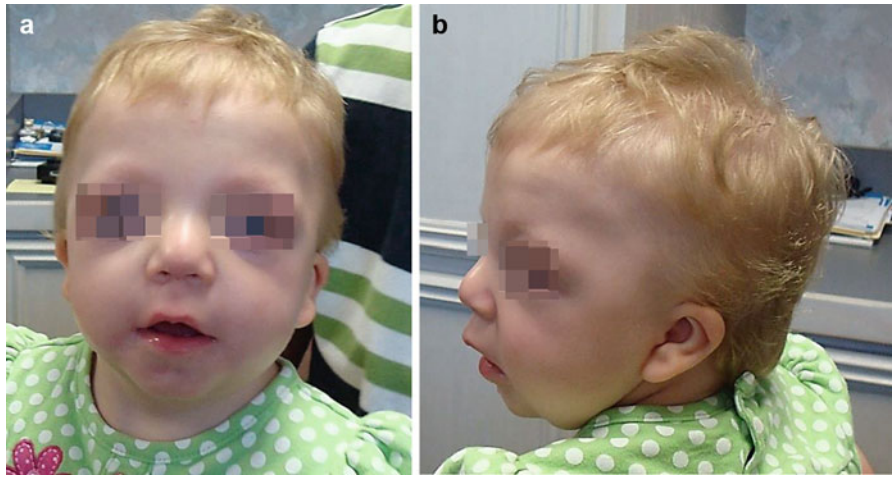

Fig. 1 (**a**, **b**) An 8-month-old infant was evaluated for sagittal suture synostosis. Her craniofacial features were characterized by palpable bonny ridge along the sagittal suture, ocular hypertelorism with proptotic eyes, and mild retrognathia. Conventional cytogenetics showed a complex chromosomal rearrangement involving chromosomes 2, 4, and 13 and deletions in chromosomes 4 and 13 [46,XX,ins (2;4)(p21;q31.2q33),del(4)(q26q28.3),t(4;13)(q31.3;q21.32), del(13)(q21.2q21.31)]. Oligonucleotide array CGH analysis showed a 22-Mb deletion in bands 4q26 to 4q28.3 and a 3.5-Mb deletion in 13q21.2 to13q21.31. The karyotype is therefore monosomic for genes in these regions

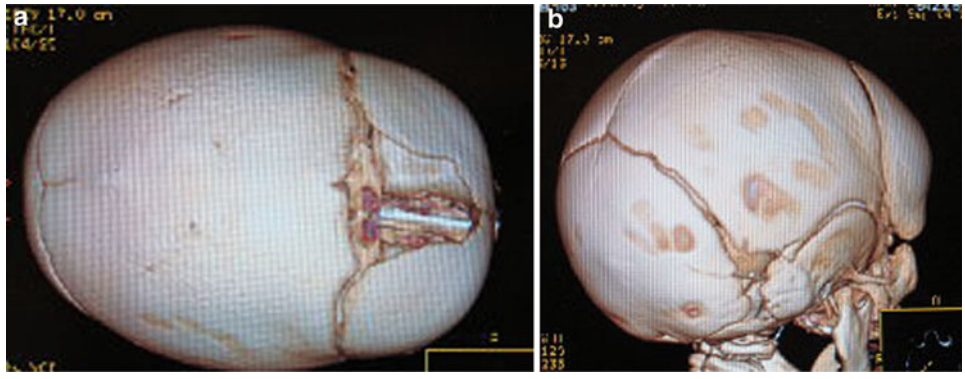

Fig. 2 (**a**, **b**) Three-dimensional CT reconstructions from the same patient shows dolichocephalic skull resulting from premature fusion of the sagittal suture (**a**) and sagittal ridge (**b**)

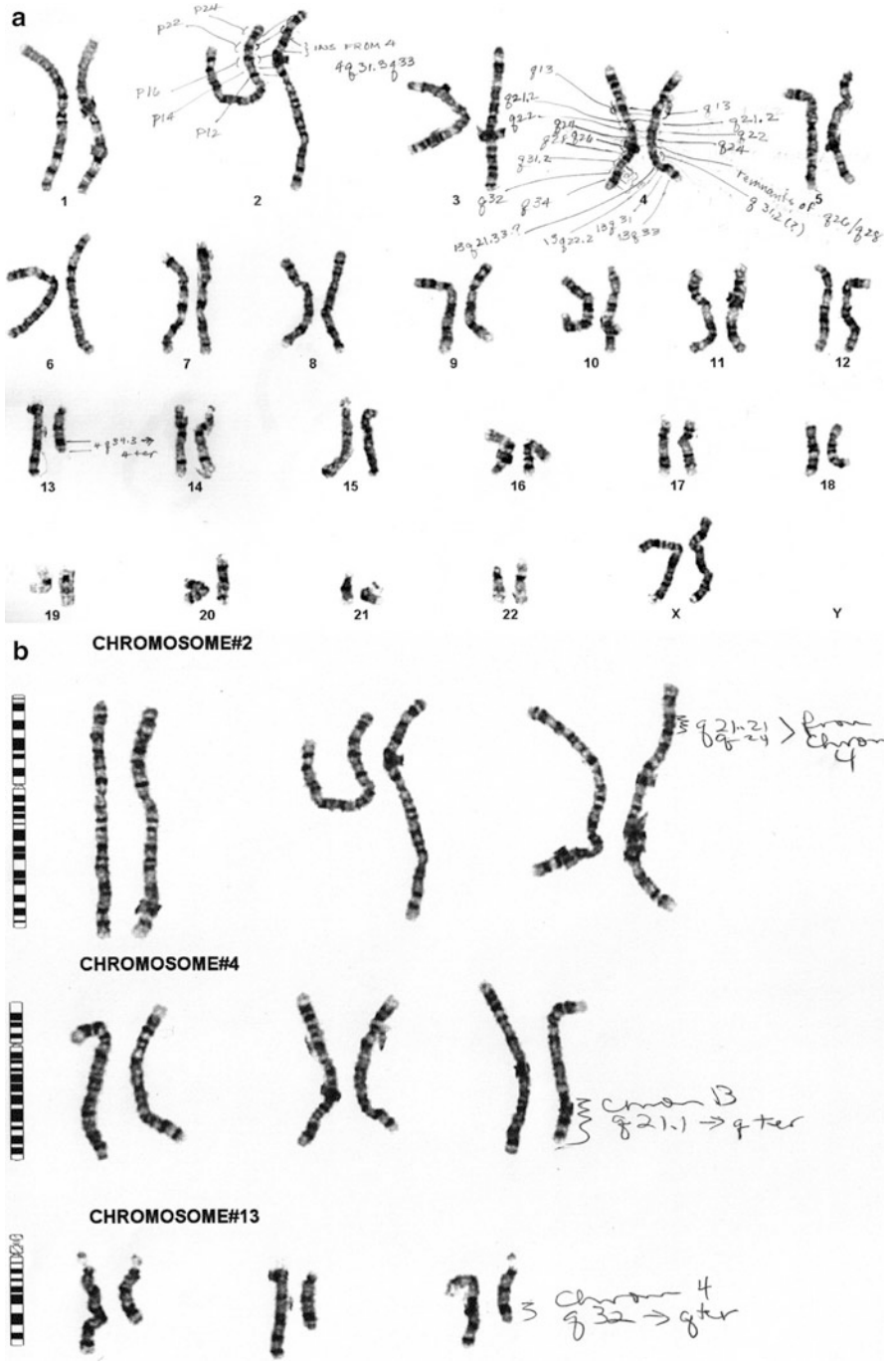

Fig. 3 (**a**, **b**) Her karyotype showed del(4)(q26 → q28.3ter) and del(13)(13q21.2 → q21.31) (pencil marks are intentionally left here to show the complex chromosome rearrangements)

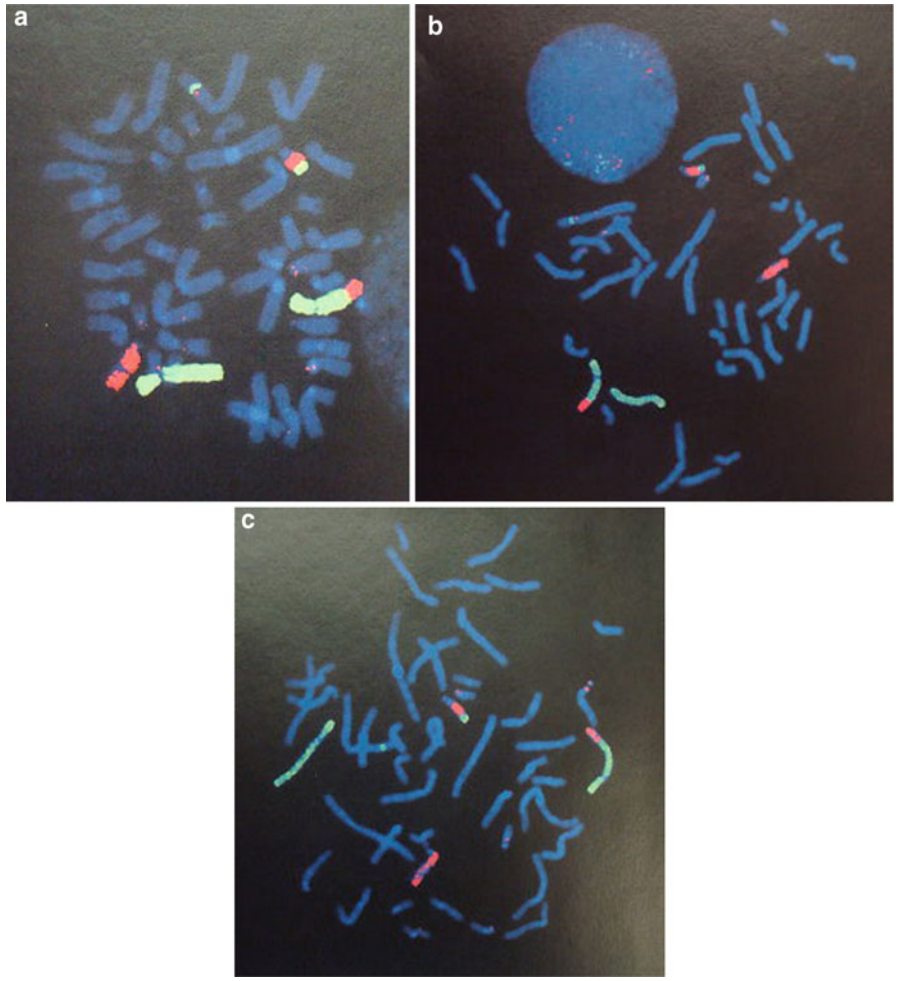

Fig. 4 (**a**–**c**) FISH with wcp2 and wcp4 confirmed an insertion of chromosome 4 material (4q31.2-33) into the short arm of 4q31.1 to 4qter. This translocation was confirmed with FISH subtelomeric probes, showing the qter of the translocation positive for the 13q subtelomere sequences, and the qter of the translocation 13 positive for 4q subtelomere

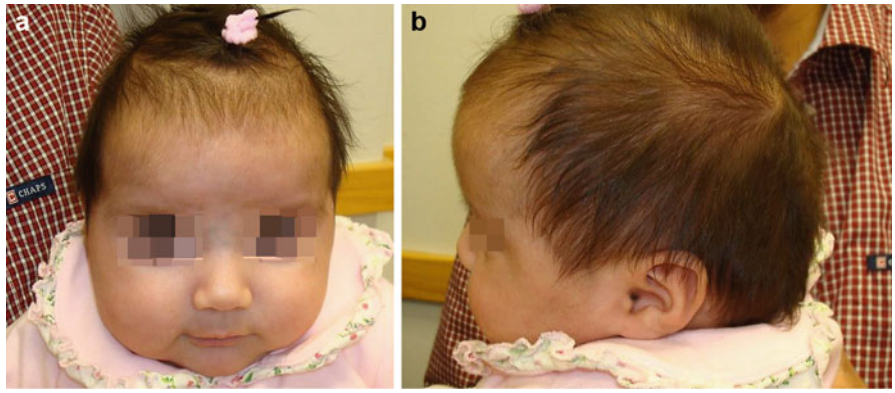

Fig. 5 (**a**, **b**) A 2-month-old infant was evaluated for scaphocephaly (sagittal suture ridge palpable) with tetralogy of Fallot

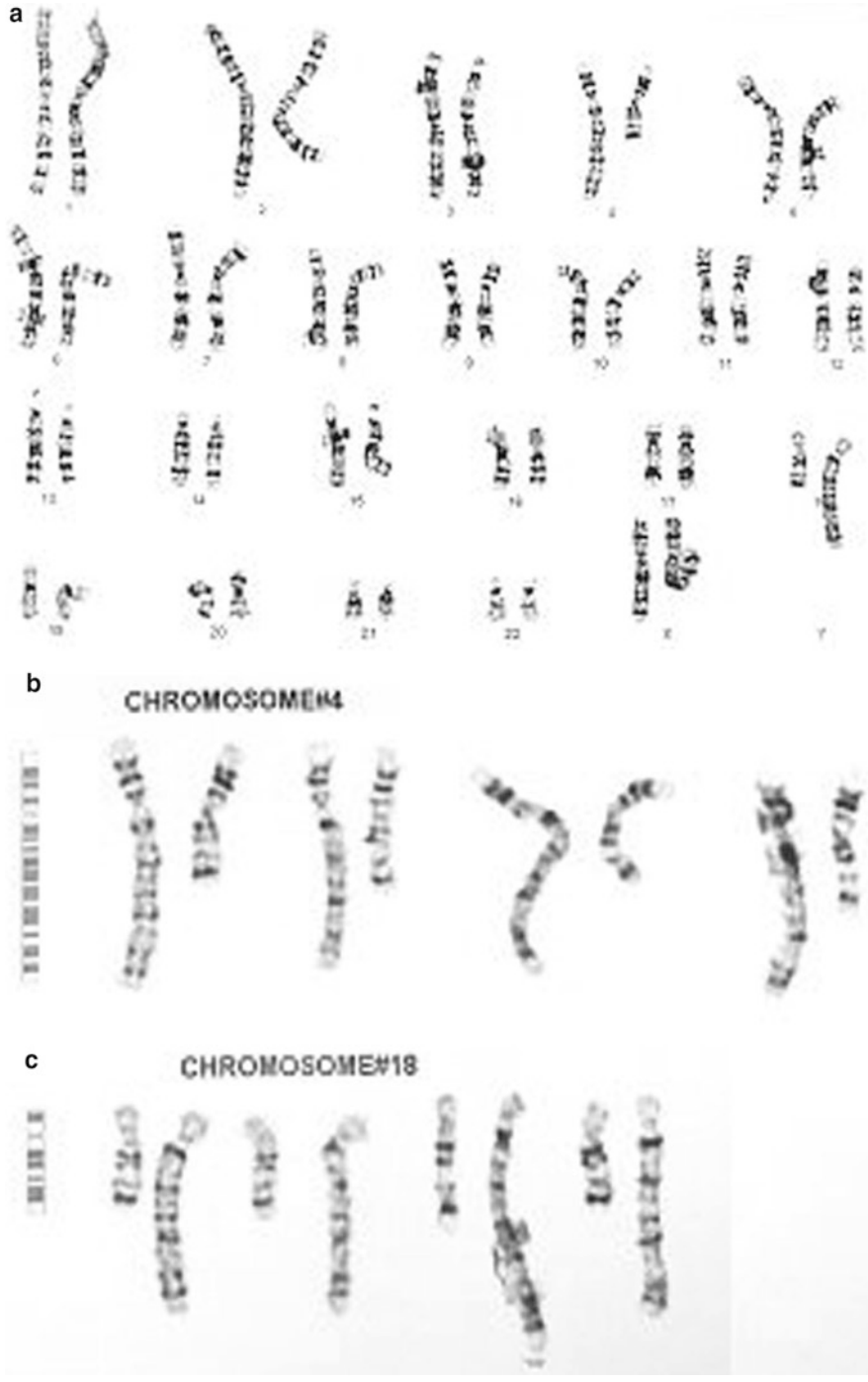

Fig. 6 (**a**–**c**) Her karyotype (**a**) and ideogram with partial karyotypes (**b**) showed a balanced translocation t(4;18)(p12; p11.2)

Schizencephaly

Contents

Schizencephaly is a rare congenital brain malformation characterized by deep clefts of the cerebral mantle that extend from the cortical surface to the lateral ventricles. Large portions of the cerebral hemispheres may be missing and are replaced by cerebrospinal fluid (Capra et al. 1996). The walls of the clefts are lined by polymicrogyric grey matter and are covered by the so-called pialependymal seam. The cleft may be unilateral or bilateral and if bilateral are fairly symmetrical. Their dimensions can be small or large. The clinical features may vary from a normal to a severe development delay. The conditions are often associated with convolutional anomalies such as polymicrogyria or nodular subependymal heterotopias.

Genetics/Birth Defects

1. Inheritance
   1. Isolated schizencephaly: mainly sporadic
   2. Rare reports of familial schizencephaly (Robinson 1991; Hosley et al. 1992; Hilburger et al. 1993; Haverkamp et al. 1995) associated with EMX2 mutation (Granata et al. 1997)
2. Etiology
   1. A developmental defect in the blood vessels supplying the cerebral cortex.
      1. Resulting in tissue death and cleft formation due to lack of oxygen (in utero vascular insufficiency)
      2. With preferential location in the parasylvian regions following the frontoparietal distribution of the middle cerebral artery
   2. Progressive destruction of brain tissue in utero: consistent with a vascular cause rather than a failure of formation of portions of the cerebral mantle (Klingensmith and Cioffi-Ragan 1986).
   3. A developmental vasculopathy could be the cause for some cases of schizencephaly and could be life-threatening until the postnatal life (Landrieu and Lacroix 1994).
   4. Mutations in the homeodomain gene *EMX2* as a possible cause of some cases of schizencephaly.
      1. At least some schizencephaly cases result from germline mutations.
      2. *EMX2*: expressed in restricted areas of the developing mammalian forebrain, including areas that develop into the cerebral cortex.

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3. Discovery of *EMX2* mutations in both sporadic and familial cases of schizencephaly marking an important advance in establishing genetic causes for brain malformations.
4. Germline mutations in the homeobox gene EMX2 in patients with schizencephaly (Brunelli et al. 1996; Faiella et al. 1997).
5. Lack of *EMX2* mutations in most schizencephaly patients has increased the likelihood of other genes being involved.
6. *EMX2* mutations were not confirmed from recent studies on large schizencephaly case series (Tietjen et al. 2007; Merello et al. 2008; Hehr et al. 2010).

5. Heterozygous mutations in *SIX3* and *SHH* are associated with schizencephaly: a subset of patients with schizencephaly may develop as one aspect of a more complex malformation of the ventral forebrain, directly result from mutations in the *SHH* pathway, and hence be considered as yet another feature of the broad phenotypic spectrum of holoprosencephaly (Hehr et al. 2010).
6. *COL4A1* mutation.
    1. Schizencephaly-associated *COL4A1* mutation (Matsumoto et al. 2015)
    2. Novel *COL4A1* mutation in an infant with severe dysmorphic syndrome with schizencephaly, periventricular calcifications, and cataract resembling congenital infection (Smigiel et al. 2016)
    3. Phenotypic spectrum of *COL4A1* mutations: porencephaly to schizencephaly (Yoneda et al. 2012)
7. Contactin-associated protein-like (CNTNAP) 2 gene mutation in a patient with bilateral schizencephaly (Samanta 2016).

3. Schizencephaly
    1. Refers to gray matter-lined clefts that extend through the entire hemisphere from the ependymal lining of the lateral ventricles to the pial covering of the cortex.
    2. Cleft.
        1. A cleft in the cerebral mantle which communicates between the subarachnoid space laterally and ventricular system medially
            1. Unilateral or bilateral cleft
            2. Symmetric or asymmetric cleft
        2. The sides of clefts generally lined with heterotopic gray matter (an abnormal accumulation of neurons)
    3. Two types of schizencephaly depending on the size of the area involved and the separation of the cleft lips (Yakovlev and Wadsworth 1946a, b).
        1. Type I (closed-lip schizencephaly).
            1. Consisting of a fused cleft.
            2. This fused pial-ependymal seam forms a furrow in the developing brain and is lined by polymicrogyric gray matter.
        2. Type II (open-lip schizencephaly) (Sharma et al. 2014): presence of a large defect, a holohemispheric cleft in the cerebral cortex filled with cerebral spinal fluid and lined by polymicrogyric gray matter.
    4. Associated malformations commonly accompanying schizencephaly. (Panda 2016)
        1. Mild hypoplasia of the corpus callosum.
        2. Total or nearly total absence of cavum septum pellucidum in 70–90% of patients with schizencephaly. 30–50% of patients show associated optic nerve hypoplasia on clinical examination (septo-optic dysplasia with schizencephaly).
        3. Focal cortical dysplasia.
        4. Coloboma of the retina.
        5. Hydrocephalus.
        6. Subependymal nodules.
        7. Microcephaly.
    4. Syndromes associated with schizencephaly
        1. Septo-optic dysplasia-schizencephaly syndrome (Barkovich et al. 1989; Kuban et al. 1989)
            1. Clinical features distinct from isolated septo-optic dysplasia

2. Frequently associated with endocrinologic, ophthalmologic, and neurologic symptoms and signs
3. Significant global developmental delay and spastic motor deficits
4. Seizures and visual symptoms rather than with endocrine abnormalities

2. Other rare schizencephaly syndromes
   1. Prenatal cytomegalovirus infection
   2. Vascular disruption related to twinning
3. Schizencephaly (plus polymicrogyria) as part of multiple congenital anomaly/mental retardation syndromes
   1. Adam-Oliver syndrome
   2. Aicardi syndrome
   3. Arima syndrome
   4. Delleman (oculocerebrocutaneous) syndrome
   5. Galloway-Mowat syndrome
   6. Micro syndrome

Clinical Features

1. Clinical manifestations depend on the size and location of involved brain.
   1. A narrow, small unilateral cleft
      1. Usually present with seizures and mild focal neurological deficits
      2. A good developmental prognosis (Barkovich and Kjos 1992)
   2. Bilateral clefts
      1. Severe developmental delay.
      2. Early intractable epilepsy.
      3. Severe motor dysfunction.
      4. Correlations between bilateral schizencephaly and presence of seizures also showed that atypical absence, generalized tonic-clonic jerks, and especially myoclonic jerks in the follow-up are more characteristic of bilateral schizencephaly (Kopyta et al. 2014).
2. Clinical features
   1. Most frequent neurological symptoms in children with schizencephaly (Stopa et al. 2014).
      1. Psychomotor retardation (varying degree).
      2. Seizures (epilepsy).
      3. Hemiparesis or quadriparesis (tetraparesis): Bilateral clefts were significantly associated with tetraparesis, whereas unilateral clefts were associated with hemiparesis (Granata et al. 1996; Denis et al. 2000).
      4. Hydrocephalus.
      5. Microcephaly (varying degree).
   2. Developmental delay: moderate to severe if the defects are large.
   3. Hypotonia in the postnatal period.
   4. Motor difficulties.
   5. All patients presented with a seizure disorder and manifest left handedness, but there was no history of familial sinistrality in first-degree relatives. This constellation of symptoms suggestive of the pathologic left handedness (PLH) syndrome described by Orsini and Satz (1986) (Aniskiewicz et al. 1990).
   6. Generalized spasticity.
   7. Blindness secondary to optic nerve hypoplasia.
   8. Unilateral homonymous hemianopia (Neves et al. 2016).
   9. Prognosis depending on the size of the clefts and the degree of neurological deficits.
      1. Patients with type I abnormalities.
         1. Almost normal
         2. May have seizures and spasticity
      2. Patients with smaller, unilateral clefts (clefts in only one hemisphere).
         1. Often paralyzed on one side of the body
         2. May have normal intelligence
      3. Patients with type II abnormalities.
         1. Mental retardation
         2. Seizures
         3. Hypotonia
         4. Spasticity
         5. Inability to walk or speak
         6. Blindness
      4. Patients with bilateral open-lip schizencephaly generally with the worst clinical symptoms.
      5. The presentation and outcome of children with schizencephaly are quite

variable but are related to the extent of cortex involved in the schizencephalic defect (Packard et al. 1997).

Diagnostic Investigations

1. Ultrasonography of the brain (Ceccherini et al. 1999) to demonstrate closed-lip or open-lip brain cleft communicating with lateral ventricle(s).
2. Magnetic resonance imaging (MRI) or computed tomography (CT) of the brain.
    1. Open-lip or closed-lip schizencephaly
    2. Associated absence of the septum pellucidum and hypoplasia of the optic chiasm
3. Common findings in US, CT, and MRI (Chamberlain et al. 1990).
    1. Bilateral cerebral clefts by CT (Komarniski et al. 1990).
    2. Parasylvian and midline clefts.
    3. Size asymmetries of the basal ganglia and thalamus.
    4. Cerebral parenchymal volume loss.
    5. Ventriculomegaly.
    6. Ventricular diverticula.
    7. Absence of the septum pellucidum.
    8. MRI and CT were superior to US in detecting calcification, gyral and sulcal abnormalities, and parasylvian clefts.
    9. MRI alone demonstrated homolateral absence of the sylvian vasculature, small medullary pyramids, low position of the fornix, and the thinning of the corpus callosum.
4. CT images (Miller et al. 1984)
    1. Cerebral clefts
    2. Infolding of cortical gray matter along the clefts
    3. An abnormal ventricular system
    4. Other associated cerebral anomalies
5. MR images (Hayashi et al. 2002)
    1. The clefts were unilateral in 51% of patients and bilateral in 49% of patients.
    2. 17% had fused lips (Yakovlev and Wadsworth 1946a) and 83% had separated-lip clefts (Yakovlev and Wadsworth 1946b).
    3. Recurrent seizures associated with unilateral opened lip schizencephaly. (Ugboma and Agi 2016)
    4. Polymicrogyria was present inside 43% clefts, while subependymal heterotopias were present at the cleft orifice in 50% clefts.
    5. Polymicrogyria was identified outside the cleft, both adjacent to and remote from the cleft, in 66% of patients.
    6. Abnormal cerebral white-matter signal intensity was present in 20% of patients, while white-matter volume diminution was noted in all patients.
    7. Neuronal migration disorders such as heterotopias and, more frequently, cortical dysplasias were observed in several patients (Pascual-Castroviejo et al. 2012)
    8. Nearly half of prenatally open schizencephaly defects had closed on postnatal imaging (Nabavizadeh et al. 2014).
6. Potential role of diffusion tensor imaging with tractography in providing insights into the evaluation of white matter tracts in patients with schizencephaly (Sarikaya 2009)
7. Angiography and pneumography (Page et al. 1975)
    1. Differentiated from the porencephalies that follow destructive lesions
    2. Differentiated from the prognostically more favorable subdural hematomas and effusions
8. Pathology
    1. Clefts most commonly in the Rolandic fissures
    2. Frequently associated with pachygyria, polymicrogyria, or lissencephaly
9. Molecular genetic testing of *EMX2* mutation for familial schizencephaly: not considered to be appropriate (Merello et al. 2008) and not available clinically

Genetic Counseling

1. Recurrence risk: low unless germline mutation is present in one of the parent
2. Prenatal diagnosis
    1. Ultrasonography, CT, and/or fetal MRI of the brain (Lituania et al. 1989; Denis et al. 2001) to demonstrate brain clefts connecting to the lateral ventricles.
    2. Intracranial sonographic features demonstrating in utero development of hemorrhagic brain damage leading to schizencephaly-associated *COL4A1* mutation (Matsumoto et al. 2015).
    3. Differential diagnosis of CSF-containing abnormalities in the fetal brain (Oh et al. 2005).
        1. Developmental lesions
            1. Arachnoid cyst
            2. Ventriculomegaly
            3. Monoventricle in holoprosencephaly
            4. Agenesis of the corpus callosum with an interhemispheric cyst
            5. Schizencephaly
        2. Destructive lesions
            1. Porencephalic cyst
            2. Ventriculomegaly (infection or bleeding)
            3. Hydranencephaly
    4. *EMX2* mutation analysis on amniocytes or CVS: not considered to be appropriate and not available clinically.
    5. Prenatal diagnosis of chromosome 8p23.1 microdeletion by array comparative genomic hybridization using uncultured amniocytes in a pregnancy associated with fetal partial corpus callosum agenesis and schizencephaly (Chen et al. 2015).
3. Management
    1. Physical therapy.
    2. Seizure control: Accurate localization of the epileptogenic zones using intracranial EEG and electrical stimulation can lead to a seizure-free outcome in patients with refractory epilepsy associated with schizencephaly (Zhang et al. 2016).
    3. Resection or multilobe disconnection for intractable epilepsy with open-lip schizencephaly (Cui et al. 2013).
    4. VP shunt for hydrocephalus.

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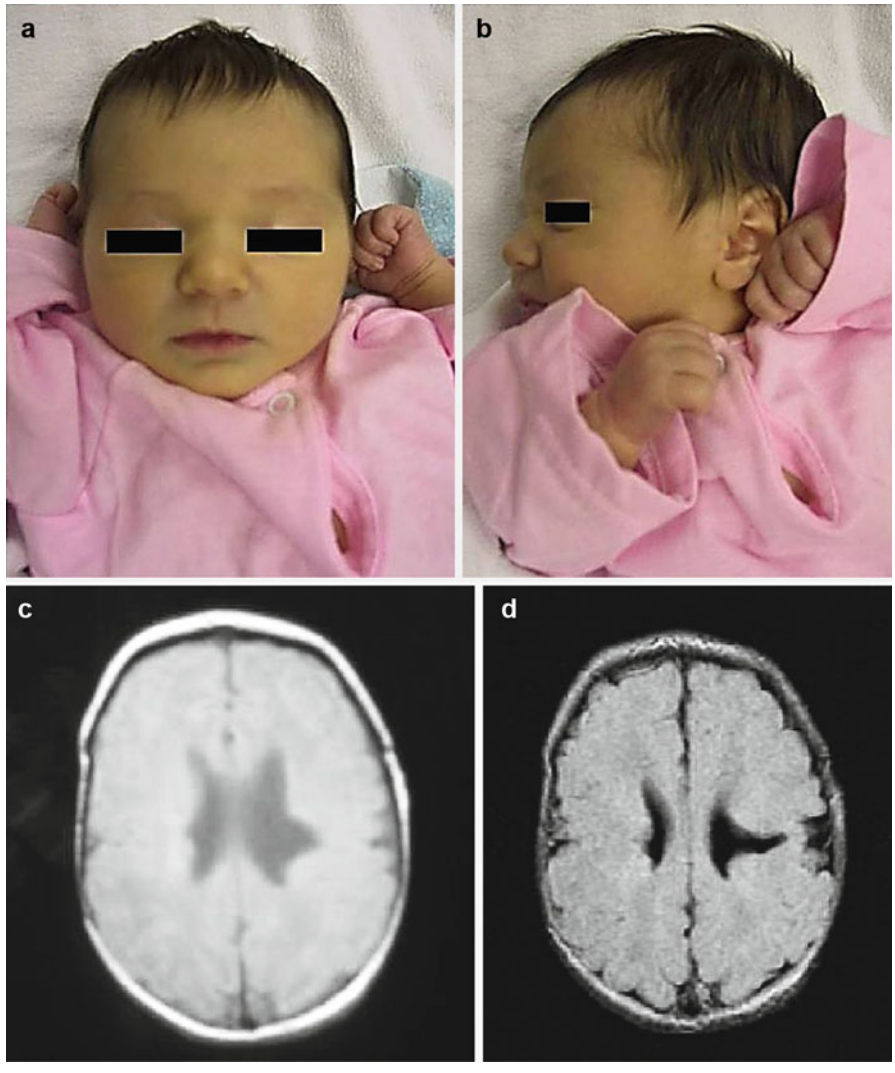

Fig. 1 (**a**-**d**) An infant (**a**, **b**) with asymmetric open-lip parietal schizencephaly, illustrated by MRI (**c**, **d**)

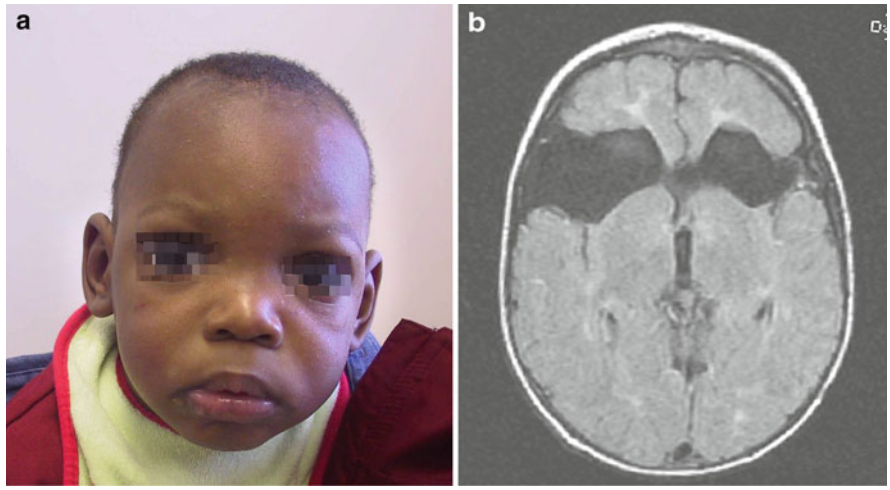

Fig. 2 (**a**, **b**) An infant (**a**) with schizencephaly, global delay and spastic quadriplegia. His MRI of the brain showed bilateral large open-lip schizencephaly in frontotemporal regions (**b**)

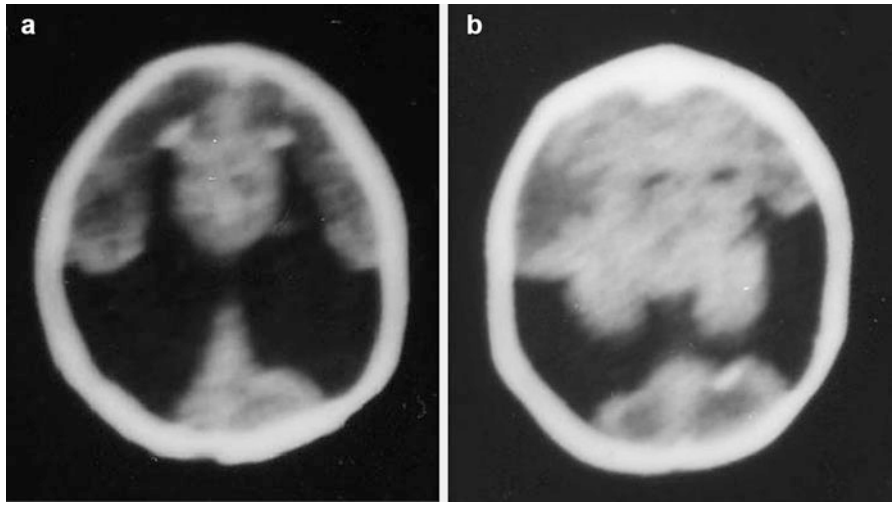

Fig. 3 (**a**, **b**) MRI of the brain of another patient showing bilateral open-lip schizencephaly in the parietal regions in communication with a large cavity filled by cerebrospinal fluid

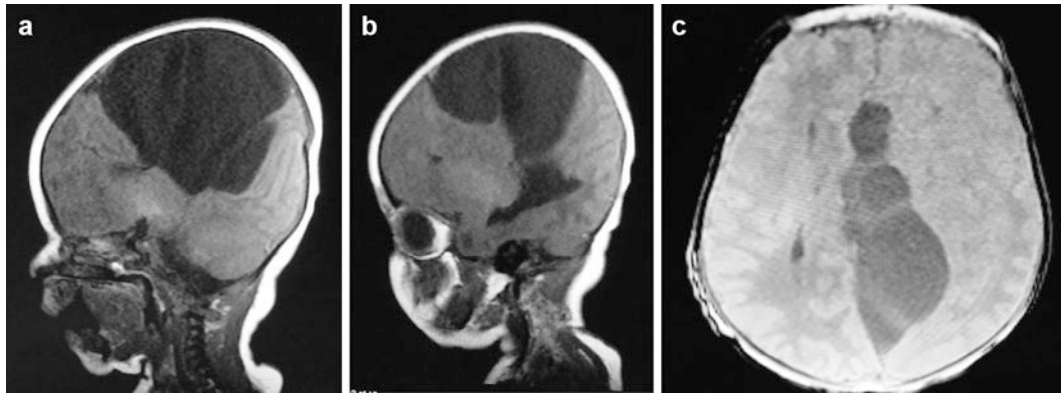

Fig. 4 (**a**–**c**) MRI of the brain of a neonate showed a large open-lip schizencephaly extending to the *right* convexity causing a large gap in the *right* cerebellar hemisphere. There is also absence of the corpus callosum

Schmid Metaphyseal Chondrodysplasia

Contents

Schmid metaphyseal chondrodysplasia (SMCD) is a mild hereditary chondrodysplasia resulting from growth plate cartilage abnormalities (Chan et al. 1998).

Genetics/Basic Defects

1. Inheritance
   1. Autosomal dominant
   2. Variable expression
2. Molecular pathogenesis
   1. Caused by heterozygous mutations in the gene *COL10A1* (Warman et al. 1993; Wallis et al. 1996; Mäkitie et al. 2005) (mapped to chromosome 6q21-q22), the gene which encodes α1(X) chains of type X collagen, a short-chain collagen whose expression is largely restricted to the hypertrophic chondrocytes of growth plate cartilage (Bateman et al. 2003).
   2. Each α1(X) chain contains a core triple helical domain, composed of uninterrupted repeats of the Gly-Xaa-Yaa tripeptide, flanked by two globular domains (NC2 and NC1) at both the amino and carboxyl-terminal ends (Bateman et al. 2005).
   3. Most mutations reside in the noncollagenous carboxyl terminal globular domain (CN1) which contains motifs that promote trimerization of α1(X) chains and subsequent formation of the triple helix to yield stable collagen X molecules (Bonaventure et al. 1995; Sawai et al. 1998; Ridanpää et al. 2003; Higuchi et al. 2016).
   4. Two mutations observed in a putative signal peptide cleavage site (Chan and Jacenko 1998; Chan et al. 1998, 2001).
   5. A novel mutation leading to elongation of the deduced α1(X) chain results in metaphyseal chondrodysplasia type Schmid (Zhu et al. 2011).
   6. Identification of a mutation in type X collagen (COL10A1) in families with Schmid metaphyseal chondrodysplasia (Dharmavaram et al. 1994; Wallis et al. 1994; Higuchi et al. 2016).
   7. The novel type X collagen gene mutation (G595R) identified supports the concept of type X collagenopathy (Matsui et al. 2000).
   8. Growth plate abnormalities of SMCD: resulting from collagen X

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_211

haploinsufficiency, a reduction by 50% in collagen X (Bateman et al. 2003).

9. Early-onset metaphyseal chondrodysplasia type Schmid associated with a COL10A1 frame-shift mutation and impaired trimerization of wild-type α1 (X) chains (Mäkitie et al. 2010).
10. The novel sequence variation involving an unusual mutational site of the COL10A1 gene can cause mild SMCD (Park et al. 2015).

Clinical Features

1. Mild to moderate short-limbed dwarfism (Beluffi et al. 1982)
2. Bowed legs
3. Waddling gait, often a presenting sign at second year
4. Coxa vara
5. Genu varum
6. Exaggerated lumbar lordosis
7. Flared anterior rib cage
8. Leg pain during childhood
9. Prognosis
    1. Radiological changes appearing early with a tendency to heal and change slowly with time, giving rise to mildly dwarfed patients.
    2. Normal intelligence.

Diagnostic Investigations

1. Radiography (Beluffi et al. 1983; Lachman et al. 1988)
    1. Hip
        1. Abnormal acetabular roofs
        2. Enlarged capital femoral epiphyses
        3. Coxa vara
        4. Coxa magna
        5. Femoral bowing
        6. Abnormal proximal femoral metaphyses
    2. Knee
        1. Abnormal distal femoral metaphyses
        2. Abnormal proximal tibial metaphyses
        3. Abnormal proximal fibular metaphyses
    3. Ankle
        1. Abnormal distal tibial metaphyses
        2. Abnormal distal fibular metaphyses
    4. Wrist
        1. Abnormal distal radial metaphyses
        2. Abnormal distal ulnar metaphyses
    5. Ribs: anterior cupping, splaying, and sclerosis
    6. Wide metaphyses with cupping and fraying
    7. Short and stubby long bones
    8. Mild hand involvement: a common feature (Elliott et al. 2005)
        1. Shortening of the tubular bones
        2. Metaphyseal cupping of the proximal phalanges and metacarpals
    9. Normal spine
2. Histology: variable bone changes (Dimson 1968)
    1. Mild sharp serrations of the metaphyses with increased density of the provisional zone of calcification
    2. Irregularity with flaring and fragmentation and widening of the growth plate
3. Molecular genetic analysis of *COL10A1* mutation (Milunsky et al. 1998)
    1. Mutation analysis
    2. Mutation scanning

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: low recurrence risk unless a parent is affected
    2. Patient's offspring: 50%
2. Prenatal diagnosis by amniocentesis or CVS: can be offered to families at-risk for DMCD with a previously characterized disease-causing *COL10A1* mutation
3. Management
    1. Supportive
    2. Orthopedic management of bowed legs: generally does not require orthopedic surgery

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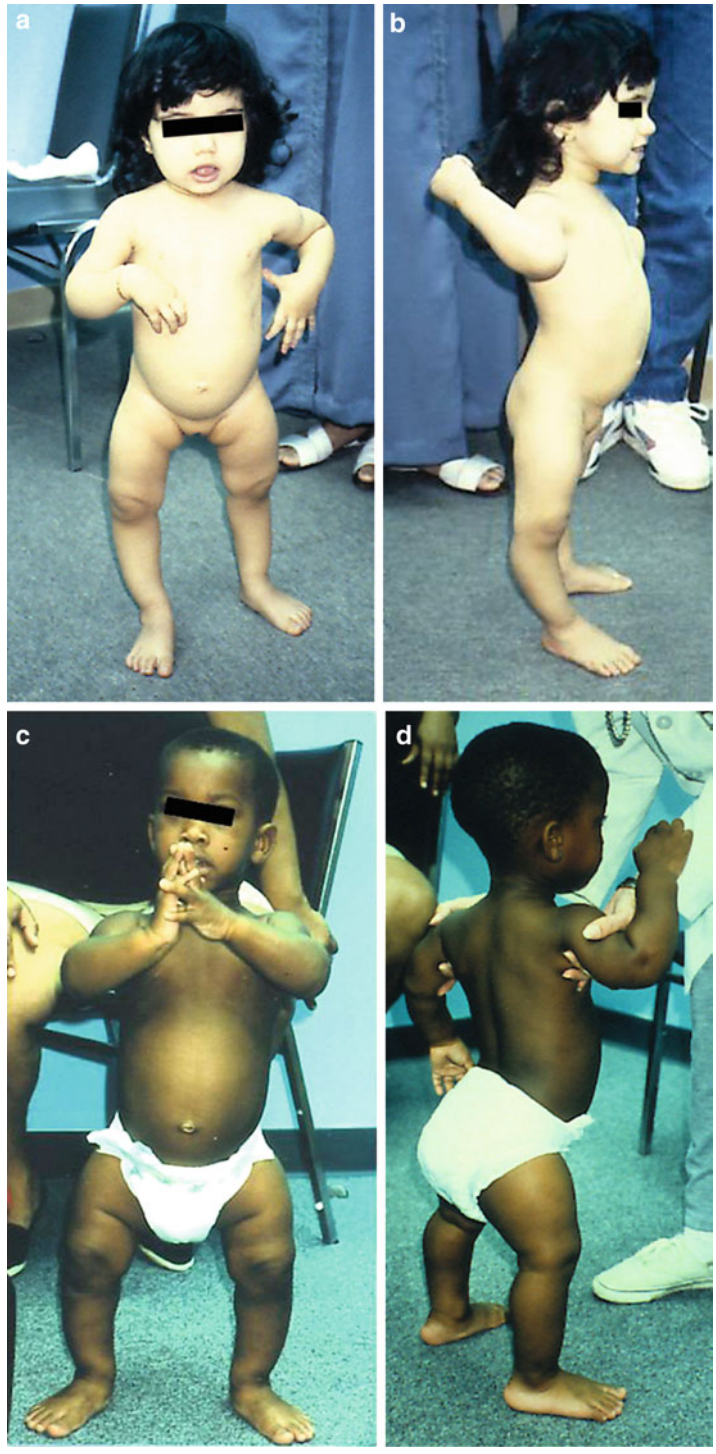

Fig. 1 (continued)

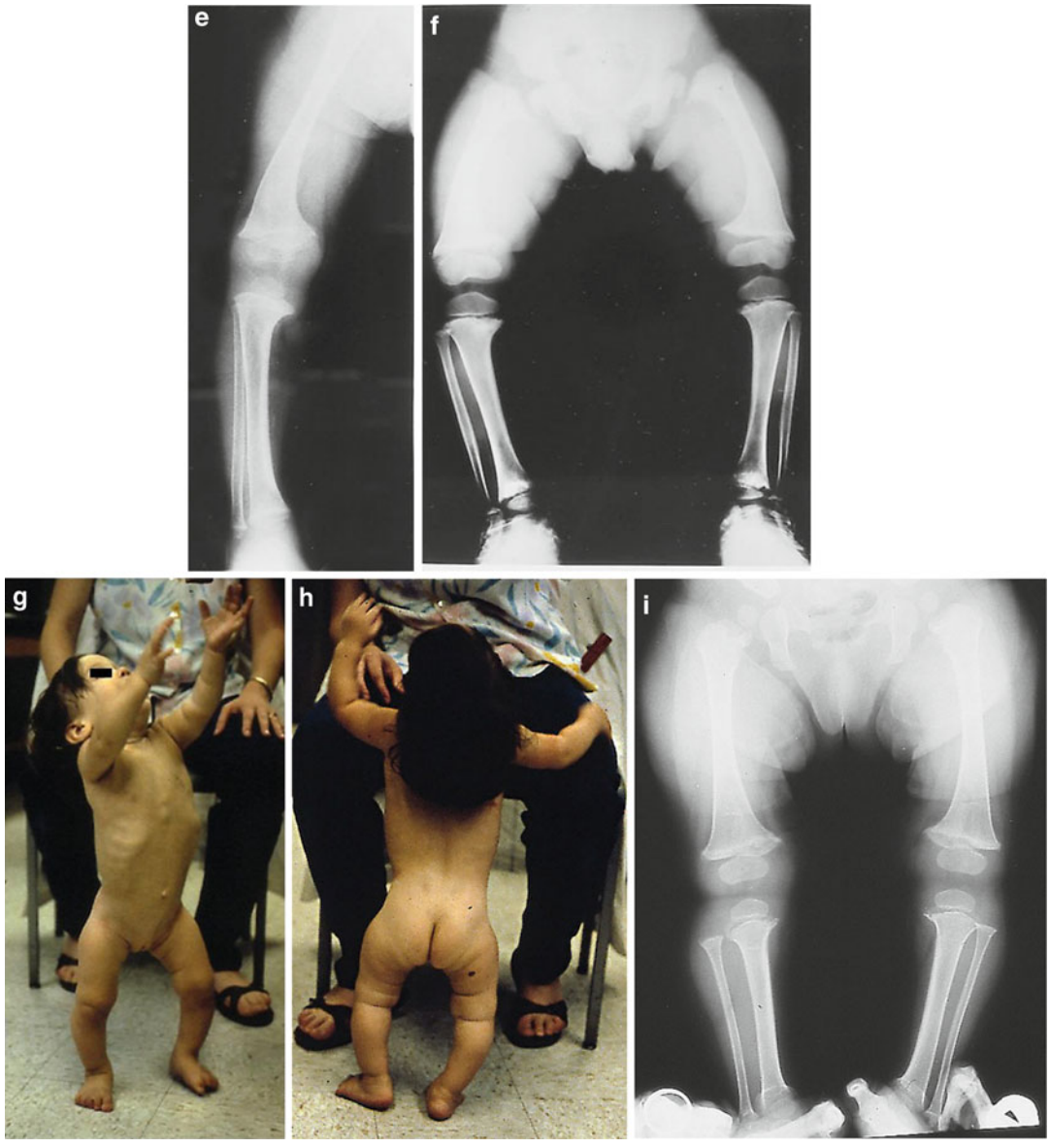

Fig. 1 (**a**–**i**) Three young children (**a**, **b**; **c**, **d**; **g**, **h**) with Schmid metaphyseal chondrodysplasia showing short stature, lumbar lordosis, and bowing of the legs. Radiographs (**e**, **f**, **i**) showed genu varum and metaphyseal widening with fraying and cupping. Epiphyses are normal

Schwartz-Jampel Syndrome

Contents

In 1962, Schwartz and Jampel (Schwartz and Jampel 1962) described the first case of Schwartz-Jampel syndrome (SJS) or chondrodystrophic myotonia.

Synonyms and Related Disorders

Chondrodysplasia myotonia; Schwartz-Jampel-Aberfeld syndrome; Stuve-Wiedemann syndrome

Genetics/Basic Defects

1. Inheritance
   1. Autosomal dominant (Ferrannini et al. 1982)
   2. Autosomal recessive: Two sisters born to consanguineous parents (Pavone et al. 1976)
2. Genetics of SJS type I (Schwartz-Jampel syndrome)
   1. Caused by partial loss-of-function mutations in *HSPG2* encoding perlecan (Iwata et al. 2015).
   2. Localization of the Schwartz-Jampel syndrome (SJS) locus to chromosome 1p34-p36.1 by homozygosity mapping (Nicole et al. 1995).
   3. Specific gene affected: the gene for perlecan (a heparan sulfate proteoglycan), the major proteoglycan of basement membranes (Nicole et al. 2000).
   4. Partial endplate acetylcholinesterase (AChE) deficiency may contribute to muscle stiffness (Stum et al. 2006).
   5. Peripheral nerve hyperexcitability with preterminal nerve and neuromuscular junction remodeling is a hallmark of Schwartz-Jampel syndrome (Bauche et al. 2013).
3. Genetics of SJS type II (Stuve-Wiedemann syndrome) (Knipe et al. 2015)
   1. Autosomal recessive bent bone skeletal dysplasia with associated autonomic involvement.
   2. The diseased gene leukemia inhibitory factor receptor (LIFR) in type II has been mapped to band 5p13.1, at locus D5S418 (Dagoneau et al. 2004).
   3. Autonomic dysfunction.
      1. Dysphagia.
      2. Respiratory failure.
      3. Pulmonary hypertension.
      4. Delayed growth.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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5. Hyperthermic episodes associated with excessive and paradoxical sweating are seen; these can be life-threatening.
6. Long-term complications: corneal opacities, along with osteopenia, pathological fractures, and progressive bone deformities.
7. Intellect: usually preserved.
8. Prognosis: poor with most sufferers dying in the first few months of life due to respiratory distress or hyperthermia.

4. Dyssegmental dysplasia of the Silverman-Handmaker type (DDSH): also caused by a recessive mutation of the perlecan gene (Arikawa-Hirasawa et al. 2001).

Clinical Features

1. Typical phenotypic features (Pascuzzi et al. 1990; Ault 2014)
   1. Short stature (90%)
   2. Characteristic facial features
      1. Fixed facies (55%)
      2. Pinched face
      3. Blepharophimosis (narrow palpebral fissures) and blepharospasm (32.5%)
      4. Epicanthal fold
      5. Puckered-small mouth (80%)
      6. Long philtrum
      7. Large ears
      8. High arched palate
   3. Musculoskeletal features
      1. Clinical myotonia (85%)
      2. Muscle hypertrophy (70%): stiff muscles (either hypertrophic or reduced in mass)
      3. Short neck
      4. Pectus carinatum
      5. Kyphosis
      6. Joint deformities and limitations of joint motion
      7. Coxa valga
      8. Irregularity of capital femoral epiphysis
      9. Delayed bone age (Kulkarni and Pillai 2004)
   4. High-pitched voice (Pfeiffer et al. 1977)
   5. Bilateral carpal tunnel syndromes (Van Meir and De Smet 2003)
   6. Malignant hyperthermia (Oue et al. 2004)
2. SJS type I (Schwartz-Jampel syndrome) (Giedion et al. 1997)
   1. Type IA: most commonly recognized
      1. Classic type described by Schwartz and Jampel.
      2. Myotonia: early childhood.
      3. Bone dysplasia: childhood.
      4. Muscle weakness: mild and largely nonprogressive.
   2. Type IB
      1. Clinically more severe than type IA
      2. Myotonia: infancy or childhood
      3. Infancy: short-limbed dysplasia with dumbbell-shaped femora (Kniest dysplasia-like)
      4. Childhood: spondylo-epi-metaphyseal dysplasia
      5. Long-term survival possible
3. SJS type II (Stuve-Wiedemann syndrome) (Giedion et al. 1997)
   1. Apparent immediately at birth
   2. Known as Stuve-Wiedemann syndrome
   3. Cardinal features
      1. Myotonia: birth
      2. Bone dysplasia: birth
      3. Severe respiratory difficulties and feeding problems
      4. Joint contractures
      5. Short stature
   4. Caused by the leukemia inhibitory factor receptor (LIFR) mutation
4. Differential diagnosis (Basiri et al. 2015)
   1. Stiff-person syndrome (Baizabal-Carvallo and Jankovic 2015).
      1. Generalized stiffness with attacks of muscle contraction.
      2. Progressive rigidity and muscle spasms affecting the axial and limb muscles.
      3. Electrodiagnostic findings: continuously firing motor unit action potentials, but no myokymic or neuromyotonic discharges.
   2. Isaacs syndrome (Ahmed and Simmons 2015)
      1. A peripheral nerve hyperexcitability syndrome that presents as continuous motor activity.

2. Clinical features (cramps, fasciculations, and myokymia).
3. Myotonic disorders
   1. Congenital myotonic dystrophy
   2. Myotonic dystrophy
   3. Myotonia congenita
   4. Paramyotonia congenita
4. Muscular dystrophies
   1. Becker muscular dystrophy
   2. Duchenne muscular dystrophy (please see the chapter of "▶ Dystrophinopathies")
   3. "▶ Congenital Muscular Dystrophy" (please see the chapter)
5. Congenital myopathies
6. Channelopathies
7. "▶ Mucopolysaccharidosis 4" (Morquio's syndrome) (please see the chapter)
8. "▶ Ehlers-Danlos Syndrome" (please see the chapter)
9. Malignant hyperthermia
10. Blepharospasm

Diagnostic Investigations

1. Serum creatine kinase or aldolase: normal or slight elevations
2. Radiological findings (Giedion et al. 1997)
   1. Type IA
      1. Mild epi-metaphyseal dysplasia with enlarged epiphyses at knees
      2. Spine: mild platyspondyly
      3. Pelvis: narrow sciatic notch
      4. Epiphyses: moderately enlarged at knees and other long bones
   2. Type IB
      1. Short-limbed dysplasia with dumbbell-shaped femora (Kniest dysplasia-like)
      2. Spondylo-epi-metaphyseal dysplasia
      3. Spine: moderate platyspondyly and coronal clefts
      4. Pelvis: some flaring of iliac wings; presence of supra-acetabular notch
      5. Epiphyses: moderately enlarged at knees
   3. Type II
      1. Short-limbed dysplasia with bowing of legs in infancy
      2. Pyle disease-like undertubulation of long bones in childhood
      3. Spine: not characteristic
      4. Pelvis: not characteristic
      5. Epiphyses: flattened at knees
3. Muscle biopsy: consistent with myopathy
4. Ultrastructural investigation of muscle: nonspecific
   1. Clusters of enlarged mitochondria and swelling of sarcoplasmic reticulum, giving the impression of a fine vacuolation of muscle fibers (Pavone et al. 1976).
   2. Swelling of sarcotubular system has been observed in myopathies characterized by an alteration of muscle contraction.
      1. Periodic paralysis
      2. Dystrophia myotonica
5. Electromyography (EMG) and nerve conduction studies
   1. EMG
      1. Showing continuous discharges, frequently with individual appearance of positive sharp waves or fibrillations, but may occur in runs of many discharges.
      2. Myotonic in some cases suggesting a waxing and waning character.
   2. Nerve conduction findings: typically normal (Regalo et al. 2005)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Autosomal recessive inheritance (25%)
      2. Autosomal dominant inheritance: not increased unless a parent is affected
   2. Patient's offspring
      1. Autosomal recessive inheritance: not increased unless the spouse is affected or a carrier
      2. Autosomal dominant inheritance (50%)

2. Prenatal diagnosis
    1. Ultrasonography at 17–19th week of pregnancy (Hunziker et al. 1989): possible for a family at risk
        1. Decreased fetal motor activity
        2. Constant flexion of the fingers
        3. Mild bowing and shortening of the femora
    2. Possible to detect fetuses at 25% risk when the disease-causing *HSPG2* (perlecan) mutation in both parents are known, by mutation analysis on fetal DNA obtained from chorionic villus sampling or amniocentesis
    3. Preimplantation genetic diagnosis: not clinically available for families in which the disease-causing mutations have been identified in an affected family member
3. Management
    1. Pharmaceutical treatment: limited usage and effective only in early diagnosed less severe cases (Ho et al. 2003; Nessler et al. 2011)
        1. Muscle relaxants: limited use
        2. Antiepileptic drugs, especially carbamazepine, give satisfactory action (Topaloglu et al. 1993; Squires and Prangley 1996)
    2. Botox injection
        1. Into the orbicularis oculi: usually helpful (Vargel et al. 2006).
        2. Into the lower eyelid (Flynn et al. 2001).
        3. Local injections of botulinum toxin A have transitional effect of relieving symptoms in mimic muscles (Vargel et al. 2006).
        4. Unresponsiveness of blepharospasm in most reported cases (Kashkouli et al. 2015), since muscle spasm in SJS is a myogenic rather than neurogenic activity (Lehmann-Horn et al. 1990).
    3. Rae surgical intervention of orbicularis oculi myectomy or levator aponeurosis resection after failure with botulinum toxin A injection (Morrison et al. 2006)

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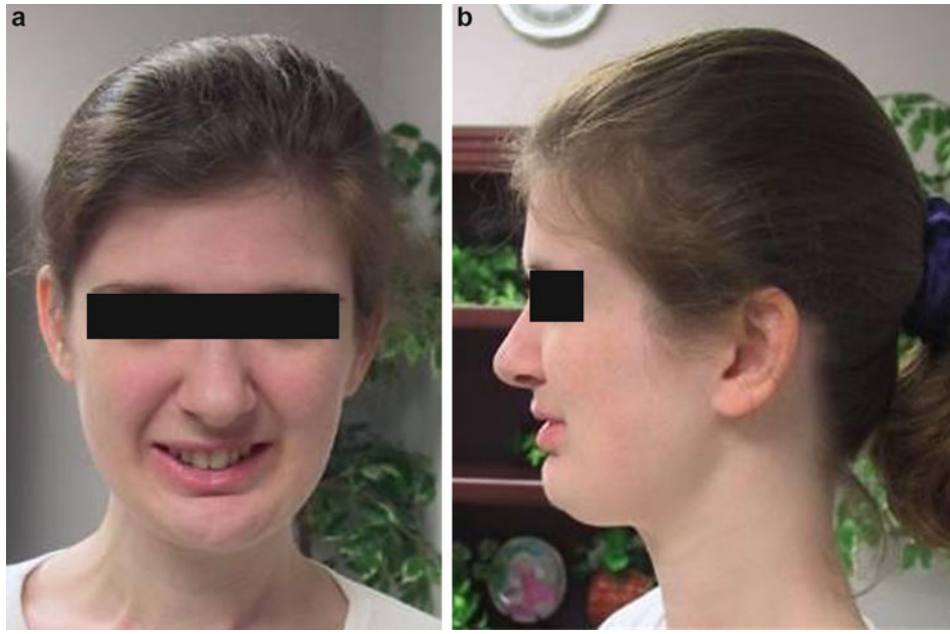

Fig. 1 (**a**, **b**) This 23-year-old white female was referred for genetic evaluation of Schwartz-Jampel syndrome. She showed fixed facial expression, bushy eyebrows, blepharophimosis, and difficulty in opening her jaw completely (**a**, **b**). She had a history of trouble swallowing and reflux. She was not able to rollover. When she was older she would fall easily and had a stiff gait. At 2 ½ years of age, she was admitted to the hospital with difficulty swallowing and overall motor difficulty. Muscle biopsy revealed possible myopathic change. At 4 years of age, she was diagnosed to have Schwartz-Jampel syndrome by Dr. Victor Ionasescu, a medical geneticist, who observed blepharophimosis, small mouth with incomplete opening, micrognathia, and high arched palate, long eyelashes in irregular rows, stiff legs, externally rotated outward legs, and percussion of thenar muscle (myotonia)

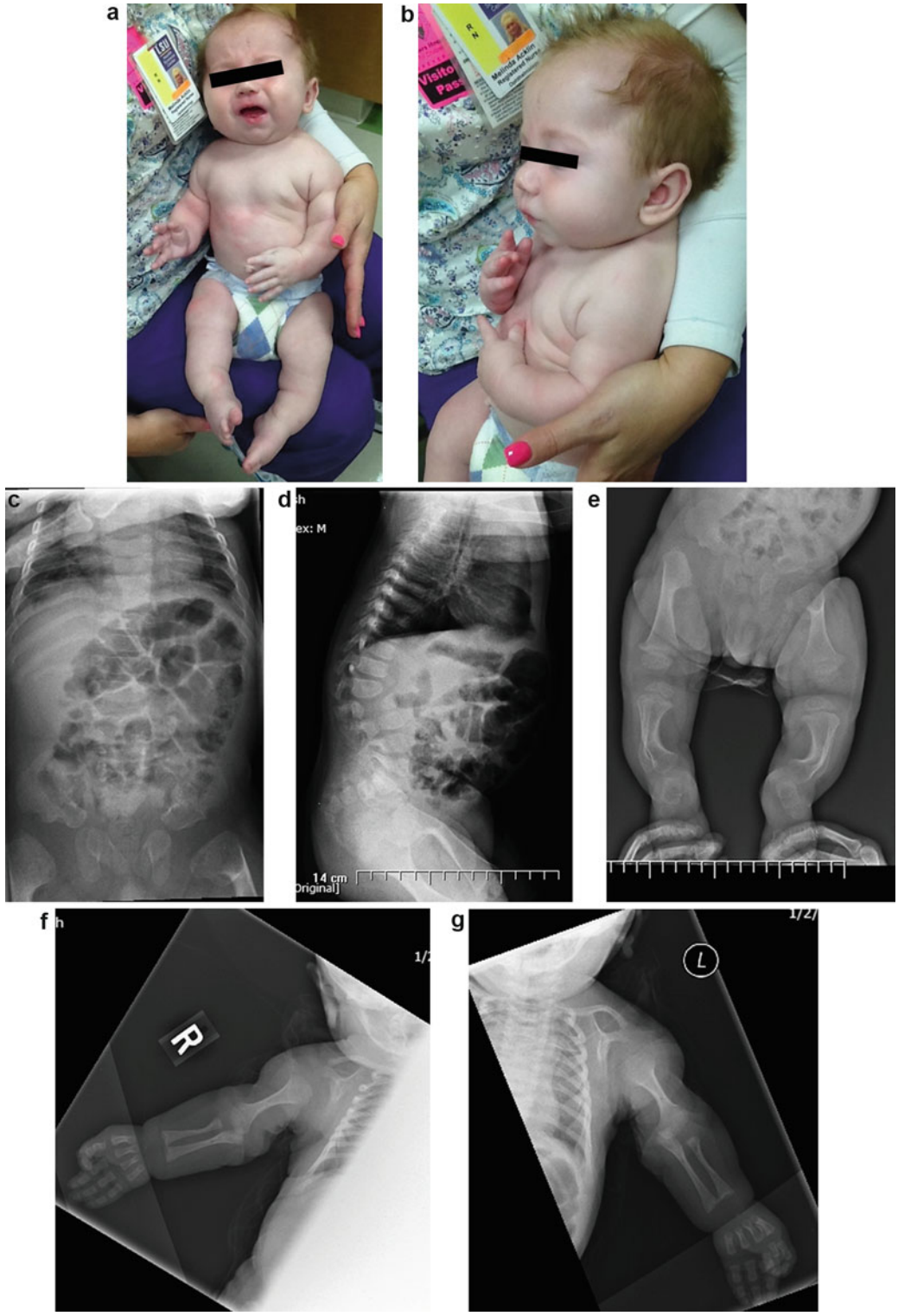

Fig. 2 (continued)

Fig. 2 (**a**–**g**) This 2-month-old infant boy was evaluated for short-limbed dwarfism. Prenatal ultrasound at 20 weeks of gestation showed the fetus with short extremities. After birth, the baby was noted to have prolonged jaundice, poor feeding, sleepiness, and sluggish. Chromosome analysis and thyroid function were normal. He was noted to have hemangiomas on the head, nose, and midface, round face, slightly receding chin, neck short, shored limbs, and curved extremities (**a**, **b**). Radiographs showed short limbs with dumbbell-shaped long bones due to splaying of the metaphyses (**c**, **e**, **f**), bowed tibiae and fibulae (**e**), dysplasia of the pelvic bones with dislocation of both hips (**c**, **e**), and lumbar coronal clefts on the lateral view on L4 and L5 (**d**). Molecular studies of *COL2A1* for Kniest dysplasia and *COL11A2* for Weissenbacher-Zweymuller syndrome were negative

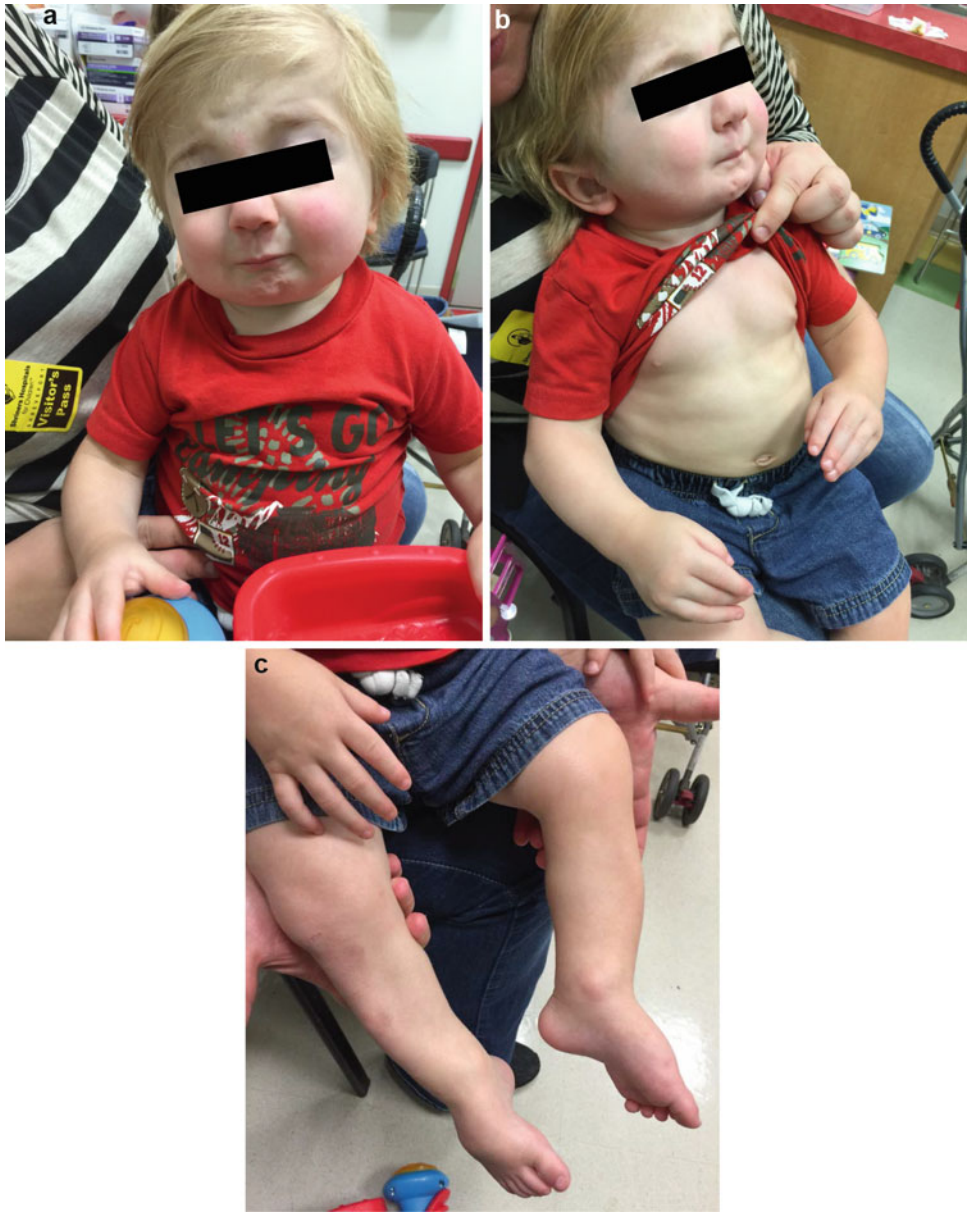

Fig. 3 (**a**–**c**) The previous boy, now 2-year-10-month old, showed a significant hypertonia, disproportionate short stature, fixed face with pursed lips, low-set ears (**a**, **b**), flexion contracture of the elbows and the knees, and bowed tubular bones (**c**). The diagnosis was made by Dr. Michael Bober of Nemours Children's Clinic with skeletal features (short stature of short-limb type, pectus carinatum with the rib flaring, flexion contractures of the elbows and the knees, and features of skeletal dysplasias consisting of absence of capital femoral epiphysis indicating a delay in bone age at his age, relatively large epiphyses at the knees, mottled and widened metaphyses throughout, bilateral bowing of the tibia and fibula, coronal cleft in the lumbar vertebrae, and some platyspondyly, indicating some type of spondylo-epi-metaphyseal dysplasia), a significant hypertonia, and questionable double row of eyelashes. Molecular testing revealed two distinct changes in *HSPG2* gene. The first change, c.10355G > A transition in exon 75 converts codon for arginine (CGA) to codon for glutamine (CAA) (performed by Connective Tissue Gene Tests Diagnosis Laboratory). The change has been previously reported as *HSPG2* mutation associated with Schwartz-Jampel syndrome type I (Stum et al. 2006 Human Mutation 27:1082). This change is consistent

Fig. 3 (continued) with disease-causing mutation. The patient is heterozygous for this mutation. The second change, c.11208-19G > A transition in IVS81, occurs in the intervening sequences. This change has the potential to create a new acceptor splice site and result in aberrant mRNA processing. To the best of their knowledge, this change has not been previously reported in either mutation or polymorphism. Additionally, this change is not listed in either the Single Nucleotide Polymorphism database (dbSNP) or the Exome Sequencing Project (ESP) database. These findings suggest that this change may be pathogenic

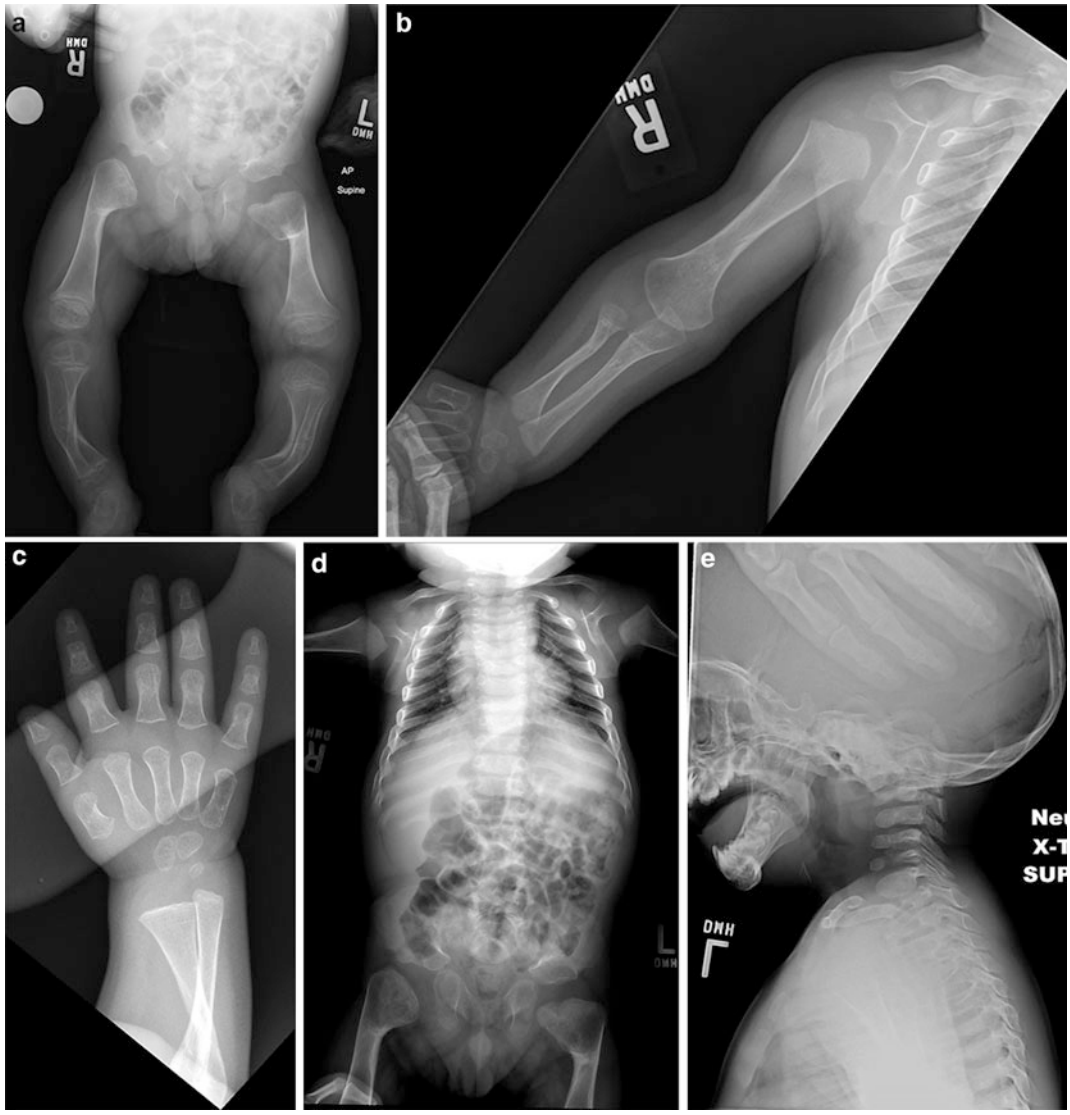

Fig. 4 (**a**–**e**) The radiographs of the extremities (**a**–**c**) at 14 months of age showed shortened and bowed long bones, broadening of the metaphyses, unossified femoral heads, and mild broadening of the tubular bones of the hands. The ribs are downward sloping bilaterally with mild broad deformity. The pelvic bones are thickened with irregular contours and with flattened acetabula (**d**). There were platyspondyly with flattening of the thoracic and lumbar vertebral bodies, dysplastic L1-3 with mild kyphosis (**e**) (Courtesy of Dr. Grace Guo)

Seckel Syndrome

Contents

In 1960, Seckel (1960) reported 2 personal cases and 13 cases from the literature of a clinical condition characterized by severe intrauterine and postnatal proportionate dwarfism, severe microcephaly, "bird-headed" profile with receding forehead and chin, large and beaked nose, severe mental retardation, and other anomalies (Majewski and Goecke 1982). Seckel syndrome (SCKL) is a rare heterogeneous type of primordial dwarfism with frequency of less than 1 in 10,000 live births.

Synonyms and Related Disorders

Bird-headed dwarfism; Familial bird-headed dwarfism; Microcephalic primordial dwarfism; Nanocephalic dwarfism; Osteodysplastic primordial dwarfism; Seckel-type dwarfism

Genetics/Basic Defects

1. Inheritance: autosomal recessive (familial occurrence) (Sauk et al. 1973; Syrrou et al. 1995)
2. Genetic heterogeneity (Abou-Zahr et al. 1999; Faivre et al. 2002)
    1. SCKL1: A gene for Seckel syndrome was mapped to human chromosome 3q22.1-q24 in two inbred Pakistani families originating from the same village (Goodship et al. 2000).
        1. The gene encoding ataxia-telangiectasia and Rad3-related (ATR) protein maps to the critical region to an interval of 5Mbp between markers D3S1316 and D3S1557.
        2. A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATRP) results in Seckel syndrome (O'Driscoll et al. 2003).
        3. A synonymous mutation in affected individuals was identified that alters *ATR* splicing.
        4. The mutation confers a phenotype including marked microcephaly and dwarfism.
        5. Identification of the first ATRIP-deficient patient and novel mutations in ATR define a clinical spectrum for

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ATR–ATRIP Seckel syndrome (Ogi et al. 2012).

2. SCKL2: Another gene locus was mapped to chromosome 18p11.31-q11.2 in one inbred Iraqi family (Børglum et al. 2001).
3. SCKL3: A novel locus at 14q23 by linkage analysis in 13 Turkish families. The novel gene locus SCKL3 is 1.18 cM and harbors ménage a trois 1, a gene with a role in DNA repair (Kilinç et al. 2003).
4. Caused by mutations of the pericentrin gene (*PCNT*) (mapped to 21q22.3) (Griffith et al. 2008; Rauch et al. 2008; Willems et al. 2009).
    1. The gene encodes centrosomal protein which plays a key role in the organization of mitotic spindles.
    2. The mutations also can cause microcephalic osteodysplastic primordial dwarfism type II (Rauch 2011).
5. Mutations in *CENPJ*, a gene that has hitherto been linked to primary microcephaly only (Bond et al. 2005; Gul et al. 2006), also can cause Seckel syndrome (Al-Dosari et al. 2009).
6. Mutations in CDK5RAP2 cause Seckel syndrome (Yigit et al. 2015).
7. Mutations in the NHEJ component *XRCC4* cause primordial dwarfism (Murray et al. 2015).
8. Interstitial deletion 2q33.3-q34 in a boy with a phenotype resembling the Seckel syndrome (Courtens et al. 1997).

Clinical Features

1. Broad interfamilial clinical heterogeneity (Arnold et al. 1999)
2. Growth
    1. Severe proportionate short stature of prenatal onset
    2. Severe postnatal growth deficiency
    3. Intrauterine growth retardation
    4. Low-birth-weight dwarfism
3. Mental retardation
4. Characteristic craniofacial features
    1. Bird-headed dwarfs (Harper et al. 1967; McKusick et al. 1967)
    2. Cranial manifestations
        1. Severe microcephaly
        2. Premature closure of cranial sutures
    3. Receding forehead
    4. "Birdlike" face
    5. Antimongoloid slant of palpebral fissures
    6. Large eyes
    7. Beaklike protrusion of the nose
    8. Narrow face
    9. Receding lower jaw (retrognathia)
    10. Micrognathia
    11. High-arched or cleft palate
    12. Ears
        1. Low set
        2. Hypoplastic lobules
    13. Dental abnormalities
        1. Enamel hypoplasia
        2. Missing permanent teeth
        3. Precocious eruption of teeth
        4. Microdontia
        5. Malocclusion
        6. Taurodontism
    14. "Dysplastic" ears
5. Associated anomalies
    1. Ocular manifestations (Guirgis et al. 2001)
        1. Severe myopia and astigmatism
        2. Severe, early onset, bilateral retinal degeneration
        3. Hypotelorism
        4. Bilateral ptosis
        5. Microphthalmos
        6. Megacornea
        7. Glaucoma
        8. Retrolental membrane
        9. Macular coloboma
        10. Optic hypoplasia
        11. Strabismus
        12. Lens dislocation
        13. Ocular changes in two female siblings with Seckel syndrome, including cataract, lens subluxation, and chorioretinal degenerations, as well as retinal detachment (Krzyżanowska-Berkowska et al. 2014)
    2. Skeletal defects
        1. Premature closure of cranial sutures

2. Dislocation of the radial head
3. Clinodactyly of the fifth fingers
4. Hip "dysplasia"/dislocation
5. Retardation of ossification
6. Clubfoot
7. Hypoplastic patella
8. Scoliosis

3. CNS anomalies (Shanske et al. 1997)
   1. Small cerebrum with simplified, ape-like convolutional pattern (pongidoid micrencephaly)
   2. Dysgenesis of cerebral cortex
   3. Agenesis of corpus callosum
   4. Cerebellar vermis hypoplasia
   5. Dorsal cerebral cyst
   6. Arachnoid cyst
   7. Dilated ventricles
   8. Pachygyria
   9. Agyria
   10. Intracranial aneurysms (D'Angelo et al. 1998)
4. Endocrine abnormalities
   1. Pituitary gland abnormalities
      1. Delayed development
      2. Decreased adrenocorticotropic hormone production
      3. Decreased growth hormone production
      4. Absence of adenohypophysis
      5. Hypophyseal hypoplasia
      6. Precocious puberty
   2. Adrenal hypoplasia
   3. Hirsutism
5. Hematopoietic abnormalities
   1. Acute myelogenous leukemia
   2. Refractory anemia with excess blasts
   3. Pancytopenia
   4. Fanconi anemia
6. Urogenital abnormalities
   1. Males
      1. Cryptorchidism
      2. Hypoplasia of the testis
   2. Females
      1. Clitoromegaly
      2. Hypoplasia of the labia majora
7. Features of premature senility
   1. Receding hair
   2. Redundant wrinkled skin on the palms
8. Miscellaneous findings
   1. Congenital heart defects
      1. Patent ductus arteriosus
      2. Atrial septal defect
      3. Ventricular septal defects
      4. Atrioventricular canal defect
   2. Multiple intestinal atresia

6. Seckel-like syndromes (Majewski and Goecke 1982; Arnold et al. 1999)
   1. Microcephalic osteodysplastic primordial dwarfism type I.
      1. Distinguished from Seckel syndrome by:
         1. Broad, low "dysplastic" pelvis with poor development of the acetabula.
         2. Disproportionately short, broad bowing of humeri and femora with rather unremarkable metaphysis.
         3. Agenesis of the corpus callosum and lissencephaly have also been noted.
      2. Classified as Seckel syndrome by Majewski and Goecke (1982)
   2. Microcephalic osteodysplastic primordial dwarfism type II (Majewski et al. 1982a; Majewski and Goecke 1998): differences from the Seckel syndrome include the following (mainly based on X-ray features):
      1. Short limbs with preferential distal involvement (disproportionate shortness of forearms and legs) in the first years of life
      2. Brachymesophalangy
      3. Brachymetacarpy I
      4. Coxa vara
      5. Epiphysiolysis
      6. Metaphyseal flaring with V-shaped distal femoral metaphyses
   3. Microcephalic osteodysplastic primordial dwarfism type III (Majewski et al. 1982b; Majewski 1992).
      1. Alopecia
      2. Seckel-like features
         1. Intrauterine growth retardation
         2. Microcephaly
         3. Receding forehead and chin
         4. Large ears
         5. Large prominent nose
         6. Platyspondyly
         7. Long dysplastic clavicles

8. Hypoplasia of iliac wing and acetabula
9. Broad femora

3. Currently considered to be the same entity as type I (Meinecke and Passarge 1991; Meinecke et al. 1991)

4. A variant of osteodysplastic bird-headed dwarfism described by Bangstad et al. (1989).
   1. Progressive ataxia
   2. Primary gonadal insufficiency
   3. Endocrine abnormalities
      1. Insulin-resistant diabetes mellitus
      2. Goiter
5. Chromosome abnormalities.
   1. Chromosome instability/breakage (Butler et al. 1987; Bobabilla-Morales et al. 2003)
   2. Deletion 1q22-q24.3
   3. Interstitial deletion 2q33.3-q34 (Courtens et al. 1997)
   4. Ring chromosome 4 mosaicism (Anderson et al. 1997)

Diagnostic Investigations

1. Hematological workup indicated in selected patients
   1. Anemia
   2. Pancytopenia
   3. Acute myeloid leukemia
2. Endocrine workup for pituitary and adrenal dysfunction
3. Radiography
   1. Microcephaly with a rather steeply sloping base of the skull
   2. Premature closure of the cranial sutures
   3. Delayed bone age
   4. Hip dysplasia
   5. Elbow dislocation
   6. Dislocation of the radial head
   7. Ivory epiphyses (dense sclerotic areas in the phalanges)
   8. Cone-shaped epiphyses
   9. Disharmonic bone development
      1. Hypoplasia of proximal radii and fibulae
      2. Absence of epiphyseal ossification centers in fingers and toes
4. Neuropathology and CT/MRI of the brain
   1. Microcephaly
   2. Neuroglial ectopia
   3. Agenesis of the corpus callosum
   4. Micropolygyria
   5. Disproportion of the cerebrum and cerebellum
   6. Dysgenetic cerebral cortex
   7. Hypoplasia of the cerebellar vermis
   8. Dorsal cerebral cyst
5. Growth plate histology
   1. Normal column formation
   2. No structural abnormality of chondrocytes
   3. Decrease in cellularity of chondrocytes

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not likely to have offspring due to severe mental retardation
2. Prenatal diagnosis possible by serial ultrasonography for families at risk for Seckel syndrome (Nadjari et al. 2000)
   1. Severe intrauterine growth retardation
   2. Craniofacial abnormalities
      1. Microcephaly
      2. Receding forehead
      3. A prominent nose
      4. Severe micrognathia
   3. Short limbs
3. Prenatal ultrasound and MR imaging in a family without a previous child with the disorder (Featherstone et al. 1996)
   1. Intrauterine growth retardation
   2. Disproportionately large fetal nose with a beaklike appearance
   3. Facial dysmorphism (beaked nose with hypotelorism with mild proptosis with micrognathia) (Gupta et al. 2014)
   4. Microcephaly
   5. A posterior fossa cyst
4. Prenatal ultrasound diagnosis of a Seckel-like syndrome (Majoor-Krakauer et al. 1987)

1. Microcephaly
2. Intrauterine growth retardation
3. A Hellenic nose
4. Severe micrognathia

5. Management
   1. Symptomatic.
   2. Psychosocial support for mental retardation.
   3. Dental cares.
   4. Orthopedic cares.
   5. Treatments for hematological abnormalities.
   6. Successful outcome of allogeneic stem cell transplantation in Seckel syndrome: bone marrow transplantation is an acceptable therapeutic option for Seckel syndrome complicated by hematological alterations (Darrigo et al. 2014).

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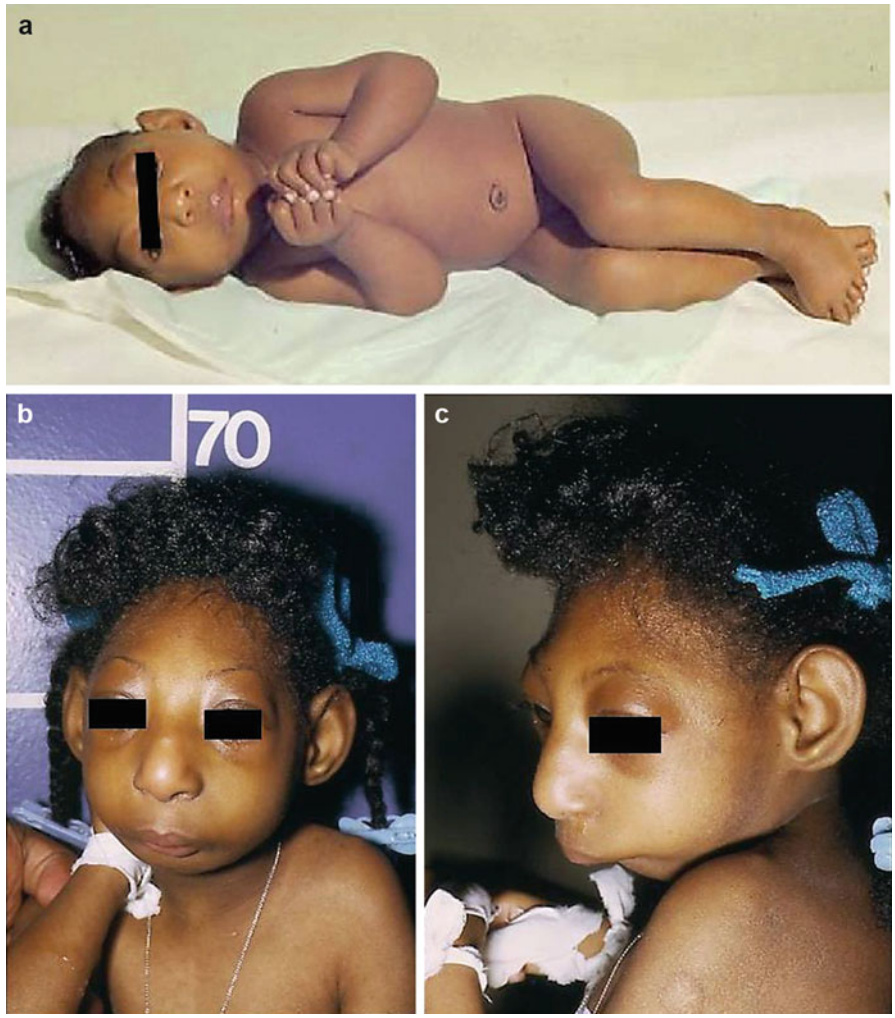

Fig. 1 (**a**–**c**) A girl with Seckel syndrome showing marked short stature, severe microcephaly, sloping forehead, "bird-headed" face, large eyes, beaked nose, and severe retro/micrognathia

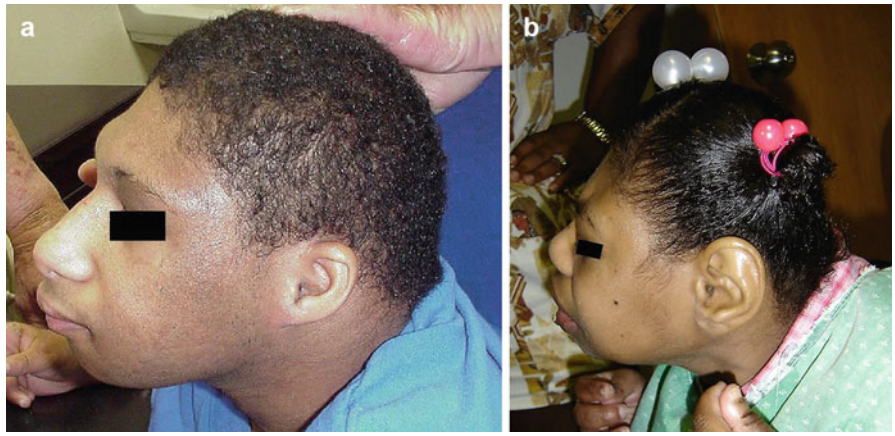

Fig. 2 (**a**–**b**) Two adults with Seckel syndrome showing severe short stature, mental retardation, extreme microcephaly, sloping forehead, a beaked nose, and retro-/micrognathia

Severe Combined Immune Deficiency

Contents

Severe combined immune deficiency (SCID) is a fatal, heterogeneous group of immune disorder, characterized by T-cell lymphopenia, a profound lack of cellular (T-cell) and humoral (B-cell) immunity, and, in some cases, decreased NK-cell number and function. All infants with SCID develop infections from both common and opportunistic pathogens because protection from maternal antibodies wanes early in life (Buckley et al. 1997; Friedrich et al. 2007). The incidence of SCID is estimated to be 1/100,000 live births, but this may be an underestimate due to some children dying before diagnosis or having unrecognized less severe disease (Stephan et al. 1993; Chan and Puck 2005; McGhee et al. 2005).

Synonyms and Related Disorders

Autosomal recessive SCID (Swiss-type agammaglobulinemia); Bare lymphocyte syndrome; Interleukin (IL)-2 deficient SCID; Janus-associated kinase 3 (JAK3) deficient SCID; Omenn syndrome; Purine nucleoside phosphorylase (PNP) deficient SCID; Reticular dysgenesis; SCID; X-linked SCID; ZAP-70 protein tyrosine kinase (PTK) deficient SCID

Genetics/Basic Defects

1. A heterogeneous syndrome of varied genetic origins (Secord 2009):
    1. X-linked type SCID (X-SCID):
        1. The most common type (50% of all patients with SCIDs), characterized by the absence of the cytokine receptor common γ chain.
        2. A combined cellular and humoral immunodeficiency resulting from lack of T and natural killer (NK) lymphocytes and nonfunctional B lymphocytes.
        3. Caused by a mutation in the X-linked gene *IL2RG*, which encodes the common γ chain, γc (mapped on Xq13), of the leukocyte receptors for interleukin-2 and multiple other cytokines (Fanos et al. 2001):
            1. Significant frequency of de novo mutations accounting for one third of the cases
            2. Occurrence of maternal germ line mosaicism
        4. A novel intronic splice site deletion of the IL-2 receptor common gamma chain

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results in expression of a dysfunctional protein and T-cell-positive X-linked severe combined immunodeficiency (Gray et al. 2015).
5. Atypical X-SCID: less frequently seen in patients with mutations that result in production of a small amount of gene product or a protein with residual activity.

2. Autosomal recessive type SCID:
1. Formerly known as Swiss-type agammaglobulinemia
2. Causes:
1. Adenosine deaminase deficiency (10–20% of all cases of SCID): the *ADA* gene mapped on chromosome 20q13.11 (Arredondo-Vega et al. 1998)
2. Purine nucleoside phosphorylase (PNP) deficiency: the *PNP* gene mapped on 14q13
3. Janus-associated kinase 3 (JAK3) deficiency causing autosomal recessive T-B + SCID: the JAK3 gene mapped on 19p13
4. Interleukin (IL)-2 deficiency
5. ZAP-70 protein tyrosine kinase (PTK) deficiency: ZAP-70 mapped on 2q12
6. Bare lymphocyte syndrome
7. Reticular dysgenesis
8. Omenn syndrome

2. Mutations in any of eight known genes, *IL2RG*, *ARTEMIS*, *RAG1*, *RAG2*, *ADA*, *CD45*, *JAK3*, and *IL7R,* cause SCID (Kalman et al. 2004).
3. Pathophysiology:
1. Varies among various forms of SCID
2. Common end point in all forms of SCID:
1. Lack of T-cell function
2. Lack of B-cell function
3. Cellular hallmarks differentiating various forms of SCID:
1. X-linked SCID:
1. Absence or near absence of T cells ($CD3^+$) and natural killer (NK) cells leading to lymphopenia
2. Variable levels of B cells that produce no functional antibodies
2. JAK3 deficiency:
1. Absence or near absence of T cells ($CD3^+$) and natural killer (NK) cells leading to lymphopenia
2. Normal or high levels of B cells that produce no functional antibodies
3. ADA deficiency:
1. Death of T and B cells secondary to the accumulation of toxic metabolites in the purine salvage pathway leading to lymphopenia
2. Decreased or absence of functional antibodies
4. PNP deficiency:
1. Death of T cells secondary to the accumulation of toxic metabolites in the purine salvage pathway leading to lymphopenia
2. Normal number of circulating B cells with poor B-cell function, evidenced by the lack of antibody formation
5. IL-2 deficiency:
1. Normal or near normal numbers of T cells (both $CD4^+$ and $CD8^+$)
2. Decreased production of functional antibody
6. ZAP-70 PTK deficiency:
1. Absence of $CD8^+$ T cells leading to lymphopenia
2. No antibody formation
7. Bare lymphocyte syndrome:
1. Normal or mildly reduced lymphocyte count
2. Decreased $CD4^+$ T cells
3. Normal or mildly increased $CD8^+$ T-cell numbers
4. Normal or mildly decreased B-cell numbers with decreased antibody production
8. Reticular dysgenesis:
1. Absence of myeloid cells in the bone marrow leading to lymphopenia
2. Presence of functioning red blood cells and platelets

9. Omenn syndrome:
    1. A variant of SCID: believed to be caused by a mutation impairing the function of immunoglobulin and TCR recombinase genes, such as *RAG1* and *RAG2* genes
    2. Presence of normal or elevated T-cell numbers of maternal origin
    3. Usually undetectable B cells
    4. Presence of NK cells
    5. Markedly low total immunoglobulin level with poor antibody production
    6. Elevated eosinophils and total serum immunoglobulin E (IgE) level
    7. Characterized by erythrodermic rash, lymphadenopathy, hepatosplenomegaly, and diarrhea

4. Molecular defects of major types of SCID (Gaspar et al. 2001):
    1. X-linked SCID:
        1. Mutation of the common gamma chain of the IL receptors (IL-2R, IL-4R, IL-7R, IL-9R, IL-15R) resulting in loss of cytokine function (Cavazzana-Calvo et al. 2000)
        2. Loss of IL-2R function leading to the loss of a lymphocyte proliferation signal
        3. Loss of IL-4R function leading to the inability of B cells to class switch
        4. Loss of IL-7R function leading to the loss of an antiapoptotic signal resulting in a loss of T-cell selection in the thymus and also associated with the loss of a T-cell receptor
        5. Loss of IL-15R function leading to the ablation of NK cell development
    2. JAK3 deficiency:
        1. JAK, a protein tyrosine kinase that associates with the common gamma chain of the IL receptors
        2. Deficiency of JAK3 resulting in the same clinical manifestations as those of X-linked SCID
    3. ADA and PNP deficiencies:
        1. Associated with enzyme deficiencies in the purine salvage pathway
        2. Toxic metabolites responsible for the destruction of lymphocytes that cause the immune deficiency
    4. IL-2 deficiency:
        1. Molecular defect unknown
        2. Often associated with other cytokine production defects
    5. ZAP-70 PTK deficiency: caused by a mutation in the gene coding for this tyrosine kinase, which is important in T-cell signaling and is critical in positive and negative selection of T cells in the thymus
    6. Bare lymphocyte syndrome:
        1. Deficiency of major histocompatibility complex (MHC)
        2. Absent or decreased MHC type I levels
        3. Decreased MHC type II levels on mononuclear cells

Clinical Features

1. Age of onset: 3–6 months of life
2. A pediatric emergency (Rosen 1997)
3. Usual presentation with infections due to lack of T-cell function:
    1. Opportunistic organisms:
        1. *Pneumocystis carinii* pneumonia
        2. Systemic candidiasis
        3. Atypical mycobacterium
        4. Cryptosporidium
        5. Pneumococcus
    2. Recurrent infections
    3. Persistence of infections despite conventional treatment
4. Failure to thrive
5. Oral or diaper candidiasis (persistent oral thrush)
6. Dehydration from chronic diarrhea
7. Fevers
8. Erythrodermic rashes
9. Cough and congestion
10. Increased respiratory rate and effort
11. Absence of tonsils and lymph nodes
12. Absence of lymphadenopathy or increased tonsillar tissue despite serious infections

13. Pneumonias
14. Sepsis
15. Disseminated infections:
    1. Salmonella
    2. Varicella
    3. Cytomegalovirus
    4. Epstein–Barr virus
    5. Herpes simplex virus
    6. BCG
    7. Vaccine strain (live) polio virus
16. Recurrent sinopulmonary infections
17. Recurrent skin infections
18. Abscesses
19. Poor wound healing
20. Lymphadenopathy
21. Hepatosplenomegaly
22. Lymphopenia
23. Transplacental transfer of maternal lymphocytes to the infant prenatally or during parturition causing graft-versus-host disease (GVHD), characterized by:
    1. Erythematous skin rashes
    2. Hepatomegaly
    3. Lymphadenopathy
24. ADA deficiency and PNP deficiency with later onset and milder or atypical clinical presentation:
    1. Diagnosis suspected in patients with:
        1. Unexplained T-cell lymphopenia
        2. Late manifestations of immunodeficiency:
            1. Chronic pulmonary insufficiency
            2. History of autoimmunity and neurologic abnormalities
            3. Onset during the first two decades of life and even later
    2. Diagnosis confirmed by finding absent or very low enzyme activity in erythrocytes or in nucleated blood cells
25. Lymphadenopathy or hepatosplenomegaly in Omenn syndrome or bare lymphocyte syndrome
26. Prognosis:
    1. Fatal if untreated
    2. Bone marrow transplantation or enzyme replacement to reconstitute the immune system compatible with long survival

Diagnostic Investigations

1. Newborn screening (Adeli and Buckley 2010; Lipstein et al. 2010; Secord 2009; Kwan and Puck 2015):
    1. Newborn screening would not only make the diagnosis at birth but would lead to measures to protect infants from becoming infected before they could receive a transplant.
    2. Newborn screening would also reveal the true incidence of SCID and define the range of conditions characterized by severely impaired T-cell development.
    3. Evidence indicates the benefits of early treatment of SCID and the possibility of population-based newborn screening.
    4. Better information on optimal treatment and the costs of treatment and screening would benefit policy makers deciding among competing health-care priorities.
    5. Newborn screening for SCID using the T-cell receptor excision circle assay has revolutionized early identification of infants with SCID or severe T-cell lymphopenia (Kelly et al. 2013).
2. Laboratory workup:
    1. X-SCID (Allenspach et al. 2016):
        1. Lymphocyte count:
            1. Usually very low number of T cells
            2. B cells generally present, but nonfunctional
            3. Low or absent number of NK cells
            4. Typical X-SCID designated as $T^{-}B^{+}NK^{-}$
        2. Lymphocyte functional tests:
            1. Absent antibody responses to vaccines and infection agents
            2. Lacking T-cell responses to mitogens
        3. Immunoglobulin concentrations:
            1. Low serum concentrations of IgA and IgM
            2. IgG generally normal at birth but declines as maternally transferred IgG disappears by 3 months of age
        4. Thymus: absent thymic shadow on chest radiogram.

5. Carrier detection in X-linked severe combined immunodeficiency based on patterns of X-chromosome inactivation (Puck et al. 1987): In the T cells of three carriers, the X chromosome bearing the X-SCID mutation was consistently inactive. Nonrandom X inactivation was also found in the T cells of one at-risk female, while two others had normal, random X inactivation.
6. Identification of X-linked severe combined immunodeficiency by mutation analysis of blood and hair roots (Ting et al. 1999): The strategy of using DNA from hair roots was particularly valuable where no pre-transplant blood was stored.
7. Molecular genetic testing clinically available: *IL2RF* is the only gene known to be associated with X-SCID:
    1. Sequence analysis
    2. Targeted mutation analysis

2. Adenosine deaminase deficiency (Hershfield 2014):
    1. Immune function:
        1. Lymphopenia, the laboratory hallmark of ADA-deficient SCID, is present at birth. The total blood lymphocyte count is usually lower than 500/μL (normal for neonates: 2,000 to >5,000).
        2. All lymphoid lineages (T, B, and NK cells) are depleted as demonstrated by flow cytometry.
        3. Lower or absent in vitro lymphocyte function, as measured by proliferative response to mitogens and antigens.
        4. Low serum immunoglobulins and absence of specific antibody response to infections and immunizations.
    2. Adenosine deaminase (ADA) catalytic activity:
        1. Affected individuals who have not been transfused have less than 1% of normal ADA catalytic activity in erythrocyte hemolysates.
        2. Affected individuals who have been recently transfused may require testing of another cell type, such as fibroblasts or leukocytes.
    3. Biochemical markers of ADA deficiency:
        1. Elevated erythrocyte deaminate 2′-deoxyadenosine (dAdo) nucleotides (dAXP): pathognomonic
        2. Reduced erythrocyte S-adenosylhomocysteine hydrolase (AdoHcyase, SAHase) activity (<5% of normal)
        3. Markedly elevated urinary excretion of dAdo
    4. Molecular genetic testing; *ADA* is the only gene associated with ADA deficiency:
        1. Sequence analysis
        2. Deletion/duplication analysis
3. ZAP70-related SCID (Rosenberg and Larkin 2014):
    1. Lymphocyte counts:
        1. T-cell counts: absent or very low CD8+ cells, normal or elevated CD4+ cells, and normal CD3+ cells
        2. B-cell counts: normal B cells and NK cells
    2. Lymphocyte function:
        1. Absence of proliferation of CD4+ cells in response to mitogens (e.g., PHA).
        2. Absence of proliferation of CD4+ cells in response to antigens (e.g., ConA).
        3. Defective $CD4^{+}$ cell-cell activation manifests as impaired Ca^{2+} flux in response to CD3 (OKT3) stimulation.
    3. ZAP-70 protein expression: absence of ZAP-70 protein in most cases by immunocytochemistry testing of CD4+ T cells.
    4. Immunoglobulin concentrations and function:
        1. Severe hypogammaglobulinemia in a majority of affected individuals but normal immunoglobulin levels have been seen

2. Although functional antibody responses to immunization are present in a few persons, this finding does not indicate that all specific antigenic responses are intact.
5. Molecular genetic testing: Sequence analysis of the *ZAP70* coding region detects missense and nonsense mutations, splice and regulatory region mutations, and insertion mutations.

4. Autosomal recessive SCID (T-B-NK+. *RAG1*/*RAG2*-related): molecular genetic testing of *RAG1*/*RAG2* gene available clinically by sequence analysis or deletion/duplication analysis

3. Chest X-ray:
   1. Absent to small thymus shadow
   2. Pneumonia
   3. Typical cupping and flaring of the costochondral junction in patients with ADA deficiency
4. Lymph node biopsy:
   1. Paucity of T and B cells
   2. Lack of germinal centers
5. Consider X-SCID in male infants with:
   1. Severe recurrent or persistent infections
   2. Infections not responding to ordinary treatment
   3. Infections caused by opportunistic pathogens
   4. Failure to thrive
6. A correct diagnosis for SCID and related disorders cannot be overstated, from T-cell receptor excision testing to targeted mutation analysis to whole exome/whole genome sequencing (Shearer et al. 2014). Genotype information provides substantial and accurate information regarding current eligibility of patients for study databanks and stratum assignment (Manolio et al. 2013). However, maternal chimerism and lymphocyte function (proliferation to phytohemagglutinin) tests in addition to the absolute numbers of T, B, and NK cells, remain essential.
7. Carrier testing of X-SCID:
   1. Testing for known family-specific *IL2RG* mutations.
   2. Sequence analysis of the *IL2RG* coding region and splice regions.
   3. Southern blot analysis is used to detect large deletions and complex mutations if the family-specific mutation is not known and sequence analysis is uninformative.
   4. X-chromosome inactivation studies on lymphocytes for at-risk females in whom sequence analysis and/or mutation analysis are not an option for carrier testing or are not informative, provided presence of the following two conditions:
      1. Skewed X-chromosome inactivation in lymphocytes
      2. Non-skewed X-chromosome inactivation in another blood lineage such as granulocytes
8. The remarkable advances in gene sequencing technology now allow the simultaneous sequencing of large number of genes or indeed whole exome or genome sequencing (Rivers and Gaspar 2015). Some studies show that targeted next-generation sequencing has sensitivity and specificity of >99% in detecting point mutations and 100% sensitivity and specificity of exonic deletions (Nijman et al. 2014). In this particular approach, accurate simultaneous detection of mutations in 161 of 170 known primary immunodeficiency (PID)-related genes was possible, meaning that screening for genetic mutations can be rapidly carried out where such conditions are suspected.

Genetic Counseling

1. Recurrence risk:
   1. X-SCID:
      1. Female germ line mosaicism present if a woman has more than one affected son and the disease-causing mutation in the *IL2RG* gene cannot be detected in her leukocytes.
      2. Over 50% of affected males do not have family history of early deaths in maternal male relatives.

3. Patient's sib if the mother is a carrier:
    1. Fifty percent of male sibs affected
    2. Fifty percent of female sib carriers
4. Patient's sib is still at increased risk even if the disease-causing mutation has not been identified in the mother's leukocytes since germ line mosaicism has been demonstrated in this condition.
5. Patient's offspring (offspring of affected males):
    1. Hundred percent of daughter carriers
    2. None of sons affected

2. Autosomal recessive SCID:
    1. Patient's sib: 25%
    2. Patient's offspring: not increased unless the spouse is a carrier in which case 25% of the offspring will be affected

2. Prenatal diagnosis:
    1. X-SCID:
        1. Determination on fetal cells obtained by CVS or amniocentesis
        2. Analysis of DNA from fetal cells for the known disease-causing mutation, provided:
            1. Karyotype revealing 46,XY.
            2. The disease-causing *IL2RG* mutation has been identified in a family member.
        3. Fetal blood sampling for immunological evaluation when the family-specific mutation is not known:
            1. Lymphocytopenia
            2. Low numbers of T cells
            3. Poor T-cell blastogenic responses to mitogens
    2. Autosomal recessive SCID:
        1. JAK3-deficient SCID (Schumacher et al. 1999):
            1. Immunophenotypic evaluation of cord blood cells at 18–20 weeks of gestation
            2. Direct gene analysis using chorionic villus sampling derived DNA in the first trimester
        2. ADA deficiency:
            1. Prenatal diagnosis established by measuring ADA enzyme activity in amniotic cells or chorionic villi (Aitken et al. 1986).
            2. Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family (Hershfield 2014).

3. Management (Secord 2009):
    1. General principles (Rivers and Gaspar 2015):
        1. Isolation of SCID infants: important to keep affected infants away from other children, infected individuals, large groups of individuals, and closed environments including public transport, in order to reduce exposure to pathogens.
        2. Vaccinations:
            1. Live vaccines must be avoided, and those who have already received *Bacillus* Calmette–Guérin vaccine (BCG) prior to diagnosis will need to start antituberculosis treatment.
            2. It is recommended that siblings of those with SCID should also not receive the rotavirus vaccine (Buckley 2004)
            3. Although routine vaccinations are unlikely to cause harm, they are unlikely to confer any additional benefit as they will not be effective.
        3. Nutrition: Nasogastric tube feeding or parenteral nutrition may be required in order to optimize nutrition.
        4. Prophylaxis: *Pneumocystis jirovecii* pneumonia prophylaxis should start with co-trimoxazole and additional antiviral and antifungal cover given depending on local guidelines and clinical circumstances.
        5. Immunoglobulin replacement: Replacement immunoglobulins should be given intravenously or subcutaneously every two to three weeks depending on response.
        6. Organism surveillance:

    1. Some centers conduct weekly screening of infants for herpes viruses (adenovirus, Epstein–Barr virus, and cytomegalovirus) as well as for respiratory and stool organisms.
    2. Early detection allows for intervention prior to end-organ damage and improved outcomes(Hiwarkar et al. 2012).
7. Breast feeding: Due to the increased risk of cytomegalovirus (CMV) transmission through breast milk, breast feeding is discouraged until the mother and infant's CMV status is known (Gaspar et al. 2013)).
8. Chicken pox: Early intervention with use of varicella zoster-specific immunoglobulin in those who have been in contact with the virus and treatment with Aciclovir in those with suspected infection are essential to avoid disseminated infection.
9. Blood products: All blood products will need to be CMV negative, irradiated, and leukocyte depleted in order to prevent donor T cells from attacking the infant and to prevent interference with future hematopoietic stem-cell transplant (HSCT).
10. Immunosuppression: Infants with Omenn's syndrome or maternal engraftment (see above) are likely to require immunosuppressive treatment such as systemic steroids and possibly cyclosporine in order to control the inflammatory reaction.
11. Enzyme replacement:
    1. In ADA-SCID, enzyme replacement therapy (ERT) can provide initial benefit in reducing the toxic accumulation of metabolites.
    2. Unfortunately, there are no equivalent agents to aid other forms of SCID.

2. X-linked SCID and JAK3 PTK deficiency:
    1. Fatal disease unless cured by bone marrow transplantation (BMT):
        1. The best results achieved by using an HLA-matched sibling as a donor (success rates of 97%)
        2. Using haploidentical T-cell-depleted BMT from a parent (haploidentical family donors resulting in lower success rates of 52%): lifesaving for the majority of X-SCID patients who lack matched sibling
    2. Monthly intravenous immunoglobulin replacement therapy is required if B cells do not engraft.
    3. Report of in utero transplantation of hematopoietic progenitor cells allowing immune reconstitution in a fetus (Wengler et al. 1996).
    4. Accurate prenatal diagnosis-assisted decision making and expanded treatment options for families at risk for having infants with a severe but treatable genetic disorder that presents early in life (Puck et al. 1997).
    5. Gene therapy (Hacein-Bey-Abina et al. 2010):
        1. Using autologous bone marrow stem/progenitor cells retrovirally transduced with a therapeutic gene.
        2. Successful in reconstituting the immune system in patients with X-SCID.
        3. Youngest two of the first ten infants treated in a French study developed leukemia due to retroviral insertional mutagenesis.
        4. After nearly 10 years of follow-up, gene therapy was shown to have corrected the immunodeficiency associated with SCID-X1. Gene therapy may be an option for patients who do not have an HLA-identical donor for hematopoietic stem-cell transplantation and for whom the risks are deemed acceptable (Hacein-Bey-Abina et al. 2010). This treatment is associated with a risk of acute leukemia.

3. ADA deficiency:
    1. Usually fatal unless:
        1. Keeping affected children in protective isolation.
        2. Allogeneic bone marrow transplantation (BMT) is the treatment of choice if an HLA-identical sibling bone marrow donor is available, resulting in almost 100% cure rate (Hoogerbrugge et al. 1996). BMT-related mortality is high in patients lacking such a donor.
        3. Reconstituting the immune system by bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling donor (therapy of choice but only available for a minority of patients).
    2. Exogenous enzyme replacement primarily with polyethylene glycol-conjugated ADA (PEG-ADA) replacement therapy (Hershfield 1993, 1995a, b; Blaese et al. 1995):
        1. Providing noncurative, lifesaving treatment for ADA-SCID patients
        2. Increased peripheral T-cell counts providing a source of T cells for gene correction not available without enzyme therapy
        3. Weight gain and decreased opportunistic infections in most patients
        4. Improved T-cell function as measured by in vitro mitogen responses in most patients
        5. Recovery of consistent immune responses to specific antigens in fewer patients
        6. An alternative to haploidentical bone marrow transplantation and an adjunct to gene therapy for adenosine deaminase deficiency
    3. The first genetic disorder treated by gene therapy: a clinical trial using retroviral-mediated transfer of the adenosine deaminase (*ADA*) gene into the T cells of children with ADA-SCID:
        1. Normalization of the number of blood T cells as well as many cellular and humoral immune responses
        2. Successful gene transfer into long-lasting progenitor cells, producing a functional multilineage progeny (Bordignon et al. 1995)
        3. Safe and effective addition to treatment for some patients
    4. Combined treatment with PEG-ADA and gene therapy
4. PNP deficiency and bare lymphocyte syndrome: primarily with bone marrow transplantation when an appropriate donor is available.
5. IL-2 production defects:
    1. Primarily with intravenous IL-2 replacement
    2. Alternatively with bone marrow transplantation when an appropriate donor is available
6. Omenn syndrome:
    1. Primarily with bone marrow transplantation when an appropriate donor is available
    2. Pretreatment ablative chemotherapy necessary because of maternal cell engraftment
7. SCID patients were the first to be successfully transplanted with nonsibling-related bone marrow, unrelated bone marrow, T-cell-depleted allogeneic hematopoietic stem-cell transplantation, and genetically corrected (gene transfer) autologous hematopoietic stem cells (Copenhagen Study Group of Immunodeficiency 1973; O'Reilly et al. 1977; Reisner et al. 1983; Bordignon et al. 1995; Rappeport et al. 2010).
8. Bone marrow transplantation from a related donor: a lifesaving and life-sustaining treatment for patients with any type of severe combined immune deficiency, even when there is no HLA-identical donor (Buckley et al. 1999).
9. While symptomatic and prophylactic treatment is available, hematopoietic

stem-cell transplantation is an option for many primary immunodeficiencies, leading to cure of the immunodeficiency and establishing normal physical and psychological health (Gennery 2015).

10. Hematopoietic stem-cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival (Myers et al. 2002).
11. Two fetuses successfully treated with gene therapy in utero by an injection of haploidentical $CD34^{+}$ cells for the γ chain deficiency.
12. In the recent past, the gene therapy field has witnessed a remarkable series of successes, many of which have involved primary immunodeficiency diseases, such as X-linked severe combined immunodeficiency, adenosine deaminase deficiency, chronic granulomatous disease, and Wiskott–Aldrich syndrome (Candotti 2016).
13. Psychosocial support for the affected family.
14. Avoid live vaccines.

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Fig. 1 A healthy 9-year-old boy with ADA-deficient SCID who has been receiving biweekly Adagen (pegademase) injections since early infancy

Short-Rib Polydactyly Syndromes

Contents

Short-rib polydactyly syndromes (SRPSs) are a heterogeneous group of recessively inherited lethal skeletal dysplasia. There are four classic subtypes: type I (Saldino-Noonan) (SRPS I), type II (Majewski) (SRPS II), type III (Verma-Naumoff) (SRPS III), and type IV (Beemer-Langer) (SRPS IV).

Synonyms and Related Disorders

Lethal short-rib polydactyly syndromes (Martinez-Frias et al. 1993); SRPS I (Saldino-Noonan syndrome, polydactyly with neonatal chondrodystrophy type I); SRPS II (Majewski syndrome, polydactyly with neonatal chondrodystrophy type II); SRPS III (Verma-Naumoff syndrome, polydactyly with neonatal chondrodystrophy type III); SRPS IV (Beemer-Langer syndrome, short-rib syndrome, Beemer type)

Genetics/Basic Defects

1. Inheritance:
   1. Autosomal recessive in all four subtypes
   2. Saldino-Noonan syndrome: affected sibs (Richardson et al. 1977)
   3. Majewski syndrome: parental consanguinity (Black et al. 1982; Cooper and Hall 1982), affected siblings (Motegi et al. 1979)
   4. Beemer type: affected sibs (Hennekam 1991)
2. Different subtypes of SRPS (Elçioğlu and Hall 2002):
   1. A great overlap of anomalies present among different subtypes contributing to diagnostic dilemmas in the short-rib polydactyly syndrome group
   2. Possibly represent a continuous spectrum with variable expressivity, suggested by some reports
3. Ciliary abnormalities due to defects in the retrograde transport protein DYNC2H1 in short-rib polydactyly syndrome (Merrill et al. 2009):
   1. Homozygosity by descent mapping in a consanguineous SRPS family identified a genomic region that contained *DYNC2H1*, a cytoplasmic dynein involved in retrograde transport in the cilium. Affected individuals in the family were homozygous for an exon 12 missense mutation that predicted the amino acid substitution R587C.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Compound heterozygosity for one missense and one null mutation were identified in two additional nonconsanguineous SRPS families.
3. Cultured chondrocytes from affected individuals showed morphologically abnormal, shortened cilia. In addition, the chondrocytes showed abnormal cytoskeletal microtubule architecture, implicating an altered microtubule network as part of the disease process.
4. These findings establish SRPS as a cilia disorder and demonstrate that *DYNC2H1* is essential for skeletogenesis and growth.
5. Mutations in *DYNC2LI1* disrupt cilia function and cause short-rib polydactyly syndrome (Taylor et al. 2015).
6. Identification of novel *DYNC2H1* mutations associated with short-rib polydactyly syndrome type III using next-generation panel sequencing (Chen et al. 2016).
7. *DYNC2H1* mutations also cause asphyxiating thoracic dystrophy: ATD and SRP type III are variants of a single disorder belonging to the ciliopathy group (Dagoneau et al. 2009).

4. *NEK1* mutations cause short-rib polydactyly syndrome type Majewski (Thiel et al. 2011).
5. *NEK1* and *DYNC2H1* are both involved in short-rib polydactyly Majewski type but not in Beemer Langer cases (Hokayem et al. 2012).
6. Short-rib polydactyly syndromes (SRPS) arise from mutations in genes involved in retrograde intraflagellar transport (IFT) and basal body homeostasis, which are critical for cilia assembly and function. Recently, mutations in *WDR34* or *WDR60* (candidate dynein intermediate chains) were identified in SRPS. Tctex1d2, which associates with Wdr34, Wdr60, and other dynein complex 1 and 2 subunits, has been identified and characterized (Gholkar et al. 2015). Tctex1d2 and Wdr60 localize to the base of the cilium and their depletion causes defects in ciliogenesis. *IFT52* mutations destabilize anterograde complex assembly, disrupt ciliogenesis, and result in short-rib polydactyly syndrome (Zhang et al. 2016).
7. Short-rib polydactyly and Jeune syndromes are caused by mutations in *WDR60* (McInerney-Leo et al. 2013).
8. Mutations in *KIAA0586* cause lethal ciliopathies ranging from a hydrolethalus phenotype to short-rib polydactyly syndrome (Alby et al. 2015).

Clinical Features

1. Variable expression of short-rib polydactyly syndrome (Sillence 1980; Sillence et al. 1987)
2. SRPS I (Saldino-Noonan)
   1. Constant findings:
      1. Severely shortened (flipper-like) limbs with postaxial polydactyly
      2. Small/narrow thorax with short ribs and hypoplastic lungs
      3. Protuberant abdomen
      4. Early neonatal death
   2. Common findings:
      1. Hydrops fetalis
      2. Gastrointestinal abnormalities:
         1. Esophageal atresia
         2. Short small intestine
         3. Malrotation of the bowel
         4. Imperforate anus
         5. Persistent cloaca
         6. Imperforate anus
         7. Pancreatic fibrosis and cysts
      3. Cardiac malformations:
         1. Transposition of the great vessels
         2. Coarctation of the aorta or hypoplastic aortic arch
         3. Ventricular septal defects
         4. Double-outlet left ventricle
   3. Occasional findings:
      1. Oligohydramnios
      2. Renal dysplasia/cystic disease
      3. Abnormal genitalia:
         1. Cryptorchidism
         2. Hypoplastic penis
      4. CNS malformations:
         1. Cerebellar hypoplasia
         2. Dandy-Walker malformation
      5. Bifid epiglottis

6. Bifid tongue
7. Cleft upper lip

3. SRPS II (Majewski) (Chen et al. 1980):
   1. Constant findings:
      1. Extremely short limbs with pre-/postaxial polydactyly of the hands and feet
      2. Small/narrow chest with short ribs and pulmonary hypoplasia
      3. Protuberant abdomen
      4. Median cleft lip or pseudocleft of the upper and lower lip or cleft palate
      5. Epiglottis and larynx hypoplasia
      6. Short/ovoid tibias with round ends
      7. Presence of premature ossification centers
      8. Early neonatal death
   2. Common findings:
      1. Polyhydramnios
      2. Hydrops fetalis
      3. Ocular hypertelorism
      4. Broad and flat nose
      5. Low-set ears
      6. Ambiguous genitalia
      7. Renal cystic disease
   3. Occasional findings:
      1. Short small intestine
      2. Malrotation of the bowel
      3. Cardiac malformations
      4. Dysplastic pancreas
4. SRPS III (Verma-Naumoff):
   1. Constant findings:
      1. Severely shortened limbs with postaxial polydactyly
      2. Small/narrow thorax with short ribs and hypoplastic lungs
      3. Early neonatal death
   2. Common findings:
      1. Hydrops fetalis
      2. Short cranial base
      3. Bulging forehead
      4. Depressed nasal bridge
      5. Flat occiput
      6. Renal cystic dysplasia
   3. Occasional findings:
      1. Congenital heart defects:
         1. Ventricular septal defect
         2. Situs inversus
      2. Epiglottic hypoplasia
      3. Intestinal malrotation
      4. Cloacal developmental abnormalities and ambiguous genitalia
5. SRPS IV (Beemer-Langer) (Beemer et al. 1983; Beemer 1987; Chen et al. 1994):
   1. Constant findings:
      1. Severely shortened limbs with (Yang et al. 1991; Elçioğlu et al. 1996) or without postaxial polydactyly
      2. Small/narrow thorax with short ribs and hypoplastic lungs
      3. Early neonatal death
   2. Common findings:
      1. Hydrops fetalis
      2. Macrocephaly with frontal bossing
      3. Ocular hypertelorism
      4. Flat nasal bridge
      5. Cleft lip and palate
      6. Protuberant abdomen
   3. Occasional findings:
      1. CNS abnormalities:
         1. Holoprosencephaly/absence of the corpus callosum/hydrocephalus
         2. Dandy-Walker cyst and/or arachnoid cyst
         3. Hypothalamic hamartomas
      2. Lobulated tongue with hamartomas
      3. Oral frenula
      4. Congenital heart defects
      5. Malrotation of the intestine
      6. Renal malformations:
         1. Renal cystic dysplasia
         2. Atresia of the ureter with hydronephrosis and hydroureter
      7. Omphalocele
      8. Inguinal hernia
6. SRPS-V (Schmidts 2014):
   1. SRPS-V was only recently described and the underlying genetic defect identified in two consecutively affected pregnancies of a mother from Maori descent from New Zealand.
   2. Hydrops, narrow chest, and severely shortened and bowed long bones displaying lack of ossification, hypoplastic scapulae, and peritoneal calcifications, postaxial polysyndactyly, and cleft palate were reported.

3. Extraskeletal findings include bilateral cystic hygroma, hypospadias, mainly glomerular kidney cysts, and intestinal malrotation.
4. Acromesomelic hypomineralization and campomelia distinguish SRPS-V from SRPS subtypes I–III (Kannu et al. 2007; Mill et al. 2011).

Diagnostic Investigations

1. Radiography:
   1. SRPS I (Saldino-Noonan):
      1. Extreme micromelia with severely dysplastic pointed (or ragged) metaphyses of the long tubular bones and absence of corticomedullary demarcation
      2. Narrow thorax with short/horizontal ribs
      3. Deficient ossification in calvarium, vertebrae, pelvis, and bones of the hands and feet
      4. Small iliac bones with horizontal acetabula
      5. Postaxial polydactyly
      6. Short tibiae
   2. SRPS II (Majewski):
      1. Extreme micromelia with smooth rounded metaphyses
      2. Extremely short horizontal ribs
      3. Normal pelvis and vertebrae
      4. Disproportionately shortened ovoid-shaped tibiae
      5. Pre- and postaxial polydactyly, syndactyly, and brachydactyly
      6. Advanced skeletal ossification maturation of the proximal femora and humeri
   3. SRPS III (Verma-Naumoff) (Naumoff et al. 1977):
      1. Extreme micromelia with severely dysplastic widened metaphyses (bones of the legs) and clear corticomedullary demarcation of the long tubular bones
      2. Extremely shortened and horizontal ribs
      3. Small and malformed vertebral bodies
      4. Shortened cranial base
      5. Short iliac bones with horizontal trident lower margin
      6. Polydactyly
   4. SRPS IV (Beemer-Langer):
      1. Extreme micromelia with smooth metaphyseal margins
      2. Extremely shortened and horizontal ribs
      3. Small, poorly ossified vertebrae and increased intervertebral spaces
      4. High clavicles and small scapulae
      5. Small iliac bones
      6. Bowed radii and ulnae
      7. Tibiae: well tabulated and longer than fibulae
      8. Postaxial polydactyly
   5. Examination of patients with the "Verma-Naumoff" short-rib polydactyly syndrome showed many radiologic and pathologic features similar to those of type 1 asphyxiating thoracic dysplasia (Yang et al. 1987).
2. Histopathology/necropsy:
   1. SRPS I (Saldino-Noonan):
      1. Markedly retarded and frequently deranged endochondral ossification. A large island of fibrous tissue may occupy the center of physeal growth zone. A premature ossification center may be seen in the epiphyseal resting cartilage.
      2. Lungs: hypoplasia which is easily assessed by abnormally small size and low weight.
      3. Identify associated multiple congenital anomalies listed in the clinical features.
   2. SRPS II (Majewski):
      1. Markedly retarded endochondral ossification. The chondrocytes in the physeal growth zones are markedly reduced in number and disorderly arranged
      2. Lungs: hypoplasia as in type I
      3. Identify associated multiple congenital anomalies listed in the clinical features.
   3. SRPS III (Verma-Naumoff):
      1. A "bajonet" deformity of the ribs for misalignment and overlap of cartilaginous and bony ends (Corsi et al. 2002). This deformity resulted from a "tandem" change in endochondral bone formation, that is, arrested orthotopic cartilage maturation and etherotopic perichondral

cartilage differentiation and ossification. At the cartilaginous end, cartilage maturation and vascular invasion were absent. At the bony end, longitudinal bone growth occurred by a perichondral ectopic growth plate.
2. Markedly retarded endochondral ossification as in type II.
3. A single patient showed chondrocytic inclusions which are PAS reactive and diastase resistant (Yang et al. 1980).
4. Lung: hypoplasia as in type I.
5. Identify associated multiple congenital anomalies which are less common in this type.

4. SRPS IV (Beemer-Langer):
   1. Physeal growth zones showing a prominent but disorganized zone of hypertrophy. The vascular penetration of physeal cartilage is irregular.
   2. Lungs: hypoplasia as in type I
   3. Identify associated multiple congenital anomalies listed in the clinical features.

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib: 25%.
   2. Patient's offspring: The patients will not survive to reproductive age.
2. Prenatal diagnosis, not always possible to differentiate the subtypes:
   1. Ultrasonography for SRPS I (Saldino-Noonan) (Meizner and Bar-Ziv 1989):
      1. Short fetal limbs
      2. Narrow thorax
      3. Polydactyly
      4. Pointed metaphyses
      5. Dysplastic cystic kidneys
      6. Congenital heart defect
      7. Genital anomalies
   2. Ultrasonography for SRPS II (Majewski) (Benacerraf 1993):
      1. With a positive family history of Majewski syndrome:
         1. Presence of short fetal limbs
         2. Other skeletal findings
      2. Without a family history:
         1. Short fetal limbs
         2. Disproportionately short tibia
         3. Very narrow fetal chest
         4. Short ribs
         5. Bilateral postaxial polydactyly of the hands and feet
         6. Median cleft lip and palate
         7. Polyhydramnios
         8. Hydrops
         9. Marked shortened humerus and femur
         10. Severe bowing and deformity of the bones of the lower leg and forearm
         11. Hypoplastic lungs
         12. Congenital heart defect
         13. Enlarged echogenic kidneys
         14. Genital anomalies
   3. Ultrasonography for SRPS III (Verma-Naumoff) (Meizner and Bar-Ziv 1985; Meizner and Barnhard 1995; Golombeck et al. 2001):
      1. Short fetal limbs
      2. Small/narrow thorax
      3. Short thin ribs
      4. Polydactyly
      5. Widened metaphyses with marginal spurs
      6. Micromelia
   4. Ultrasonography for SRPS IV (Beemer-Langer):
      1. Short fetal bones
      2. Small/narrow thorax
      3. Short thin ribs
      4. Polydactyly
   5. Prenatal diagnosis of short-rib polydactyly syndrome type 3 (Verma-Naumoff type) by three-dimensional helical computed tomography (Yamada et al. 2011)
   6. Fetoscopy (Toftager-Larsen and Benzie 1984):
      1. To identify fetus with SRPS phenotype
      2. An invasive procedure currently replaced by ultrasonography
3. Management:
   1. Supportive therapy only for these lethal entities.

2. In cases with SRPS, persistent pulmonary hypertension of the newborn (PPHN) can develop dependent on the degree of thoracic narrowness and pulmonary hypoplasia and that PPHN can be resistant to therapy (Demir et al. 2015).

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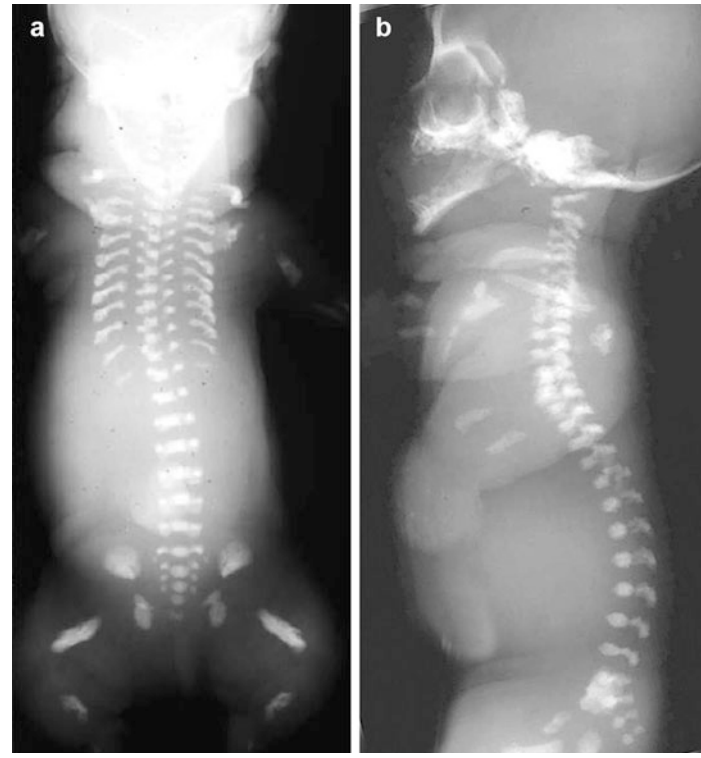

Fig. 1 (**a**, **b**) Radiograph of a neonate with Saldino-Noonan syndrome (SRPS I) showing extremely shortened horizontal ribs, very small and dysplastic vertebral bodies and iliac cones, and very short tubular bones with irregular metaphyses

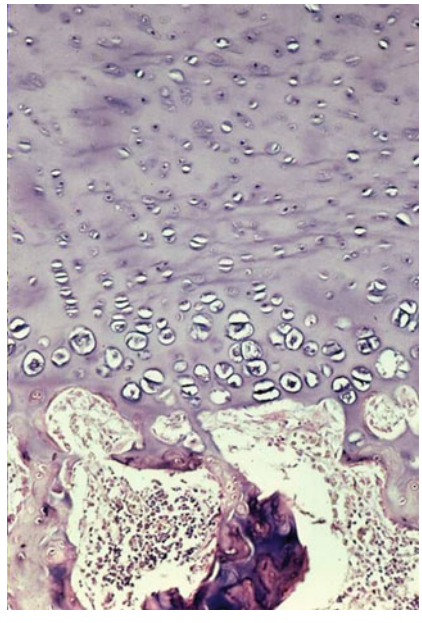

Fig. 2 Photomicrograph of femur (SRPS I) shows markedly retarded and disorganized physeal growth zone

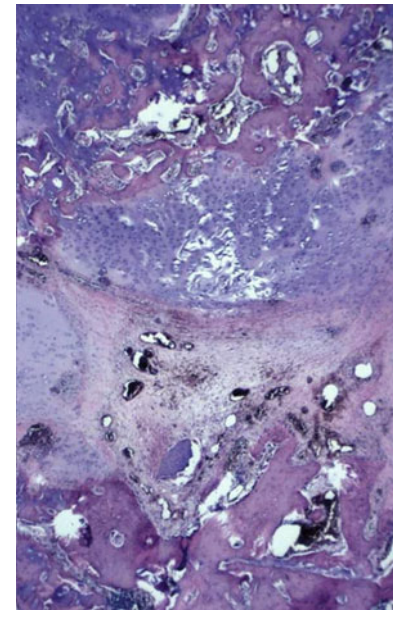

Fig. 3 Photomicrograph of humerus (SRPS I) shows markedly disrupted physeal growth zone by a large cartilage canal-like vascular fibrous tissue. In addition, there is a large premature ossification center (*upper* one third of the picture)

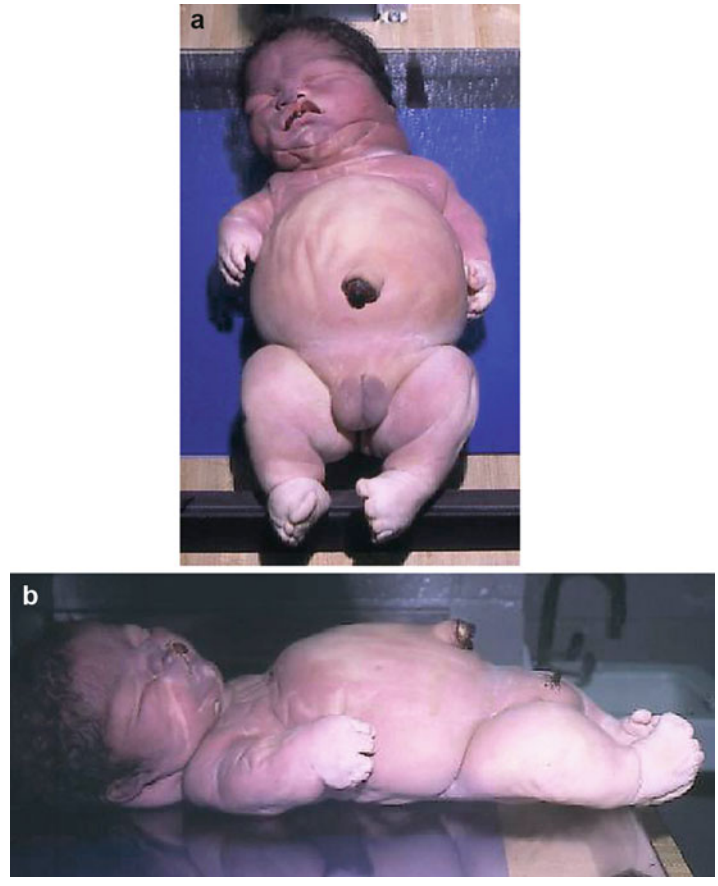

Fig. 4 (**a**, **b**) A neonate with Majewski syndrome (SRPS II) showed hydrops; a large head; hairy forehead; small, malformed, and low-set ears; telecanthus; short nose; a flat nasal bridge; a central cleft of upper and lower lips; short neck; short and narrow chest; markedly distended abdomen with ascites; and extremely short limbs with pre- and postaxial polydactyly, syndactyly, and brachydactyly

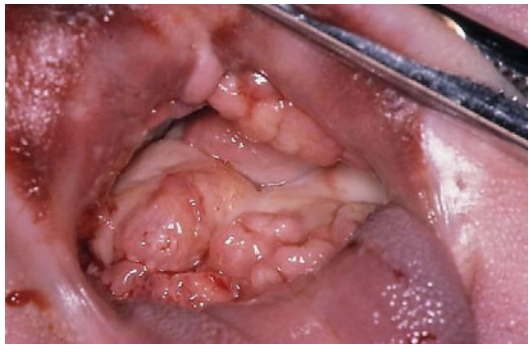

Fig. 5 Mouth of the neonate in Fig. 4 showing lobulated tongue and mucosal frenula

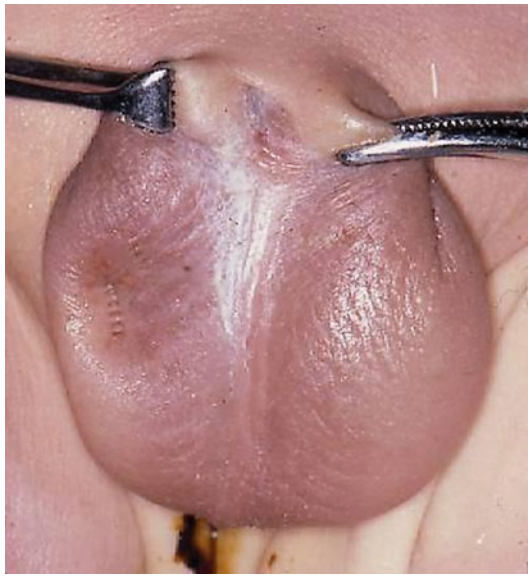

Fig. 6 Ambiguous genitalia with a barely visible micropenis (SRPS II)

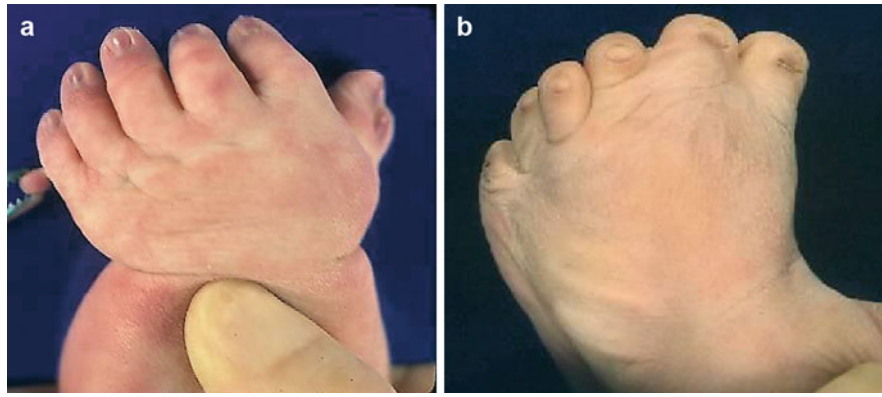

Fig. 7 (**a**, **b**) Hands and feet showed pre- and postaxial polydactyly, syndactyly, and brachydactyly (SRPS II)

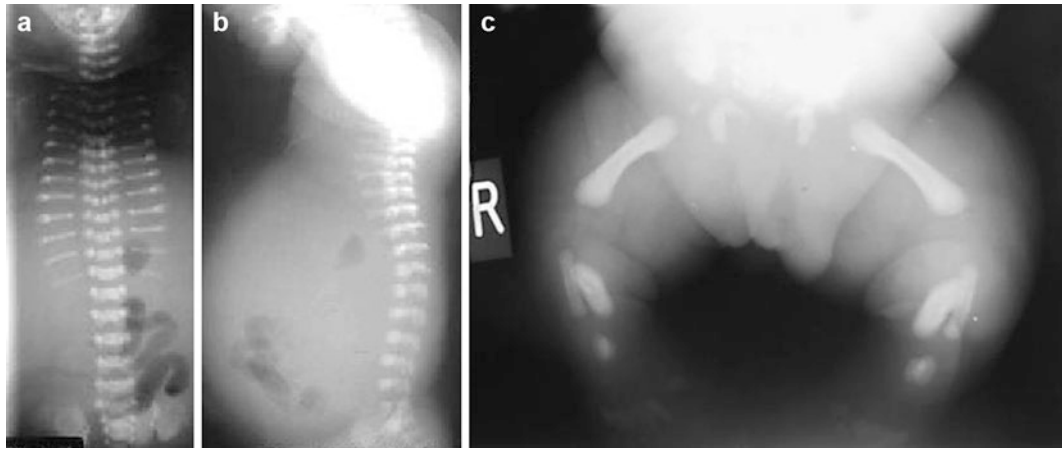

Fig. 8 (**a**–**c**) Radiographs (SRPS II) showing extremely short and horizontal ribs, high clavicles, unremarkable spine and pelvis, and premature ossification of the proximal epiphyses of the humeri, femora, and lateral cuboids. The tubular bones were extremely short, especially the mesomelic segments. The tibiae were disproportionately short and oval in shape

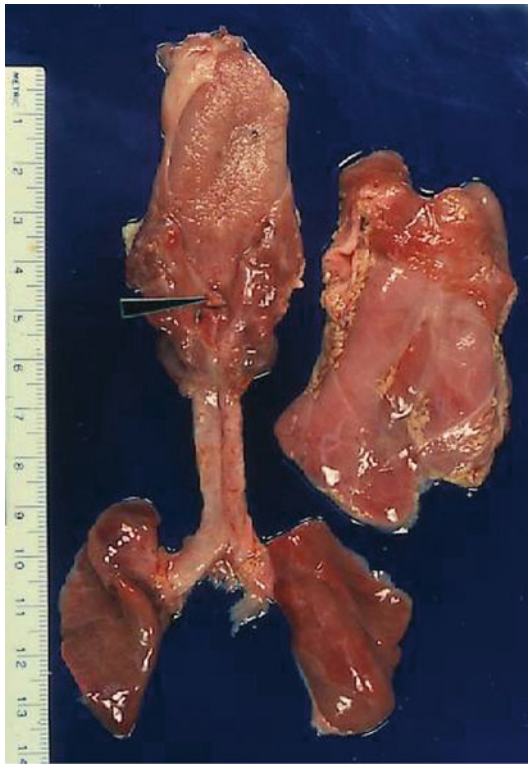

Fig. 9 Respiratory system (necropsy) (SRPS II) showing a small larynx with hypoplastic epiglottis (*arrow*) and remarkably small and hypoplastic lungs. The patient's thymus is juxtaposed for comparison

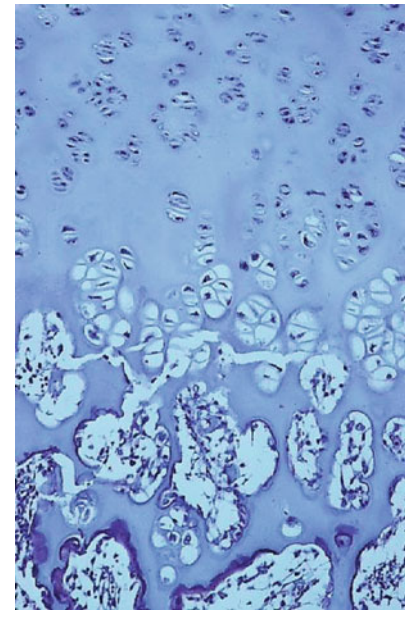

Fig. 10 Photomicrograph of tibia cartilage (SRPS II) (Hematoxylin-eosin, ×108) showing a markedly stunted and disorganized physeal growth zone

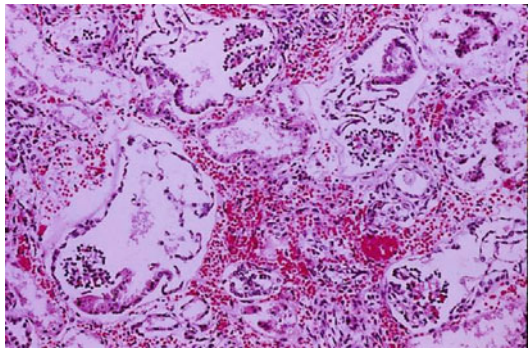

Fig. 11 Photomicrograph of renal cortex showing many dilated glomeruli and mildly cystic renal tubules (SRPS II)

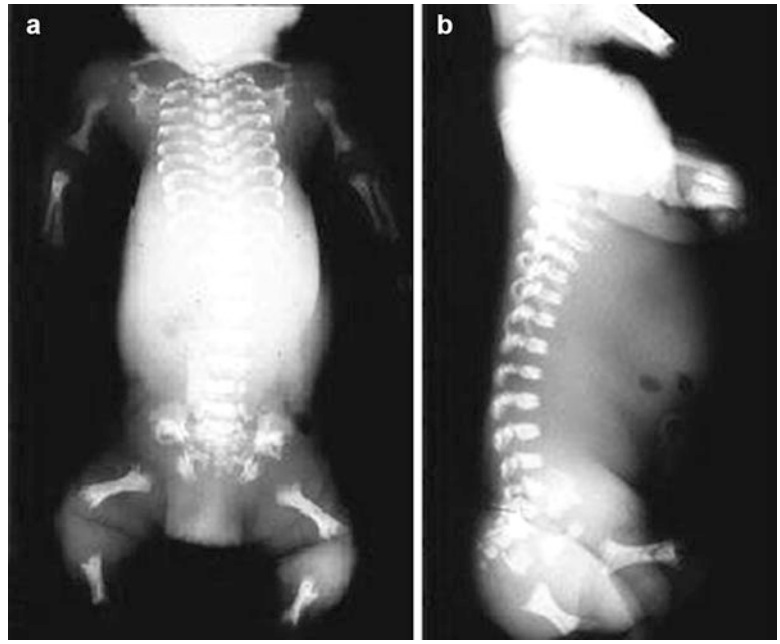

Fig. 12 (**a**, **b**) Radiographs of the skeletal system (SRPS III) showing extremely short and horizontal ribs, small dysplastic vertebral bodies and ilia, and short tubular bones with widened metaphyses with longitudinal spurs

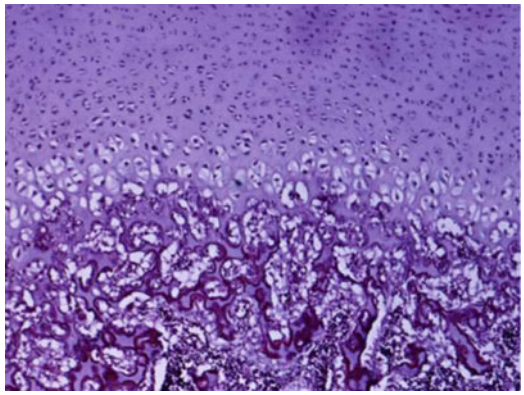

Fig. 13 Photomicrograph of the cartilage of the iliac crest (SRPS III) showing retardation and disorganization of physeal growth zone

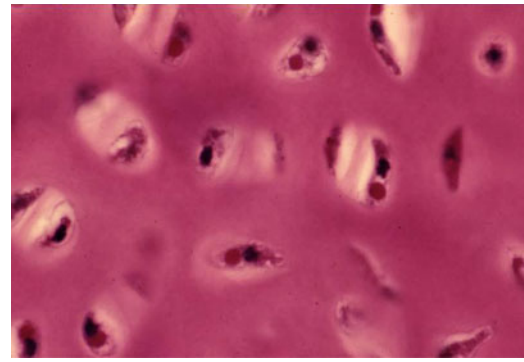

Fig. 14 Higher magnification of the chondrocytes in the resting cartilage and the physeal zone of proliferation frequently show cytoplasmic inclusions (PAS after diastase digestion) (SRPS III)

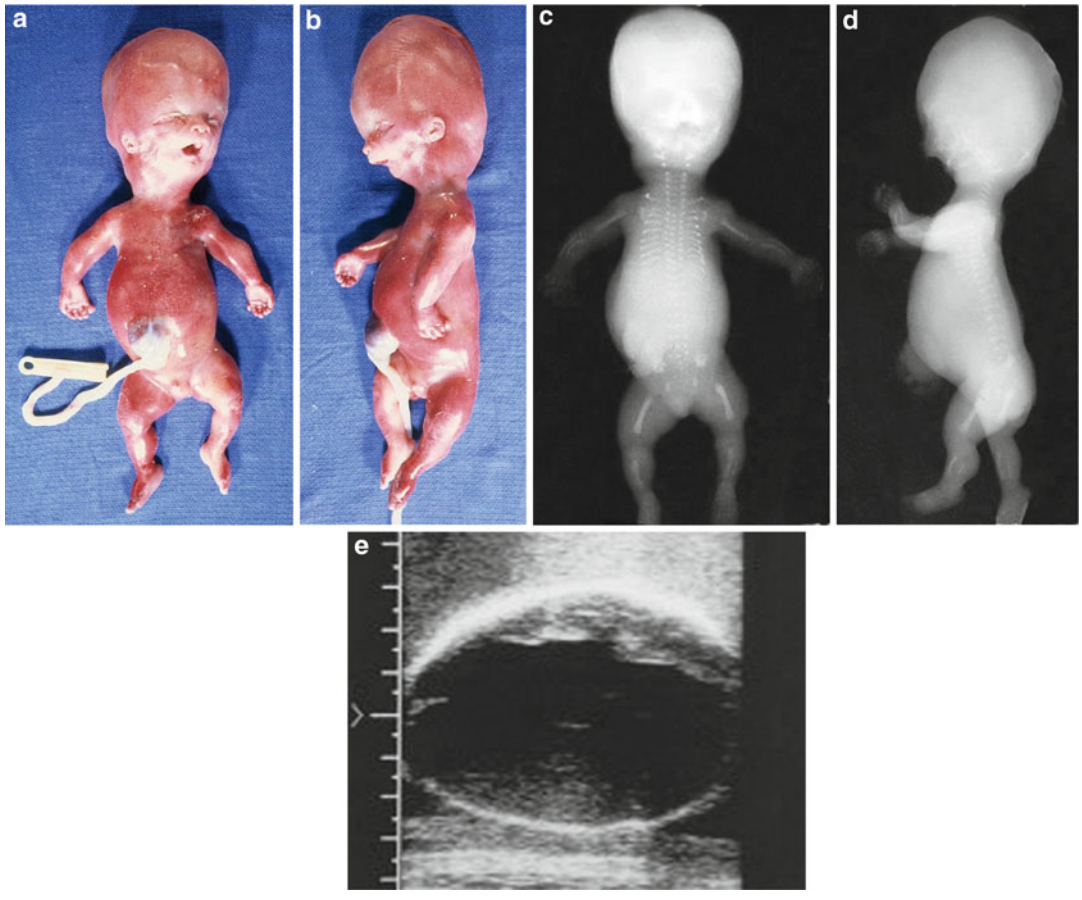

Fig. 15 (**a**–**e**) A fetus with Beemer-Langer syndrome showing macrocephaly, cystic hygroma, severe micro-/retrognathia with cleft palate, low-set and malformed ears, short limbs, narrow thorax, protuberant abdomen with an omphalocele, and polydactyly. The radiographs show short and horizontal ribs, small scapulae, relatively poorly ossified vertebral bodies, small ilia, short tubular bones with absence of metaphyseal spicules, bowed radii and ulnae, and postaxial polydactyly. The ultrasonography shows porencephalic cyst. The fetus also had a de novo paracentric inversion of chromosome 17q (q12;q25)

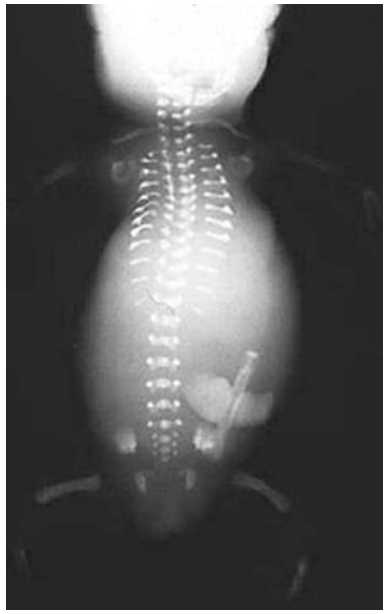

Fig. 16 Radiograph of another premature neonate (SRPS IV) showing extremely short and horizontal ribs, small dysplastic vertebral bodies, small iliac wings, and short tubular bone

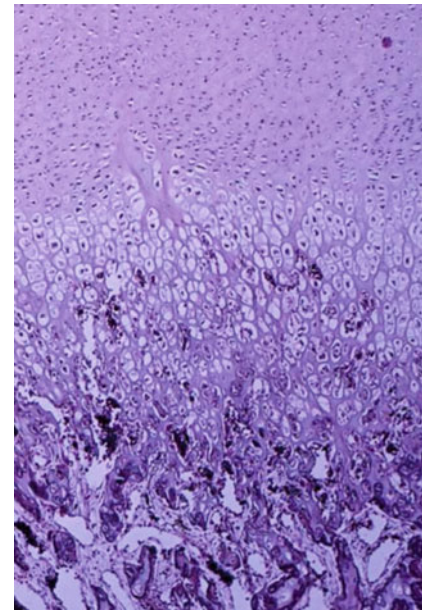

Fig. 17 Physeal growth zone of femur showing prominent but disorganized zone of hypertrophy (SRPS IV)

Sickle Cell Disease

Contents

Sickle cell disease (SCD) is the most common single gene disorder in Afro-Americans, affecting approximately 1 in 375 persons of African ancestry. The frequency of sickle cell trait is about 8% in the US blacks. Sickle blood cells have an increased resistance to malaria. Protection from malaria helps maintain the high prevalence of the sickle gene in areas where malaria is endemic (Fixler and Styles 2002).

Synonyms and Related Disorders

Sickle cell anemia; Sickle cell trait; Sickle β^{+}-thalassemia; Sickle β-thalassemia (Sβ-thalassemia and $S\beta^{o}$ thalassemia); Sickle-hemoglobin C disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. Caused by a point mutation at the second nucleotide of codon 6 of the β-globin gene. The base change of A to T causes the amino acid substitution of valine for glutamic acid (GAG to GTG):
    1. Immediate consequence of the mutation: Deoxygenated hemoglobin S polymerizes and distorts the shape of the red blood cell, causing vasoocclusion in the small vessels.
    2. Adverse effects of sickle hemoglobin on the red cell membrane:
        1. Oxidative damage
        2. Cellular dehydration
        3. Abnormal phospholipid asymmetry
        4. Increased adherence to endothelial cells
    3. Results of cellular abnormalities:
        1. Shortened red cell lifespan causing a lifelong hemolytic anemia
        2. Intermittent episodes of vascular occlusion causing tissue ischemia and acute and chronic organ dysfunction
3. Four genotypes: Sickle cell anemia (HbSS), sickle-hemoglobin C disease (HbSC), and 2 types of sickle β-thalassemia (Sβ-thalassemia and $S\beta^{o}$ thalassemia) account for most SCD in the USA (American Academy of Pediatrics 2002). Less common forms of SCD are caused by coinheritance of HbS with other hemoglobin variants, such as hemoglobin D-Punjab. Genes for SCD are common in persons of African, Mediterranean, Middle Eastern, and Indian ancestry and persons from the Caribbean and parts of Central and South America.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Sickle cell disease (Lane 1996; Driscoll 2007):
    1. Sickle cell anemia (homozygous sickle cell disease, Hb SS):
        1. Accounts for 60–70% of sickle cell disease in the USA
        2. The most common form of sickle cell disease
        3. Caused by inheritance of hemoglobin S from both parents
    2. Other clinically significant sickle cell disorders caused by coinheritance of a sickle gene with a gene for:
        1. β-thalassemia:
            1. The β-thalassemias are divided into β^{+}-thalassemia (in which some β-globin chains are produced) and β^{o}-thalassemia (in which there is no β-chain synthesis).
            2. Clinical pictures of patients with hemoglobin S β^{+}-thalassemia and S β^{o}-thalassemia resemble sickle cell disease rather than thalassemia, because the sickle β-globin predominates in the presence of underproduction of normal β-globin.
        2. Hb C
        3. Hb $D_{Los\ Angels}$
        4. Hb E (HBB Glu25Lys) (Masiello et al. 2007):
            1. One of the world's most common hemoglobin variants.
            2. Found primarily in Sri Lanka, Eastern India, Southeast Asia, and Southwest China.
            3. Individuals homozygous for Hb E have mild anemia and microcytosis and are clinically asymptomatic.
            4. Compound heterozygotes for Hb S and Hb E are increasingly found throughout the world due to population migrations and racial intermarriages over the last century.
            5. Clinical course of adults with Hb SE disease resembles that of Hb S/β^{+}-thalassemia.
            6. Patients who are compound heterozygotes for Hb E and a β-thalassemia mutation have variable phenotypes from mild to severe; the latter is virtually indistinguishable from β-thalassemia major (Fucharoen and Winichagoon 2000).
            7. This is because the Hb E mutation creates a cryptic splice site and therefore manifests also as a mild β^{+}-thalassemia mutation (Orkin et al. 1982).
        5. Hb Lepore
        6. Hb O_{Arab}
        7. Hb C_{Harlem}
        8. Hb Quebec-CHORI
5. Pathophysiology of sickle cell disease (Bookchin and Lew 1996):
    1. Hemolysis: The shortened survival of SS red blood cells results from the following two apparently independent properties of Hb S:
        1. Propensity of the concentrated Hb to polymerization resulting in:
            1. Morphologic sickling
            2. RBC dehydration
            3. A marked decrease in RBC deformability
        2. Hemoglobin S instability
    2. Erythropoiesis:
        1. Submaximal erythropoietic response
        2. Abnormally low affinity for oxygen of SS cells
        3. Response of the red cells' glycolytic metabolism to hypoxia

Clinical Features

1. Infection:
    1. The most immediate risk for infants diagnosed with sickle cell disease
    2. Prone to many bacterial infections, especially from encapsulated organisms, because of lack of splenic function resulting from progressive infarction of the spleen due to sickling of the red cells
2. Hemolysis:
    1. Chronic anemia: Hemolytic anemia develops around 3 months of age.

2. Jaundice (indirect hyperbilirubinemia).
3. Aplastic crises (Rao et al. 1992):
    1. Erythrocyte production by the bone marrow may pause temporarily in children with sickle cell disease.
    2. Human parvovirus B19 infection responsible for 80% of aplastic crises
4. Cholelithiasis:
    1. Prone to develop pigmented gallstones due to large load of bilirubin from hemoglobin breakdown (chronic hemolysis)
    2. Presenting symptoms: severe recurrent right upper quadrant pain, episode of cholecystitis, common duct obstruction, or pancreatitis
5. Delayed growth and sexual maturation

3. Vasoocclusion due to occlusion of the microcirculation by rigid red cells and consequent tissue anoxia and infarction:
    1. Recurrent acute pain:
        1. Dactylitis (hand and foot syndrome) occurs in 25–45% of the patients and can be the earliest manifestation of sickle cell disease. The syndrome is rare after 4 years of age. It is believed to be due to infarction of the red marrow and associated periosteal inflammation. The clinical manifestations are fever and painful swelling of the hands or feet or both.
        2. Musculoskeletal pain
        3. Abdominal pain
    2. Functional asplenia (Lane 1996):
        1. The proportion of children with Hb SS who are functionally asplenic: 1 year (28%), 2 years (58%), 3 years (78%), and 5 years (94%)
        2. At risk for fulminant septicemia and meningitis with pneumococci and other encapsulated bacteria and death during the first 3 years of life in most patients with Hb SS
    3. Splenic sequestration (10–30% of children with Hb SS most commonly between 6 months and 3 years of life):
        1. Sudden massive collection of blood in the spleen due to sickle cells blocking outflow
        2. Rapid enlargement of the spleen causing acute fall of the hemoglobin level of more than 2 g/dL, despite a persistently elevated reticulocyte count
        3. Mild to moderate thrombocytopenia caused by sequestered platelets
        4. Symptoms:
            1. Acute pallor
            2. Lethargy
            3. Increased thirst
            4. Abdominal fullness
            5. Tachycardia
            6. Tachypnea
        5. May be associated with other complications of sickle cell disease, such as acute chest syndrome, vasoocclusive pain, bacterial infection, stroke, or aplastic crisis
        6. Increased tendency of recurrence (50%)
        7. High mortality (second leading cause of death in children with sickle cell anemia)
4. Head and neck manifestations: a significant component of the disease (Steven et al. 2016):
    1. Bony changes and lymphoid enlargement are characteristic.
    2. Orbital and inner ear crises may induce significant visual and hearing impairments.
5. Acute chest syndrome (Lane 1996; Quinn and Buchanan 1999):
    1. Appearance of a new pulmonary infiltrate on chest radiography
    2. Causes:
        1. Infection (bacterial pneumonia, atypical bacterial pneumonia by *Mycoplasma* or *Chlamydia*, viral pneumonia, parvovirus B19)
        2. Pulmonary vascular occlusion (in situ pulmonary thrombosis, fat embolism, peripheral thromboembolism)
        3. Hypoventilation/atelectasis (thoracic bony infarction, abdominal pain, opioids)

4. Pulmonary edema (intravenous fluids, opioids, pulmonary vascular injury)
5. Bronchospasm

3. The most frequent presenting symptoms:
   1. Varying degrees of fever
   2. Cough
   3. Tachypnea
   4. Shortness of breath
   5. Pleuritic chest pain
   6. Chills
   7. Wheezing
   8. Hemoptysis
   9. Hypoxemia
4. Occurs in more than 50% of pediatric patients with Hb SS
5. The second leading cause for hospitalization
6. Predispose to chronic restrictive lung disease with pulmonary hypertension (Gladwin et al. 2004) and cor pulmonale (important causes of morbidity and mortality in adulthood)

6. Stroke (Lane 1996):
   1. Caused by complete occlusion or severe narrowing of large cerebral vessels
   2. Occurs in 7–8% of children with Hb SS after the first year of life, less commonly in children with Hb SC and sickle β-thalassemia
   3. Presenting symptoms:
      1. Hemiparesis
      2. Monoparesis
      3. Aphasia
      4. Dysphasia
      5. Seizures
      6. Semicoma
      7. Coma
      8. Transient ischemic attack
   4. High rate of recurrence (60–90% have a second stroke within 3 years without transfusion therapy)
   5. Silent cerebral infarctions in 10–20% of children with Hb SS without clinically apparent neurologic event
7. Chronic nephropathy: an important cause of mortality in adult patients (Saborio and Scheinman 1999; Molitierno 2003; Gargiulo et al. 2014; Nath and Hebbel 2015):
   1. Hematuria:
      1. Persistent microscopic (asymptomatic) hematuria: one of the most prevalent features of the disease
      2. Gross hematuria
   2. Renal tubular acidosis
   3. Significant proteinuria (30%)
   4. Papillary necrosis
   5. Hyposthenuria and enuresis: inability to concentrate urine resulting in a high incidence of enuresis
   6. Nephrotic syndrome (40%)
   7. Renal infarction
   8. Pyelonephritis
   9. Renal medullary carcinoma
   10. Hypertension (2–6% in patients with Hb SS)
   11. Renal failure (5–18%)
8. Priapism (painful erection) (Powars and Johnson 1996):
   1. Affects about two thirds of male patients
   2. Recurrent attacks eventuate in impotence in 50% of the patients
9. Bone disorders (Smith 1996):
   1. Dactylitis (hand and foot syndrome).
   2. Bone infarction: Manifestations include pain, tenderness, and frequently swelling at the involved site(s).
   3. Aseptic necrosis of the long bones: Manifestations include pain or limitation of motion in the hip, shoulder, or other joints and during walking and climbing stairs.
10. Proliferative retinopathy
11. Leg ulcers (Eckman 1996):
    1. Most common cutaneous complication in sickle cell anemia
    2. Causing pain, physical disfigurement, social isolation, vocational adversity, and high utilization of health-care resources
    3. Most common in the ankle area over the medial or lateral malleoli and less

common over the dorsum of the foot and near the Achilles tendon
4. Universal secondary infections (*Staphylococcus aureus* and *Pseudomonas aeruginosa* most common pathogens)

12. Osteomyelitis (Burnett et al. 1998):
1. *Salmonella* (most common cause)
2. *Staphylococcus aureus*

13. Transfusional hemosiderosis

4. Prognosis:
1. Natural history of sickle cell anemia (Powars 1975) conducted before mandated newborn screening programs: 15% of children die from acute infections or acute anemic events in the first 5 years of life. The overall mortality rate for patients with sickle cell anemia diagnosed in the newborn period was 1.8% (Vichinsky et al. 1988).
2. Hb SC disease:
1. Clinical manifestations milder than Hb SS disease
2. Mild hemolytic anemia
3. Risk of overwhelming sepsis and death: less than that in Hb SS disease because of the later onset of splenic dysfunction
4. Risk of splenic sequestration up to young adulthood
5. Splenomegaly
6. Vasoocclusion
7. Proliferative retinopathy
8. Aseptic necrosis of femoral head

3. Early infectious morbidity and mortality (Vichinsky 1991) in Hb SS and sickle β^o-thalassemia preventable by:
1. Presymptomatic diagnosis by neonatal screening
2. Extensive parental education
3. Prophylactic penicillin for infants with Hb SS and Sβ^o-thalassemia (125 mg by mouth twice a day begun between 2 months and 3 years of age and 250 mg twice daily until at least 5 years of age)
4. Timely immunizations (all routine immunizations in a timely fashion; new heptavalent conjugated pneumococcal vaccine administered at 2 months of age; influenza virus vaccines yearly after 6 months of age; meningococcal vaccine for children with splenic dysfunction)
5. Prompt medical evaluation and management of febrile illness

4. Sickle cell disease and pregnancy (Sun et al. 2001). Affected pregnant women are at risk for:
1. Crisis.
2. Toxemia.
3. Pyelonephritis.
4. Thrombophlebitis.
5. Spontaneous abortion.
6. Intrauterine growth restriction.
7. Antepartum hospital admission.
8. Postpartum infection.
9. In addition, deliveries among women with Hb SS were more likely to be complicated by low birth weight, prematurity, and preterm labor or preterm premature rupture of membranes when compared with deliveries among women with hemoglobin AA.

5. Progress toward specific therapies:
1. Transfusion therapy
2. Bone marrow transplantation
3. Hydroxyurea

Diagnostic Investigations

1. Laboratory studies (Chen 1992; Lane 1996):
1. CBC and reticulocyte counts to document anemia and brisk marrow response
2. Peripheral blood smear to document presence of sickled erythrocytes, target cells, and Howell-Jolly body (indicating functional asplenism)
3. Differential white cell count
4. Arterial blood gases to reflect the severity of pulmonary crises
5. Hemoglobin electrophoresis to document Hb SS or Hb S with another mutant hemoglobin in compound heterozygotes
6. Liver function tests, BUN, creatinine, and serum electrolytes

7. Fetal hemoglobin

2. Imaging studies (Madani et al. 2007):
    1. Radiography:
        1. Performed in patients with respiratory symptoms:
            1. Pneumonia
            2. Acute chest syndrome: a new focus of opacity (which may be segmental, lobar, or multilobar) or collapse with or without a pleural effusion on a chest radiograph, associated with a variable combination of signs and symptoms including fever, leukocytosis, hypoxia, and chest pain (Charache et al. 1979)
        2. To detect areas of infarction for painful bones
    2. MRI:
        1. To detect areas of avascular necrosis for the femoral and humeral heads and to distinguish osteomyelitis from bony infarction.
        2. The majority of overt stroke and silent cerebral infarction occur from a distribution of the internal carotid artery, and pathologies are frequently observed in tissue within the anterior cerebral and middle cerebral arterial distribution (Zhang et al. 2016).
    3. MRI and MR angiography (MRA) of the brain:
        1. To detect infarction, ischemia and atrophy (44% prevalence), and vasculopathy (55% prevalence) in children with sickle cell disease (Steen et al. 2003)
        2. Moyamoya (Japanese for a "hazy puff of smoke"): an angiographic pattern of large vessel occlusion and telangiectatica collateral circulation, seen in patients with sickle cell disease (Dobson et al. 2002), as well as other conditions, such as tuberous sclerosis, neurofibromatosis, vasculitides, and infection
    4. Abdominal sonogram to document spleen size and the presence of biliary stones.
    5. Transcranial Doppler ultrasonography useful in selecting patients at risk for stroke.
    6. Cavernosonography and radionuclide scanning to assess penile hemodynamics are useful in determining whether priapism is of the low-flow type (Powars and Johnson 1996).
3. Sickle cell anemia (Hb SS) (Wethers 2000a):
    1. Relative clinical severity:
        1. Markedly severe hemolysis
        2. Markedly severe vasoocclusion
    2. Neonatal screening: hemoglobin FS
    3. Hemoglobin electrophoresis (Lane 1996):
        1. Hb A: 0%
        2. Hb S: 80–95%
        3. Hb F: 2–20%
        4. Hb A_2: <3.5%
        5. Hb C: 0%
    4. Thin layer isoelectric focusing:
        1. Gives better resolution of hemoglobins other than Hb A, Hb S, Hb C, and Hb F
        2. Less experience using this method for screening and more costly
    5. High-performance liquid chromatography:
        1. Differentiates many Hbs (Hbs F, A, S, C, D, E)
        2. Hb S + Hb F + Hb A_2 (probable sickle cell disease)
        3. Hb A + Hb S + Hb A_2 (Sickle cell trait)
        4. Hb A + Hb C (Hb C trait)
        5. Hb C (Hb C disease)
        6. Hb S + Hb C (sickle C disease)
        7. Is quantitative (can differentiate sickle trait from sickle β-thalassemia and identify β-thalassemia)
    6. Sickle prep:
        1. Does not distinguish between heterozygote and homozygote
        2. Easy for mass screening
        3. Inappropriate for newborn screening
    7. Solubility test:
        1. Hb S detected by precipitation/turbidity
        2. Does not distinguish sickle cell anemia from other sickle diseases
        3. May give false negative if Hb is low

4. May give false positive if lipidemia is present
5. Easy to use for mass screening if only the presence of Hb S is desired
6. Inappropriate for newborn screening

8. DNA diagnosis

4. Sickle β^o-thalassemia (Wethers 2000a)
   1. Relative clinical severity:
      1. Moderate severe hemolysis
      2. Moderate severe vasoocclusion
   2. Neonatal screening: hemoglobin FS
   3. Hemoglobin electrophoresis:
      1. Hb A: 0%
      2. Hb S: 80–92%
      3. Hb F: 2–15%
      4. Hb A_2: 3.5–7.0%
      5. Hb C: 0%
5. Sickle-hemoglobin C disease (Hb SC) (Wethers 2000a):
   1. Relative clinical severity:
      1. Mild hemolysis
      2. Mild vasoocclusion
   2. Neonatal screening: hemoglobin FSC
   3. Hemoglobin electrophoresis:
      1. Hb A: 0%.
      2. Hb S: 45–50%.
      3. Hb F: 1–5%.
      4. Hb A_2: Quantity of A_2 cannot be measured in the presence of Hb C.
      5. Hb C: 45–50%.
6. Sickle β^+-thalassemia (Wethers 2000a):
   1. Relative clinical severity:
      1. Mild to moderate hemolysis
      2. Mild to moderate vasoocclusion
   2. Neonatal screening: hemoglobins FSA and FS
   3. Hemoglobin electrophoresis:
      1. Hb A: 5–30%
      2. Hb S: 65–90%
      3. Hb F: 2–10%
      4. Hb A_2: 3.5–6.0%
      5. Hb C: 0%
7. Sickle cell trait:
   1. Relative clinical severity: normal phenotype
   2. Neonatal screening: hemoglobin FAS
   3. Hemoglobin electrophoresis:
      1. Hb A: 50–60%
      2. Hb S: 35–45%
      3. Hb F: <2%
      4. Hb A_2: <3.5%
      5. Hb C: 0%
8. Normal:
   1. Relative clinical severity: normal phenotype
   2. Neonatal screening: hemoglobin FA
   3. Hemoglobin electrophoresis:
      1. Hb A: 95–98%
      2. Hb S: 0%
      3. Hb F: <2%
      4. Hb A_2: <3.5%
      5. Hb C: 0%
9. Newborn hemoglobinopathy screening:
   1. Provided in all 50 states in the USA.
   2. The most commonly used screening method: electrophoresis and high-performance liquid chromatography.
   3. Fetal hemoglobin present predominantly in young infants.
   4. Positive results to be followed by fetal hemoglobin electrophoresis for confirmation.
   5. Results with only Hb F and S: suggest the infant has either sickle cell anemia or sickle β^o-thalassemia.
   6. Results with Hb F, S, and C: suggest the infant has hemoglobin SC disease.
   7. Results with Hb F, S, and A, and the infant has not been transfused:
      1. Hb S > Hb A: most likely sickle β^+-thalassemia
      2. Hb A > Hb S: presumed sickle cell trait
      3. Hb A ≈ Hb S:
         1. Study the parents to determine if one of them has the thalassemia trait
         2. Repeat Hb electrophoresis after several months
10. Molecular genetic testing:
    1. Carrier testing:
       1. Most commonly accomplished by high-performance liquid chromatography
       2. Isoelectric focusing
       3. DNA-based assays

2. Prenatal diagnosis: most commonly use DNA-based assays for the detection of the Hb S mutation
3. Testing methods
    1. Targeted mutation analysis:
        1. Hb S (E6V)
        2. Hb C (E6K)
        3. Hb D (E121Q)
        4. Hb O-Arab (E121K)
    2. Sequence analysis for Hb mutations

Genetic Counseling

1. Recurrence risk:
    1. Homozygous sickle cell disease (Hb SS). The child inherits a sickle (S) gene from each parent:
        1. Risk to patient's sibs: 25%
        2. Risk to patient's offspring: not increased unless the spouse is a carrier
    2. Sickle-hemoglobin C disease (Hb SC). The child inherits an S gene from one parent and a C gene from the other parent:
        1. Risk to patient's sibs: 25% if Hb AS in one parent and Hb AC in other parent
        2. Risk to patient's offspring: not increased unless the spouse is either Hb AS or Hb AC carrier
    3. Sickle β-thalassemias. The child inherits an S gene from one parent and a β-thalassemia gene from the other parent:
        1. Risk to patient's sibs: 25% if sickle cell carrier in one parent and β-thalassemia carrier in other parent
        2. Risk to patient's offspring: not increased unless the spouse is a carrier for either Hb S or β-thalassemia gene
2. Prenatal diagnosis:
    1. Possible by analysis of DNA extracted from fetal cells obtained by amniocentesis or CVS
    2. Both disease-causing hemoglobin alleles of the carrier parents must be identified before prenatal testing.
    3. Formal genetic counseling needed when the mother is a known carrier and the father is unknown and/or unavailable for testing.
3. Preimplantation genetic diagnosis (PGD) (El-Toukhy et al. 2010):
    1. PGD may be an option for some families in which the HBB (hemoglobin subunit beta, a protein coding gene) pathogenic variants have been identified (Bender and Hobbs 2014).
    2. PGD for SCD has been performed using PCR and RFLP for detection of the SCD mutation with linked markers (Kuliev et al. 1998, 2005; De Rycke et al. 2001).
    3. The A > T point mutation at codon 7 of the β-globin gene, responsible for SCA, can be easily identified by the *Ddel* or *MstII* restriction enzymes.
4. Management (Wethers 2000b; American Academy of Pediatrics 2002):
    1. Preventive care (health maintenance):
        1. Immunizations:
            1. *Haemophillus influenzae* type b (Hib) vaccine
            2. 7-valent pneumococcal conjugate vaccine
            3. 23-valent pneumococcal polysaccharide vaccine
            4. Consider quadrivalent meningococcal polysaccharide vaccine
            5. Influenza immunization recommended yearly
        2. Prophylactic medications:
            1. Penicillin prophylaxis: effective in preventing 80% of life-threatening episodes of childhood *Streptococcus pneumoniae* sepsis
            2. Erythromycin prophylaxis: an alternative for individuals allergic to penicillin
            3. Consider folic acid supplementation
        3. Other preventive strategies:
            1. Transcranial Doppler to screen the presence of abnormal velocity of arterial blood flow (at risk for stroke)
            2. Screening for pulmonary hypertension, proteinuria, retinopathy, osteonecrosis, neurocognitive dysfunction, liver disease, growth failure, nutritional deficiency, and gallbladder disease

2. Acute illness:
    1. Infection/fever:
        1. Broad-spectrum antibiotics (e.g., ceftriaxone) pending culture results
        2. Vancomycin only for proven or suspected meningitis or other severe illness
    2. Painful crisis:
        1. Oral hydration
        2. Oral analgesics including narcotics, acetaminophen, and ibuprofen
        3. Hospitalization for more severe pain episodes with parental analgesics and hydration
    3. Splenic sequestration:
        1. Emergency transfusion indicated when the signs of cardiovascular instability are present
        2. Splenectomy for multiple or severe episodes of splenic sequestration
    4. Acute chest syndrome:
        1. Treat aggressively with oxygen, analgesics, and antibiotics
        2. Simple transfusion
        3. Exchange transfusion
    5. Aplastic crisis:
        1. Characterized by an exacerbation of the patient's baseline anemia with a substantially decreased reticulocyte count, typically less than 1%.
        2. Most cases are caused by acute infection with human parvovirus B19, usually without the characteristic rash.
    6. Stroke:
        1. Monitor neurologic status.
        2. Aggressive treatment of increased intracranial pressure and seizures.
        3. Exchange transfusion generally indicated with the goal of decreasing Hb S percentage to $<30\%$ of the total hemoglobin.
        4. A preventive chronic transfusion protocol initiated after a CNS event to prevent a second stroke.
        5. Prophylactic transfusion with folic acid replacement shown to decrease the incidence of vasoocclusive crisis during pregnancy.
    7. Priapism:
        1. Hydration
        2. Analgesia administration
        3. Aspiration and irrigation by a urologist
3. Different nutritional approaches (Khan et al. 2016):
    1. Traditional herbal therapies.
    2. Antioxidants.
    3. Flavonoids.
    4. Vitamins.
    5. Minerals.
    6. Reducing oxidative stress.
    7. Blood aggregation.
    8. Nutritional therapies may also serve complementary to the newer therapies using ozone, hematopoietic stem-cell transplantation, antifungal medications, and erythropoietin.
4. Surgical care, limited to treat complications:
    1. Skin graft to help heal chronic leg ulcers
    2. Hip replacement or other orthopedic procedures to treat avascular necrosis
    3. Surgical draining of the penile corpora for resistant priapism
    4. Cholecystectomy for gallstones
5. Disease-modulating therapy:
    1. Hydroxyurea (Vichinsky 1997):
        1. Principle: The most prescribed therapy causes myelosuppressive-induced Hb F synthesis by decreasing terminal differentiation of erythroid stem cells, resulting in decreased sickling and improved red cell survival.
        2. Effects of therapy (Brawley et al. 2008): Patients treated have improved blood markers (increased hemoglobin level, fetal hemoglobin percentage, mean corpuscular volume, and leukocyte count), fewer acute episodes of pain crisis and acute chest syndrome, decreased need for transfusion, and improved survival.
        3. Not effective for cerebrovascular complications of sickle cell disease.
    2. Other medications that increase the percentage of Hb F, currently under investigation:

    1. Short-chain fatty acids, such as butyrate or valproic acid: Individual reports of response have been dramatic, with almost complete correction of anemia (Vichinsky 2002).
    2. 5-azacytidine.
3. Chronic red blood cell transfusion:
    1. To prevent stroke in patients with an abnormal transcranial Doppler and stroke recurrence
    2. To treat chronic debilitating pain and pulmonary hypertension
    3. Goal: to maintain the percentage of Hb S between 30% and 50%
    4. Complications: iron overload, alloimmunization, and infection
4. A major risk factor for development of chronic vasculopathy and pulmonary hypertension (PH) in patients with SCD is hemolytic anemia (37), caused by the pathological effects of plasma cell free hemoglobin and other erythrocyte damage-associated molecular pattern molecules (eDAMPs). Screening patients with SCD for PH for early diagnosis and disease modifying therapy is recommended (Potoka and Gladwin 2015).
5. Hydroxyurea and transfusion therapy are strongly recommended for many individuals with SCD (Yawn et al. 2014).
6. Psychological treatment (Anie and Green 2015):
    1. To help people cope with sickle cell disease might complement current medical treatment.
    2. Four types of treatment: patient education, cognitive therapy (to do with thoughts and feelings), behavioral therapy (to do with actions), and psychodynamic psychotherapy (talking to relieve emotional pain).
7. Bone marrow transplant (BMT): a curative option for patients with sickle cell disease and other hemoglobinopathies (Bolaños-Meade and Brodsky 2009):
    1. Bone marrow transplant from a nonaffected donor, usually a human lymphocyte antigen (HLA)-matched sibling, is the only known curative therapy (Walters et al. 1996, 2000; Vermylen et al. 1998; Bernaudin et al. 2007).
    2. The cure rate in children using an HLA-matched sibling donor following a myeloablative conditioning regimen is over 85%. Unfortunately, most sickle cell patients in need of a BMT are not eligible due to an inability to tolerate myeloablative conditioning and/or the lack of a matched sibling donor. Moreover, gonadal failure is a major drawback of myeloablative regimens (Bolaños-Meade and Brodsky 2014).
    3. Proposed selection criteria: Patients should be less than 16 years of age, have an HLA-identical related donor, and have at least one of the following signs or symptoms – stroke or central nervous system event lasting for more than 24 h, acute chest syndrome, recurrent severe pain episodes, impaired neuropsychological function with an abnormal MRI scan, stage I or II sickle lung disease, sickle nephropathy, bilateral proliferative retinopathy, osteonecrosis of multiple joints, or red blood cell alloimmunization during long-term transfusion therapy (Walters et al. 1996).
8. Allogeneic hematopoietic stem-cell transplantation (HSCT):
    1. The only curative treatment for sickle cell disease (SCD); nevertheless, its use has been limited by the risk of transplantation-related mortality (TRM). HLA-identical sibling HSCT after myeloablative conditioning with antithymocyte globulin (ATG) (Talano and Cairo 2015) should be considered as a standard

of care for SCD children who are at high risk for stroke (Bernaudin et al. 2007).
2. Although curative options with HSCT exist for SCD, they still remain limited due to a lack of appropriate donors and concerns with procedural toxicities (Kanter and Kruse-Jarres 2013).
3. Shown to reverse or at least halt the progression of end-organ damage secondary to SCD (Robinson and Fuchs 2016).
4. Today, almost all children treated by HLA-ID sibling bone marrow transplantation will survive free of SCD. The future of this treatment, however, hinges on the ability to broaden the availability of donors and to achieve success rates after alternate donor HCT that approach those observed after HLA-ID sibling HCT (Walters 2015).

9. Gene therapy:
   1. Principle: A single nucleotide substitution in the pathogenesis of sickle cell disease makes the presence of the sickle cell allele an ideal candidate for gene therapy.
   2. Question of the safety of this type of approach: development of leukemia in two patients participating in a clinical trial of gene therapy for X-linked severe combined immunodeficiency disease.
   3. There is a need for trials that assess the benefits or risks of gene therapy for sickle cell disease (Olowoyeye and Okwundu 2015).

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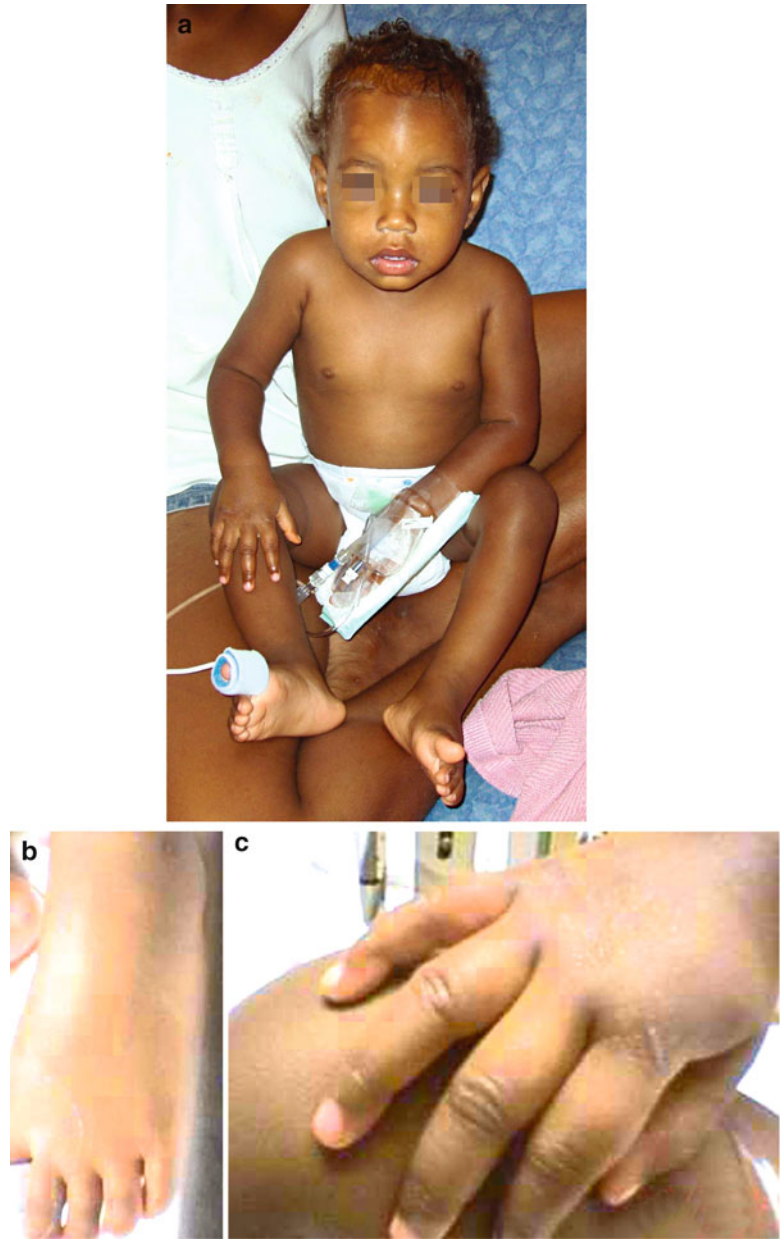

Fig. 1 (**a**–**c**) A young child (**a**) with sickle cell anemia showing hand and foot syndrome (dactylitis) (**b**, **c**)

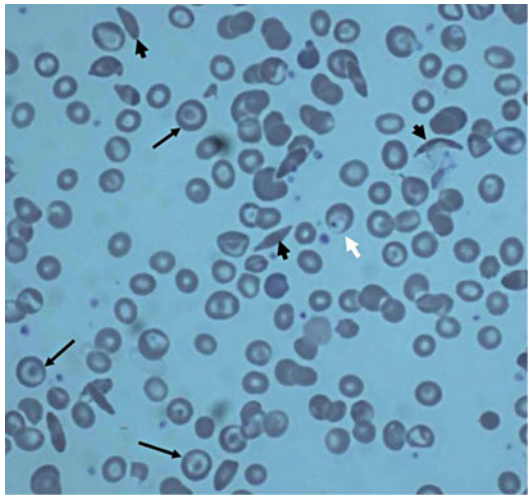

Fig. 2 Peripheral blood smear from a 28-year-old man with hemoglobin SS disease showing several sickle cells (drepanocytes) (*short arrows*), Howell-Jolly body (*white arrow*), and target cells (*long arrows*)

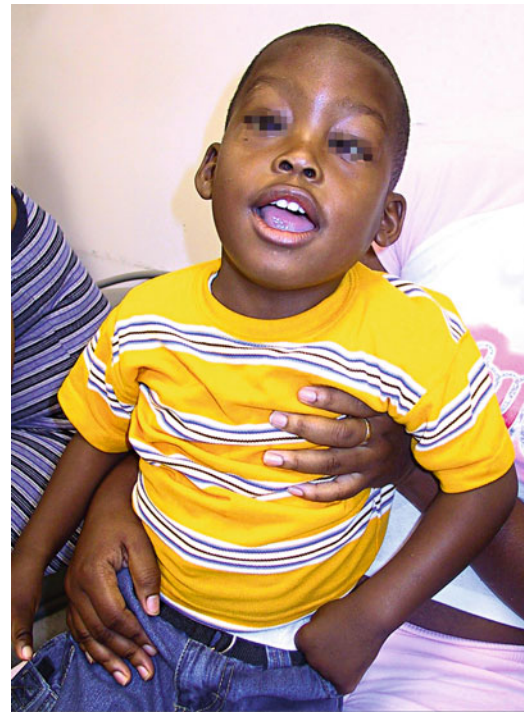

Fig. 4 A 3-year-old black male with sickle cell anemia with a history of meningitis at 3 months and splenic sequestration and pain crisis, resulting in splenectomy at 8 months of age

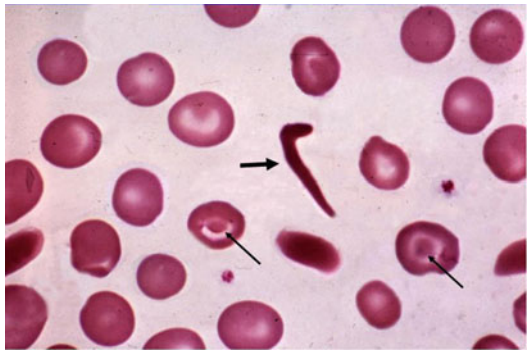

Fig. 3 Peripheral blood smear from another patient with sickle cell disease showing a sickle erythrocyte (*short arrow*) and target cells (*long arrows*) (Wright-Giemsa stain, ×1,000)

Silver–Russell Syndrome

Contents

Silver–Russell syndrome (SRS) is a clinically and genetically heterogeneous disorder, characterized by severe prenatal/postnatal growth retardation, characteristic facies, skeletal asymmetry, and other congenital anomalies. The incidence is estimated as 1:50,000–1:100,000 live births.

Synonyms and Related Disorders

Primordial dwarfism; Russell–Silver syndrome; Silver–Russell dwarfism

Genetic/Basic Defects

1. Inheritance (Duncan et al. 1990; Preece 2002):
    1. Sporadic occurrence in majority of cases
    2. 19% of cases with more than one affected individuals in the family, providing evidence for a genetic cause
    3. A genetically (and clinically) heterogeneous disorder:
        1. Autosomal recessive (17.4%) (Fuleihan et al. 1971; Teebi 1992)
        2. Autosomal dominant (8.7%) (Al-Fifi et al. 1996)
        3. X-linked dominant (74%) (Partington 1986)
2. Chromosomal basis (Preece 2002):
    1. Small number of cases with Silver–Russell syndrome reported in association with numerous chromosomal abnormalities:
        1. R(15) and deletion of 15q (Wilson et al. 1985; Rogan et al. 1996)
        2. Diploid–triploid mixoploidy (Graham et al. 1981)
        3. 45,X/46,XY
        4. XXY (Bianchi et al. 1983)
        5. Trisomy 18 mosaicism
        6. Del(8)(q11-q13) (Schinzel et al. 1994)
        7. Del(18p) (Christensen and Nielson 1978)
        8. Dup(1)(q32.1-q42.1) (van Haelst et al. 2002)
        9. Dup(7p12.1-p13), including GRB10 and IGFBP1, in a mother and daughter with features of Silver–Russell syndrome (Joyce et al. 1999)
        10. One had a partial duplication [46, XX, dup(7)(p12 p14)] and the second contained a paracentric inversion [46, XY, inv(7)(p14 p21)] (Nakabayashi et al. 2002)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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11. Familial reciprocal translocation t(7;16) associated with maternal uniparental disomy 7 in a Silver–Russell patient (Dupont et al. 2002)
12. Distal chromosome 17q (Hitchins et al. 2002):
    1. Balanced translocation (17;20)(q25; q13) and severe Russell–Silver syndrome (Ramírez-Dueñas et al. 1992) inherited from clinically normal father.
    2. De novo translocation (1;17)(q31; q25) with breakpoint recently cloned and localized to 17q23.3-q24.
    3. Heterozygous deletion of the chorionic somatomammotropin hormone 1 (*CSH1*) gene located within the growth hormone and CSH gene cluster on 17q24.1 (Eggermann et al. 1998). The deletion was inherited from the father who appeared clinically normal but had short stature.

2. Maternal uniparental disomy (UPD) for chromosome 7 (about 7–10% of cases) (Preece et al. 1997; Bernard et al. 1999; Hannula et al. 2001b; Eggermann et al. 2001; Hitchins et al. 2001):
    1. Inheritance of both chromosome 7 from the mother: Maternal UPD7 was detected in several SRS patients, accounting for approximately 7-10% of the tested SRS patients (Eggermann et al. 1997; Preece et al. 1999).
    2. A possible novel imprinted region at 7p12-p14 (Monk et al. 2002), 7q32, and 7q31-ter: UPD can disrupt the balance between imprinted genes and thereby lead to phenotypic manifestations.
    3. Strong evidence of disruption of imprinted gene expression rather than mutation of a recessive gene underlying the Silver–Russell phenotype in these cases.
3. Genetic and epigenetic disturbances can meanwhile be detected in approximately 50% of patients with typical SRS features (Eggermann et al. 2010):
    1. Nearly one tenth of patients carry a maternal uniparental disomy of chromosome 7 (UPD(7)mat).
    2. More than 38% show a hypomethylation in the imprinting control region 1 in 11p15.
    3. More than 1% of patients show (sub) microscopic chromosomal aberrations.
    4. Interestingly, in 7% of 11p15 hypomethylation carriers, demethylation of other imprinted loci can be detected.
4. A splicing mutation of the *HMGA2* gene is associated with Silver–Russell syndrome phenotype (De Crescenzo et al. 2015).
5. Silver–Russell syndrome without body asymmetry in three patients with duplications of maternally derived chromosome 11p15 involving *CDKN1C* (Nakashima et al. 2015).
6. 14q32 disturbances significantly contribute to the mutation spectrum in this cohort. Furthermore, maternal uniparental disomy of chromosomes 6, 16, and 20 can be observed, but are rare. In case they occur, they can be regarded as causative for clinical features (Sachwitz et al. 2016b).

3. Clinical findings and molecular aberrations in the three congenital disorders associated with *CDKN1C* mutations (Eggermann et al. 2014):
    1. Silver–Russell syndrome:
        1. Frequency, 1:100,000
        2. Clinical findings (please see this chapter)
        3. Molecular aberrations:
            1. Aberrant *ICR1* (H19/IGF2) methylation: hypomethylation (40%)
            2. Large 11p15 duplications (including *ICR1* and *ICR2*): maternal (1%)
            3. Small *ICR2* duplications and deletions: single cases (the clinical outcome depends on the size and genomic content of the affected segment)
            4. Genomic imbalance in the centromeric 11p15 imprinting center in three families: further evidence of a role for *IC2* (or *ICR2*) as a cause of

Russell–Silver syndrome (Cytrynbaum et al. 2016)
5. UPD 11p15: upd(11p15)mat (single cases)
6. *CDKN1C* point mutations: gain-of-function mutations (sporadic cases, $n = 128$; familial cases, one case)

2. Beckwith–Wiedemann syndrome:
   1. Frequency: 1:13,700
   2. Clinical findings (please see the chapter on "► Beckwith-Wiedemann Syndrome")
   3. Molecular aberrations:
      1. Aberrant *ICR1* (H19/IGF2) methylation: hypermethylation (5–7%)
      2. Aberrant ICR2 (LIT1/KvDMR1) methylation: hypomethylation (50–60%)
      3. Large 11p15 duplications (including *ICR1* and *ICR2*): paternal (1%)
      4. Small *ICR2* duplications and deletions: single cases (the clinical outcome depends on the size and genomic content of the affected segment)
      5. UPD 11p15: upd(11p15)pat (20–25%)
      6. *CDKN1C* point mutations: loss-of-function mutations (sporadic cases, 5%; familial cases, 50%)
3. IMAGe syndrome: named for the acronym of its major features (intrauterine growth retardation (IUGR), metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies) (Bergadá et al. 2005; Bennett et al. 2014):
   1. Frequency, 25 patients reported worldwide
   2. Clinical findings:
      1. IUGR
      2. Skeletal abnormalities (most commonly delayed bone age and short stature; occasionally, metaphyseal and epiphyseal dysplasia of varying severity)
      3. Adrenal insufficiency presenting typically in the first month of life as an adrenal crisis or, rarely, later in childhood with failure to thrive and recurrent vomiting
      4. Genital abnormalities in males (cryptorchidism, micropenis, and hypospadias)
   3. Molecular aberrations: *CDKN1C* point mutations (gain-of-function mutations)
4. Epimutations of the IG-DMR and the MEG3-DMR at the 14q32.2 imprinted region in two patients with Silver–Russell Syndrome-compatible phenotype (Kagami et al. 2015)

Clinical Features

1. Existence of both the "Silver" (Silver et al. 1953; Silver 1964) and "Russell" (1954) variants in a nuclear family: provides additional evidence for considering SRS to be a single syndrome with a wide spectrum of clinical manifestations (Robichaux et al. 1981).
2. Diagnostic criteria: the presence of three major features plus one or more minor features is generally required for a positive diagnosis:
   1. Major criteria:
      1. Low birth weight (intrauterine growth retardation)
      2. Proportionate short stature (postnatal growth retardation): mature height about −3.6 standard deviation scores in both sexes (Tanner et al. 1975; Davies et al. 1988)
      3. Small triangular face
      4. Fifth finger clinodactyly
   2. Minor criteria:
      1. Relative macrocephaly due to sparing of cranial growth
      2. Ear anomalies
      3. Skeletal asymmetry (face, limb, or body)
      4. Brachydactyly of the fifth fingers
      5. Bilateral camptodactyly with terminal interphalangeal contractures
      6. Syndactyly
      7. Transverse palmar crease
      8. Downward-slanting corner of the mouth
      9. Muscular hypotrophy/hypotonia

10. Motor/neurological delay
11. Irregular spacing of the teeth
12. Café-au-lait spots
13. Precocious puberty
14. Squeaky voice
15. Genital abnormalities
16. Speech delay
17. Feeding difficulties (Blissett et al. 2001)

3. Other manifestations:
   1. Significant cognitive impairment (50%) (Lai et al. 1994)
   2. Gastrointestinal symptoms (77%):
      1. Gastroesophageal reflux disease (34%)
      2. Esophagitis (25%)
      3. Food aversion (32%)
      4. Failure to thrive (63%)
   3. Skeletal anomalies:
      1. Large anterior fontanelle (delayed closure)
      2. Absence of asymmetry (Gareis et al. 1971)
      3. Syndactyly of the toes
   4. Genitourinary anomalies:
      1. Hypospadias
      2. Posterior urethral valves
   5. Cardiac defects
   6. Various tumors:
      1. Craniopharyngioma
      2. Testicular seminoma (Funada et al. 2016)
      3. Hepatocellular carcinoma
      4. Wilms tumor
   7. Essentially normal pattern of puberty and adolescent growth (Davies et al. 1988)
   8. Fertility not necessarily impaired, at least in females (Abramowicz and Nitowsky 1977)
   9. Other features:
      1. Blue sclera
      2. Café-au-lait spots
      3. Excessive sweating
      4. Hypoglycemia
4. Silver–Russell syndrome should be considered in the differential diagnosis of children with severe pre- and postnatal growth deficiency (Donnai et al. 1989).
5. Netchine–Harbison clinical scoring system (Azzi et al. 2015): Patients with four or more items of the score are suspected to have Silver–Russell syndrome and should undergo molecular testing (Giabicani et al. 2016):
   1. Factor 1: Being born small-for-gestational-age: $\leq$2 (standard deviation score)* birth length and/or weight adjusted for gestational age (GA).
   2. Factor 2: Relative macrocephaly at birth: Head circumference at birth $\geq$1.5 SDS above birth weight and/or length adjusted for GA.
   3. Factor 3: Postnatal growth failure: Height $\leq$ 2 SDS at 24 months relative to mean or to midparental target height.
   4. Factor 4: Feeding difficulties and/or low BMI at 24 months: BMI $\leq$2 SDS at 24 months OR tube feeding OR cyproheptadine for appetite stimulation.
   5. Factor 5: Protruding forehead: The forehead protrudes from the facial plan (viewed laterally) between 1 and 3 years of age.
   6. Factor 6: Body asymmetry: Leg length discrepancy (LLD) of $\geq$ 0.5 cm OR arm asymmetry OR LLD $<$ 0.5 cm with at least two; other asymmetric body parts (with one being a nonface part).
6. A possible associations of Mayer–Rokitansky–Küster–Hauser syndrome and Silver–Russell syndrome (Abraham et al. 2016).
7. Clinical characterization (Hannula et al. 2001a; Binder et al. 2008; Bruce et al. 2009; Eggermann et al. 2010):
   1. Phenotype of maternal UPD7 carriers is generally milder.
   2. 11p15 epimutation (*H19* imprinting control region hypomethylation) carriers usually present the typical picture of SRS.
8. Differential diagnosis (Patton 1988):
   1. Intrauterine growth retardation owing to placental insufficiency:
      1. Chronic intrauterine growth retardation leads to a decrease in all growth parameters, that is, a "perfect miniature," and is

followed in most cases by catch-up growth in the first year of life.
    2. Late intrauterine growth retardation, especially in the postmature fetus, leads to a thin, low birth weight baby with normal length and head circumference
2. Chromosomal mosaicism:
    1. The phenotype has been reported in patients with mosaic trisomy 18 (Chauvel et al. 1975) a diploid–triploid mosaicism (Ferrier et al. 1964) and a 45,X/46,XY mosaicism. Consideration should be given to examining skin fibroblasts in addition to peripheral blood, especially where there is mental retardation or sexual ambiguity.
3. 3-M syndrome (Winter et al. 1984) This autosomal recessive syndrome has several features in common with the Russell–Silver syndrome, including intrauterine growth retardation, relatively large head, and short fifth fingers. It can be distinguished from the Russell–Silver syndrome by the presence of prominent heels, tall vertebral bodies, and facial features, which include a broad, fleshy nose and a hatchet-shaped profile.
4. X-linked short stature with skin pigmentation (Partington) (Partington 1986) This syndrome has been described as a variant of the Russell–Silver syndrome. There is a diffuse brown pigmentation with some achromic patches.
5. Neonatal progeroid (Rautenstrauch) (Wiedermann 1979) This syndrome has pseudohydrocephalus, generalized deficiency of subcutaneous fat, and natal teeth.

9. Subtypes existing in primordial dwarfism, their inheritance pattern, and distinguishing clinical features (Khetarpal et al. 2016):
    1. Seckel syndrome (please see the chapter on "► Seckel Syndrome")
        1. Autosomal recessive
        2. Microcephalic primordial dwarfism (brain size reduced to a third of normal volume)
        3. Extremely small head with narrow face, dental alterations, beak-like protrusion of nose, and receding mandible
    2. Majewski/microcephalic osteodysplastic primordial dwarfism (MOPD) types I/III
        1. Autosomal recessive
        2. Dry skin
        3. Sparsity of hairs and eyebrows
    3. MOPD type II
        1. Autosomal recessive
        2. Prominent nose and eyes
        3. Abnormally small or missing teeth
        4. A high squeaky voice
    4. Meier–Gorlin syndrome
        1. Autosomal recessive
        2. Underdeveloped ears
        3. Absent/hypoplastic patellae
    5. Silver–Russel syndrome
        1. Autosomal dominant or autosomal recessive and genomic imprinting
        2. Normal head size
        3. Small triangular face
        4. Micrognathia
        5. Dental anomalies

Diagnostic Investigations

1. Increased serum or urinary gonadotropin levels in the prepubertal age (Curi et al. 1967)
2. Hypoglycemia
3. Growth hormone studies
4. Metabolic acidosis due to renal tubular acidosis in a few patients
5. Radiography (Herman et al. 1987)
    1. Delayed bone age
    2. Limb asymmetry
    3. Ivory epiphyses of the distal phalanges
    4. Clinodactyly of the fifth fingers
    5. Fifth middle or distal phalangeal hypoplasia
    6. Pseudoepiphyses at the base of the second metacarpal
6. Chromosome analysis to define chromosome basis
    1. Mosaic trisomy 7 (Flori et al. 2005; Font-Montgomery et al. 2005)

2. Interstitial deletion of chromosome 7q [del (7)(q21.1q21.3)] (Courtens et al. 2005)
7. Molecular karyotyping in patients with SRS features: NSD1 duplication in Silver–Russell syndrome (Sachwitz et al. 2016a)
8. Molecular genetic testing (Eggermann et al. 2009; Saal 2007)
    1. Maternal uniparental disomy (UDP) of chromosome 7 (7–10%) clinically available: both maternal isodisomy and heterodisomy have been reported (Bernard et al. 1999; Price et al. 1999).
    2. Genetic or epigenetic mutations in the imprinted region on chromosome 11p15.5: methylation analysis of *H19* (35%) clinically available.
    3. 11p15 epimutation and UPD (7) mat carriers do not always show the unambiguous SRS phenotype.
    4. In addition to patients with the classical SRS phenotype fulfilling the SRS-specific scores, genetic testing for the 11p15 epimutation and/or UPD (7) mat should also be considered in case of SRS-like phenotypes, for example, mild IUGR and postnatal growth retardation (more than −2 SD) associated with a prominent forehead and triangular face or asymmetry as the only clinical sign.
    5. In particular, the lack of IUGR in patients with an SRS-like phenotype should not automatically result in exclusion from molecular testing.
    6. Silver–Russell syndrome in a patient with somatic mosaicism for upd(11)mat identified by buccal cell analysis (Luk et al. 2016).

Genetic Counseling

1. Recurrence risk (Saal 2007)
    1. Multiple etiologies of SRS
        1. Maternal uniparental disomy for chromosome 7: both parents are predicted to be unaffected.
        2. Possible mutations or epigenetic changes that modify expression of genes in the imprinted region of chromosome 11p15.5.
        3. Autosomal dominant inheritance.
        4. Autosomal recessive inheritance.
    2. Patient's sibs
        1. Not increased in a nongenetic sporadic case or as the result of maternal uniparental disomy for chromosome 7 (both parents are predicted to be unaffected)
        2. Increased depending on the inheritance pattern
    3. Patient's offspring
        1. Not increased in a nongenetic sporadic case and probably low in case of maternal uniparental disomy for chromosome 7
        2. Increased depending on the inheritance pattern
2. Recurrence risk estimation in SRS and Beckwith–Wiedemann syndrome (BWS) (Eggermann et al. 2016a)
    1. The majority of cases with SRS and BWS have been reported to occur sporadically. This is reflected by the type of (epi)mutations in both disorders (ICR1 hypomethylation in SRS as well as ICR2 hypomethylation and upd(11)pat in BWS) mainly occur as mosaicism and probably originate from postzygotic errors.
    2. In contrast, constitutional mutations (point mutations, duplications/deletions) are associated with a significantly increased recurrence risk of up to 50% depending from the affected paternal allele.
3. Molecular subtypes and recurrence risk (Eggermann et al. 2016b)
    1. 11p15.5
        1. *H19*/*IGF2*:IG-DMR hypomethylation: empirically low, only in rare cases increased due to genomic transacting mutations
        2. Duplications/deletions: Up to 50%, depending on the gene content of the aberration and the sex of the parent contributing the affected allele (in case of

duplication of the whole 11p15 region; in case of a maternal transmission)
3. UPD: empirically low
4. *CDKN1C* point mutation: 0% or 50%, depending on the sex of the parent contributing the affected allele
5. *IGF2* point mutation: 0 or 50%, depending on the sex of the parent contributing the affected allele

2. 7
1. upd(7)mat: empirically low, but some may be high because of familial translocations
2. upd(7q)mat: empirically low
3. Duplications/deletions/translocations affecting 7p13 and 7q32: up to 50%

3. 14q32
1. upd(14)mat, epimutation, duplications.
2. A number of SRS patients exhibiting (epi)mutations in 14q32 have recently been reported, and these molecular alterations correspond to findings in patients with Temple syndrome (Goto et al. 2016; TS14, OMIM616222).
3. TS14 is an ID with changes affecting the IG-DMR and/or MEG3-DMR in 14q32, and its phenotype (Ioannides et al. 2014) overlaps with SRS (for a review see Kagami et al. (2015)).
4. In single cases, maternal uniparental disomy of chromosomes 16 and 20 (upd(16)mat, upd(20)mat) has been reported (Azzi et al. 2015; Mulchandani et al. 2015) (for a review see Eggermann et al. (2015)).

4. Whole genome
1. (Mosaic) maternal unidiploidy: no
2. (Submicroscopic) chromosomal imbalances: up 50%, depending on the chromosome and type of rearrangement

4. Prenatal diagnosis
1. Ultrasonography of the fetus at risk by family history.
1. Delayed fetal skeletal growth may not be evident until the late second trimester.
2. Asymmetry of fetal limbs may not be evident until the third trimester.
2. Usually not possible because most occurrences are in a single individual in a family; therefore, most pregnancies are not identified to be at increased risk for recurrence (Saal 2007).
3. Russel–Silver syndrome should be considered in the differential diagnosis of fetal growth restriction with short, asymmetric, but morphologically normal limbs (Wax et al. 1996).
4. Molecular findings and interpretations in prenatal testing of SRS (and BWS) (Eggermann et al. 2016a).
1. Type of mutation: UPD, CNVs (copy number variations), epimutation, and point mutation.
2. Mosaicism: In case of a positive testing result, the suspected diagnosis can be confirmed, but a prediction of the phenotypic outcome is not possible but might be delineated from the ultrasound findings.
3. Mosaicism: In case of a negative testing result, the mosaic presence of UPD or epimutations can never be excluded. Mosaicism in case of constitutional mutations (CNVs, monogenic point mutations) can be neglected.
4. How to interpret the results in case of a twin pregnancy (the majority of monozygotic twins are clinically discordant)?

5. Management
1. Growth deficiency
1. Optimize caloric intake.
2. Consider nasogastric or gastrostomy feeding for severe gastroesophageal reflux and failure to thrive.
3. Consider growth hormone treatment in patients with documented growth hormone deficiency.
4. Growth hormone treatment of short children born small for gestational age or with Silver–Russell syndrome (Ranke and Lindberg 1996).
2. Dental cares for overcrowding of teeth
3. Orthopedic management for asymmetry of legs

4. Early intervention programs including physical therapy for developmental delay due to hypotonia
5. Special education for learning disabilities
6. Psychological counseling related to body image and peer relationship

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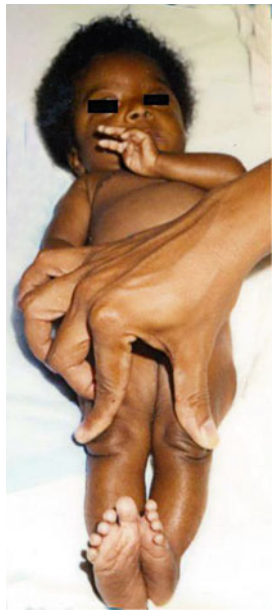

Fig. 1 An infant with Silver–Russell syndrome showing prenatal and postnatal growth deficiency, triangular face, and asymmetry of legs

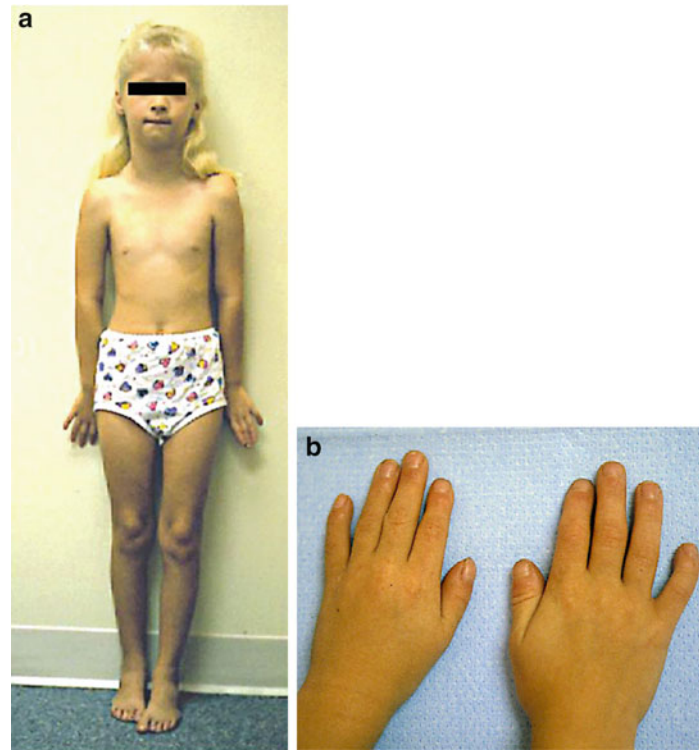

Fig. 2 (**a**, **b**) A girl (**a**) with Silver–Russell syndrome showing prenatal and postnatal growth deficiency, triangular face, and clinodactyly of the fifth fingers (**b**)

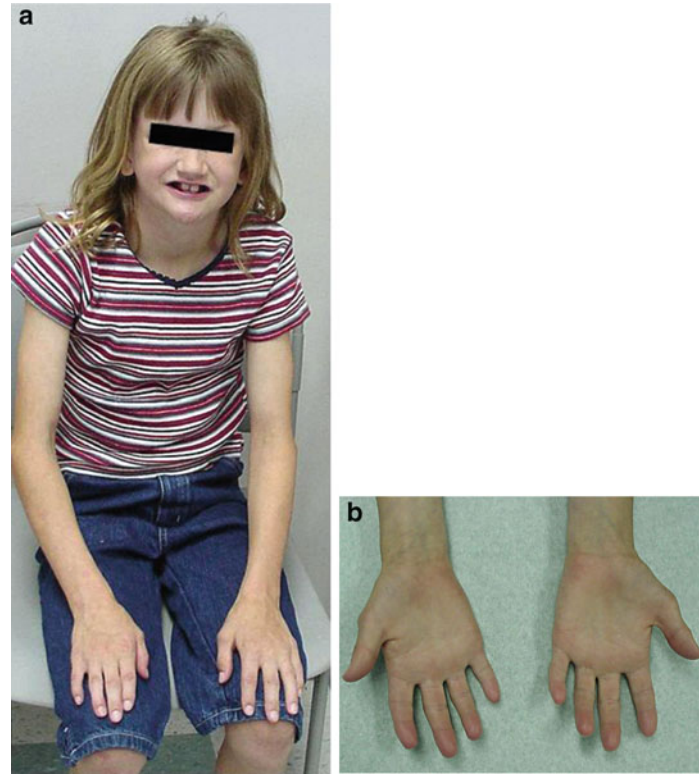

Fig. 3 (**a**, **b**) A girl (**a**) with Silver–Russell syndrome showing prenatal and postnatal growth deficiency with brachydactyly and clinodactyly of the fifth fingers (**b**)

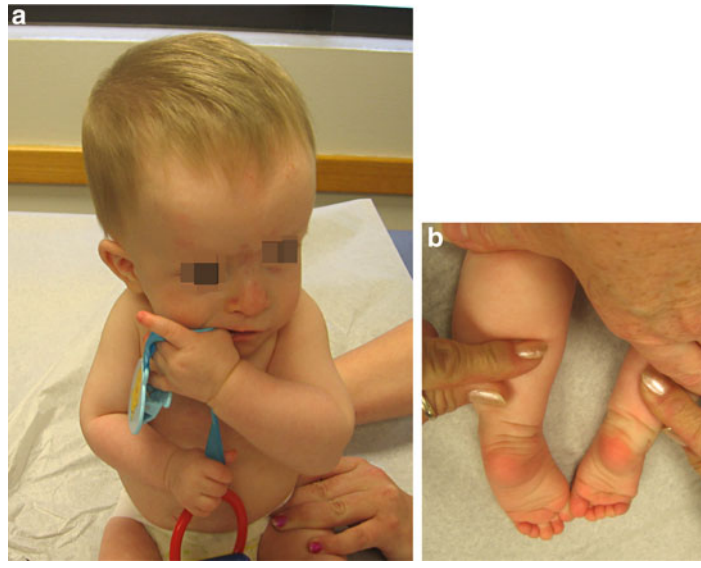

Fig. 4 (**a**, **b**) A 6-month-old male infant (**a**) was evaluated for intrauterine growth retardation, postnatal growth retardation, a relatively large head, a triangular face, and left side of the body larger than the right (**a**, **b**). Clinically, he was suspected to have Silver–Russell syndrome. Molecular genetic testing detected loss of methylation at differentially methylated region 1 (*DMR1*), upstream of the *H19* gene at 11p15. This result is consistent with a diagnosis of Silver–Russell syndrome due to hypomethylation of DMR1

Sirenomelia

Contents

Sirenomelia is a rare malformation sequence characterized by a partial or complete fusion of the lower limbs associated with urogenital, anal, lower spine, and other anomalies. The term sirenomelia comes from "siren" or "mermaid" because of the characteristic fusion of the lower extremities. Because of its physical resemblance to the mythical mermaid, the topic of sirenomelia has fascinated public for centuries. Sirenomelia occurs in approximately 1 in 60,000 births.

Synonyms and Related Disorders

Caudal regression syndrome; Mermaid syndrome; Sirenomelia mermaid syndrome; Sirenomelia sequence

Genetics/Basic Defects

1. Sporadic occurrence.
2. Familial occurrence of sirenomelia (Gerard et al. 2012):
    1. Only one family had true recurrence of sirenomelia, with four malformed siblings, two sirenomelic, one with renal agenesis, and one with imperforate anus (Rudd and Klimek 1990). The father had anomalies of the spine detected on radiographs, with narrow lumbosacral interpediculate distance, without sacral anomaly.
    2. In another family, there were four siblings, one sirenomelic, one with bilateral renal agenesis and tetralogy of Fallot, one with "posterior urethral valves," and the last with megacystis (Selig et al. 1993). The last family is the one reported by Castori et al. (2010) with an overweight diabetic mother giving birth to a first child with sirenomelia and another with bilateral renal agenesis, narrow pubic and ischial bones, atrial septal defect, and vertebral anomalies (T7 hemivertebrae and abnormal sacrum), in the VACTERL sequence, which is again a link to the embryological field of the malformations of VATER and sirenomelia.
3. Incidence of sirenomelia in monozygotic twins markedly increased over dizygotic twins or singletons.
4. Caudal regression syndrome (CRS) (a severe form of caudal regression syndrome) (Goodlaw et al. 1988) represents a continuum of congenital malformations ranging from

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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agenesis of the lumbosacral spine to the most severe cases of sirenomelia with lower extremities fusion and major visceral anomalies (Adra et al. 1994).

5. Cause obscure:
    1. Malformations as developmental field defects, probably arising during blastogenesis (Opitz et al. 2002). Previously considered a vascular disruption anomaly, sirenomelia is a quintessential primary defect of blastogenesis affecting multiple midline primordia during the final stages of granulation at the caudal eminence.
    2. The fusion theory: the lower extremities develop in lateral contact to each other and subsequently become fused.
    3. The classical theory: deficiency of the caudal axial area in the embryo allows the approximation of the side plates where the limbs develop.
    4. The single umbilical artery theory: resulting vascular insufficiency does not allow the normal process of lower limb development.
    5. The vascular steal theory: the sirenomelic malformations result from diversion of the blood flow from caudal structures of the embryo to the placenta. The tissues distal to the diversion receive diminished vascular supply; consequently, the development is arrested at some stage during fetal life.
    6. The extrinsic theory: any mechanical pressure on the caudal portion of the embryo may impede normal rotation of the limb buds as it has been observed in chick embryos exposed to such influences.
    7. The neural tube distention theory: overdistention of the neural tube in the caudal region expands the roof plate of the tube, displacing and laterally rotating the mesoderm, which allows the fusion of the limb buds.
    8. Caudal mesoderm pattern of anomalies: from renal agenesis to sirenomelia (Källén and Winberg 1974).
6. Sirenomelia and severe caudal regression syndrome: both cases of caudal regression syndrome (CRS) were infants of type II diabetic mother with poor control, supporting the strong correlation of CRS and maternal diabetes (Zeidahmed et al. 2014).
7. Exposure to methylergonovine maleate as a cause of sirenomelia (Cozzolino et al. 2016).

Clinical Features

1. Fusion of the lower limbs
    1. The most striking feature of the syndrome
    2. Fusion of the lower limbs and abnormalities of the feet creating the appearance of a mermaid
    3. Often with rotated feet
    4. Posteriorly located patella
2. Sirtori's classification into three types according to the number of the feet (Sepulveda et al. 1998; Heflin 2007)
    1. Sympus apus (absence of both feet)
        1. The most common form of sirenomelia.
        2. Characterized by a completely fused single lower extremity with one femur, no fibulae, and one or two tibiae.
        3. Both feet may be absent or rudimentary feet may be present.
    2. Sympus unipus or monopus (presence of only one foot)
        1. Characterized by a single fused lower extremity with two femora, two tibiae, and two fibulae.
        2. Only one foot is present with a varying number of toes (up to ten) on the single foot.
    3. Sympus dipus (presence of both feet)
        1. Characterized by a single fused lower extremity
        2. Presence of two distinct feet that appear like a fin or flipper
3. Stocker's more detailed classification into seven subtypes according to the fused bones (Stocker and Heifetz 1987)
    1. Type I: paired femora, tibiae, and fibulae (all thigh and leg bones are present)
    2. Type II: a single, fused fibula
    3. Type III: absent fibula
    4. Type IV: partially fused femora and a single fibula

5. Type V: partially fused femora and absent fibulae
6. Type VI: a single femur and tibia
7. Type VII: a single femur and absent tibiae and fibulae

4. Sirenomelia: a new type showing VACTERL association with Thomas syndrome (Lhuaire et al. 2013)
   1. Morphological appearance of the fetus
      1. Potter facies
      2. Bilateral labio-maxillary cleft
      3. Cleft hands
      4. Agenesis of right thumb
      5. Single inferior limb with anterior sole of the single foot
   2. 3D CT reconstructions
      1. Agenesis of right thumb
      2. Right radial hemimelia
      3. Cervical hemivertebrae
      4. Lumbar and sacral spine agenesis
   3. Thomas syndrome
      1. Thomas et al. (1993) reported a new syndrome that associated Potter sequence, cleft lip and palate, and cardiac abnormalities.
      2. The case by Lhuaire et al. (2013) presented a Thomas syndrome associated with a Potter sequence and a bilateral cleft lip and palate, agenesis of the right branch of the pulmonary artery, and agenesis of the right pulmonary veins and interatrial communication.
5. Oligohydramnios
6. Single umbilical artery (Perez-Aytes et al. 1997)
   1. With hypoplasia of the aorta below the origin of the umbilical artery
   2. Presents virtually in every case of sirenomelia
7. Vascular anomalies
   1. Single umbilical artery
   2. Persistent vitelline artery
   3. Hypoplastic distal aorta
   4. Aberrant femoral arteries
8. Urogenital anomalies
   1. Unilateral or bilateral renal agenesis (the most common finding)
   2. Renal cystic dysplasia
   3. Fusion of the renal pelvis
   4. Absent bladder
   5. Urethral atresia
   6. Ectopic urethra
   7. Posterior urethral valves
   8. Male
      1. Absent external genitalia
      2. Small/rudimentary phallus
      3. Absent testis
   9. Females
      1. Absent/ambiguous external genitalia
      2. Absent ovaries
      3. Anomalous/rudimentary uterus
      4. Anomalous vagina
9. Gastrointestinal anomalies
   1. Meckel's diverticulum
   2. Duodenal atresia
   3. Absent gallbladder
   4. Annular pancreas
   5. Omphalocele
   6. Intestinal malrotation
   7. Blind-end colon/rectum
   8. Colon duplication
   9. Absent spleen
   10. Imperforate anus
   11. Limb–body wall complex
10. Cardiac anomalies
    1. Tetralogy of Fallot
    2. Totally anomalous pulmonary venous return
    3. Ventricular septal defect
    4. Atrial septal defect
    5. Truncus arteriosus
    6. Hypoplastic ventricles
    7. Mitral atresia
    8. Transposition of the aorta
    9. Coarctation of the aorta
    10. Hypoplastic left heart
    11. Acardius amorphus
11. Pulmonary anomalies
    1. Pulmonary hypoplasia
    2. Tracheoesophageal fistula
    3. Laryngeal stenosis and tracheal atresia
    4. Cystic adenomatoid malformation
    5. Diaphragmatic hernia
    6. Abnormal lung lobation
    7. Pulmonary agenesis associated with acardius amorphus

12. CNS anomalies
    1. Craniorachischisis totalis (Rodriguez and Palacios 1992)
    2. Holoprosencephaly: report of cebocephaly, alobar holoprosencephaly, spina bifida, and sirenomelia in a stillbirth (Chen et al. 1997)
    3. Hydrocephalus
    4. Arnold–Chiari malformation
    5. Absent corpus callosum
    6. Meningomyelocele
13. Pelvis/sacral anomalies
    1. Dysplastic pelvis
    2. Sacral agenesis/dysplasia
14. Vertebral anomalies
    1. Hemivertebrae
    2. Spina bifida
    3. Kyphoscoliosis
15. Upper limb anomalies
    1. Absent radius.
    2. Abnormal thumb.
    3. Absent limb.
    4. Preaxial polydactyly.
    5. Rarer associated abnormalities, which include asymmetrical upper limb defects, not confined to the radial ray (Moosa et al. 2012). The clinical phenotypic overlap between caudal dysgenesis, VACTERL association, and sirenomelia in four patients lends support to the theory that these entities may be different manifestations of a single pathogenic process.
16. Face
    1. Potter facies
        1. Large, floppy low-set ears
        2. Flat nose
        3. Micrognathia
    2. Skin tags
17. Prognosis
    1. Generally lethal
        1. Stillborn in more than half of cases.
        2. Remainder of cases most likely die shortly after birth due to severe associated visceral anomalies, incompatible with life.
    2. Occasional long-term survival possible
        1. Reports of survival of infants with sirenomelia (associated with fused lower extremities, colon atresia, renal dysplasia, imperforate anus, pelvic and sacral "dysplasia," genital abnormalities, preauricular skin tag, and rib fusion) (Murphy et al. 1992; Clark et al. 1993).
        2. A report of a unique occurrence of sirenomelia in a healthy infant who exhibits the most significant external manifestations typical of the syndrome, but who has well-developed and functional kidneys and lungs. This resulted in a sirenomelus infant with an anatomy and physiology compatible with long-term survival (Savader et al. 1989).

Diagnostic Investigations

1. Radiography
    1. Classification based on osseous findings:
        1. Type I (all bones of the thigh and lower leg present and unfused)
        2. Type II (fused fibulae)
        3. Type III (absent fibulae)
        4. Type IV (partially fused femora and fused fibulae)
        5. Type V (partially fused femora)
        6. Type VI (fused femora and fused tibiae)
        7. Type VII (fused femora and absent tibiae)
    2. Rotation of the legs and feet.
    3. Abnormalities of the vertebrae, especially sacral bones.
    4. Deficient bony pelvis.
    5. A fetus with a single lower extremity and a single foot with four toes: radiograph showed a single femur with broad metaphyses, paired tibiae, scoliosis with hemivertebrae, and minimal ossification of the lumbosacral spine (Van Zalen-Sprock et al. 1995).
2. Angiography for vascular anomalies (Talamo et al. 1982)
3. Chromosome analysis: normal in most cases

Genetic Counseling

1. Recurrence risk
    1. Patient's sibs: negligible.
    2. Patient's offspring: affected individuals do not expect to survive to reproduce.
2. Prenatal diagnosis
    1. Ultrasonography (Sirtori et al. 1989; Van Zalen-Sprock et al. 1995; Nori et al. 2016)
        1. Three major US findings suggesting the diagnosis of "mermaid syndrome" (Raabe et al. 1983):
            1. Oligohydramnios
            2. Bilateral renal agenesis
            3. Most importantly lower extremity fusion
        2. Inability to demonstrate separate lower limbs.
        3. Identification of varying degree of a single or "fused" lower limb.
        4. Lower spine agenesis/dysgenesis.
        5. CNS, cardiac, GI, and other abnormalities.
        6. A single umbilical artery.
        7. Oligohydramnios associated with urogenital anomalies, especially renal agenesis/dysgenesis.
        8. Prenatal diagnosis of sirenomelia difficult to make because of the associated anhydramnios.
        9. The additional information obtained from the 3D images was the overall view, the confirmation of 2D findings, and especially the observation of abnormal fetal movements due to conjoined fetal legs (Blaicher et al. 2001).
        10. US findings of caudal regression versus sirenomelia (Twickler et al. 1993):
            1. Normal or increased amniotic fluid
            2. Mild dilation or normal urinary systems
            3. Nonfused extremities
            4. Sacral agenesis
        11. 3D-SUIS seems to be a useful complementary method to 2D-US and may improve the accuracy of identifying prenatal skeletal abnormalities related to sirenomelia (Liu et al. 2015).
    2. Color Doppler imaging (Sepulveda et al. 1994, 1998)
        1. A simple, noninvasive method to detect vascular abnormalities associated with sirenomelia
        2. Two vascular hallmarks of the syndrome in utero
            1. Persistence of the vitelline artery: a single large artery arising from the high abdominal aorta to become the single umbilical artery, leaving an atretic or absent distal aorta. Such a vascular abnormality is thought to be responsible for a vascular steal phenomenon and poor perfusion distal to the anomalous artery, leading to the sirenomelia sequence (Stevenson et al. 1986).
            2. Absence of renal vessels.
    3. Prenatal diagnosis by ultrasonography of fetus made as early as first trimester (Monteagudo et al. 2002; Schiesser et al. 2003; van Keirsbilck et al. 2006; Contu et al. 2009; Cuillier et al. 2013; Singh et al. 2014)
    4. Three-dimensional ultrasound imaging and first trimester diagnosis in a case of mosaic 69,XXX/46,XX fetus (Gabriele and Gianpaolo 2013)
    5. MRI of aberrant lower extremity and the spine compared with normal age-matched fetus (Nori et al. 2016): fused lower extremities, hyperextension at the knee, absence of the soft tissue cleft/separation between the thighs, and absent sacral tapering with prominent gluteal concavity
3. Management (Guidera et al. 1991)
    1. Orthopedic treatment of patients with less severe spectrum of caudal regression
        1. Soft tissue release.
        2. Osteotomies.
        3. Separation of the lower limbs. Long-term functional results of the separation are unknown.
        4. Orthotics.
    2. Anticipate extensive reconstruction in the event of survival

3. Goal of orthopedic intervention: proper seating and standing, achievable without amputation
4. Severe form of sirenomelia: a lethal condition

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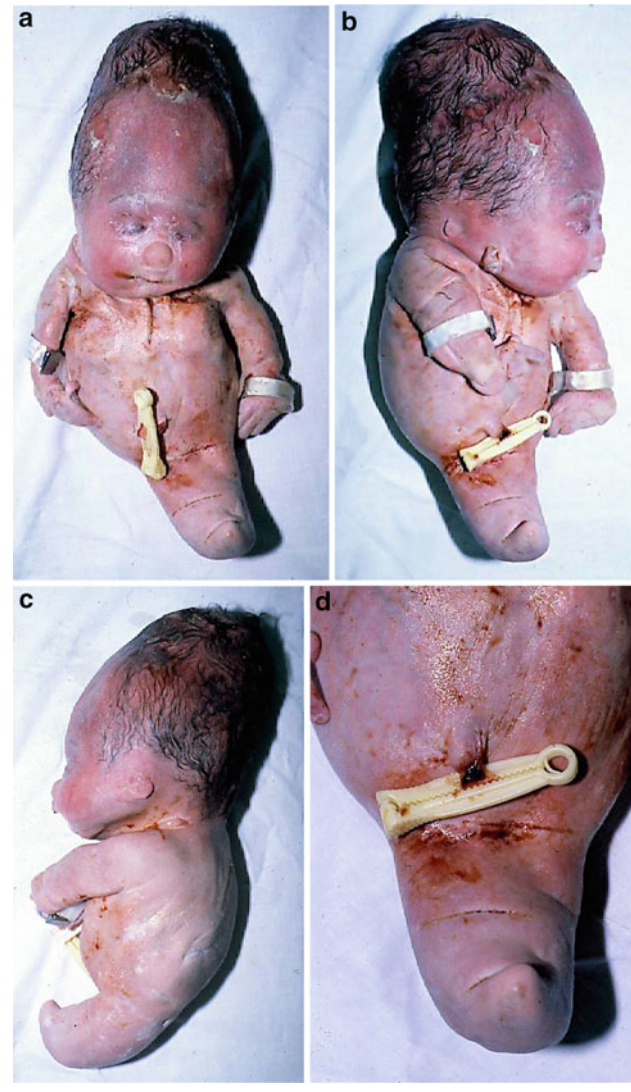

Fig. 1 (**a**–**d**) A stillborn with sirenomelia showing Potter facies, short neck, absent external genitalia, and fused single lower limb with absent feet. This infant also had holoprosencephaly

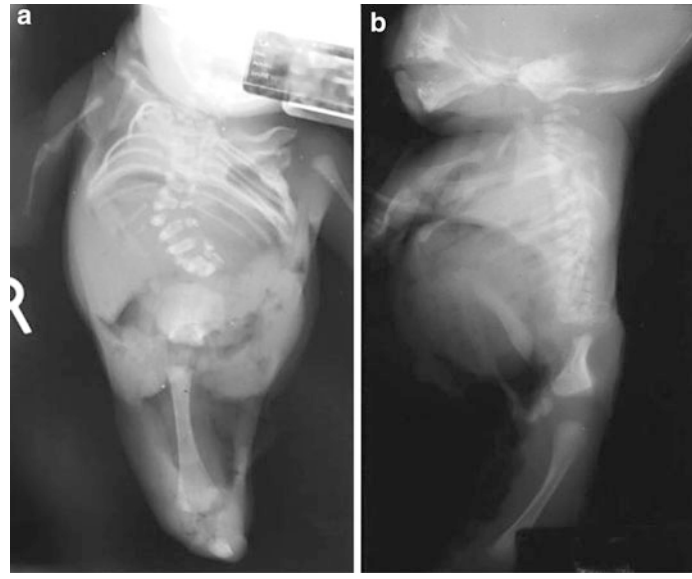

Fig. 2 (**a**, **b**) Radiographs of the previous infant showed vertebral segmentation defects, malformed ribs, absent sacrum, dysplastic pelvic bones, single femur, and absent tibiae/fibulae/tarsal/metatarsals/phalanges

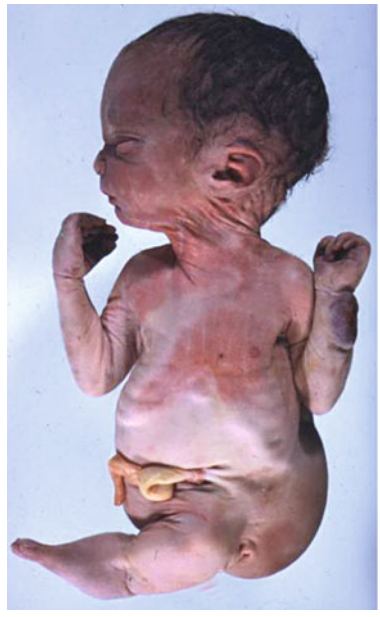

Fig. 3 A female stillborn (35 weeks gestation) with sirenomelia (monomelia). The infant had a single femur with one bone below knee; agenesis of urinary system (ureters, bladder, and urethra); ectopic rudimentary renal tissue; absence of uterus, vagina, and external genitalia; and imperforate anus

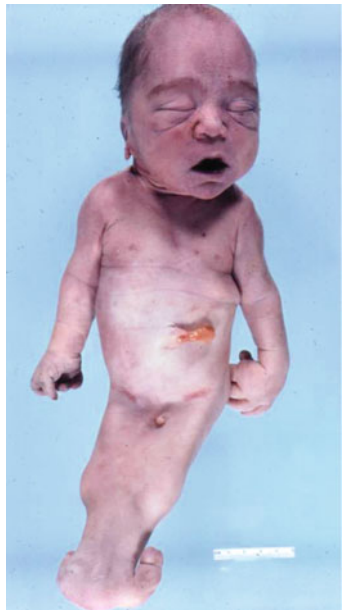

Fig. 4 A male premature neonate with sirenomelia showing fused lower extremities and posterior alignment of the knees and feet. The *left* foot was malformed. Other major anomalies included absence of external genitalia; bilateral renal agenesis; agenesis of the ureters, bladder, urethra, and prostate; esophageal atresia with TE fistula; imperforate anus with absence of the rectum; intestinal malrotation; persistent *left* superior vena cava; bifid cardiac apex; and scoliosis with two hemivertebrae

Smith–Lemli–Opitz Syndrome

Contents

In 1964, Smith et al. (1964) reported three patients with a common distinctive facial appearance, microcephaly, broad alveolar ridges, hypospadias, a characteristic dermatoglyphics pattern, severe feeding disorder, and global developmental delay. The incidence of the Smith–Lemli–Opitz syndrome is estimated to be approximately 1 in 10,000 to 1 in 40,000 births based on clinical diagnosis and 1 in 60,000 to 1 in 100,000 births based on biochemical testing. There appears to be strikingly different incidences among various ethnic groups.

Synonyms and Related Disorders

RSH syndrome; Rutledge multiple congenital anomaly syndrome; SLO syndrome; SLOS

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. Basic defect.
   1. Caused by a defect of cholesterol biosynthesis.
   2. Underlying biochemical defect: deficiency of 7-dehydrocholesterol reductase (DHCR7), an enzyme catalyzing the last step of the Kandutsch–Russell cholesterol biosynthesis pathway, resulting in generalized cholesterol deficiency.
   3. Mutations of *DHCR7* gene (Waterham et al. 1998) lead to deficient activity of 7-dehydrocholesterol reductase (DHCR7), the final enzyme of the cholesterol biosynthesis pathway. Functional null alleles of the *DHCR7* locus result in lethal form of Smith–Lemli–Opitz (SLO) syndrome.
   4. Human *DHCR7* gene has been cloned and localized to 11q12-13.
   5. An example of metabolic deficiency as a cause of a dysmorphic syndrome.
   6. First-trimester exposure to DHCR7 inhibitors resulted in outcomes similar to those of known teratogens (50 vs. 48% born healthy) (Boland and Tatonetti 2016). DHCR7 activity should be considered during drug development and prenatal toxicity assessment.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Clues pointing to an underlying biochemical defect of cholesterol metabolism.
    1. Holoprosencephaly, microcephaly, pituitary agenesis, limb defects, and genital anomalies produced by in utero exposure of rat and mouse pups to chemical inhibitors of the cholesterol biosynthetic pathway
    2. Large adrenal glands with complete absence of lipid in adrenal cortex of patients with Smith–Lemli–Opitz syndrome (SLOS)
    3. Abnormalities of the pituitary–adrenal axis
    4. Suppressed fetal estriol production in pregnancies affected with Smith–Lemli–Opitz syndrome
    5. Neonatal liver disease in severe Smith–Lemli–Opitz syndrome associated with low serum cholesterol level
    6. Male pseudohermaphroditism not caused by dihydrotestosterone receptor defects
    7. Observation of two patients with Smith–Lemli–Opitz syndrome with low plasma cholesterol and elevated levels of 7-dehydrocholesterol (7DHC), the immediate precursor of cholesterol in the Kandutsch–Russell biosynthetic pathway, suggesting that this multiple malformation was caused by a simple Garrodian enzymatic defect
4. The apparent 7-DHC reductase deficiency makes the RSH (Smith–Lemli–Opitz) syndrome the first true metabolic malformation syndrome (Tint et al. 1994; Opitz and de la Cruz 1994).
5. The RSH syndrome has been identified as another metabolic multiple congenital anomalies/mental retardation (MCA/MR) syndrome (prototype Zellweger syndrome) in which deficient cholesterol synthesis must be held responsible for all parts of the syndrome, including blastogenetic and organogenetic malformations, minor anomalies, more or less severe abnormalities of CNS and PNS structure and function, postnatal failure to thrive, and, in some cases, stillbirth or infancy/childhood death (Opitz 1994).
6. The RSH (so-called Smith–Lemli–Opitz) syndrome has become a paradigmatic metabolic malformation syndrome in a pathway that also involves cause and pathogenesis of desmosterolosis, two forms of the Conradi–Hünermann–Happle-type chondrodysplasia punctata and its mouse homologues and the Greenberg "moth-eaten" skeletal dysplasia and the CHILD syndrome. Many other defects in this pathway remain to be discovered (Opitz 1999).
7. Rutledge multiple congenital anomaly syndrome (Rakheja et al. 2003).
    1. A "new" lethal multiple congenital anomaly syndrome: joint contractures, cerebellar hypoplasia, renal hypoplasia, urogenital anomalies, tongue cysts, shortness of limbs, eye abnormalities, defects of the heart, gallbladder agenesis, and ear malformations (Rutledge et al. 1984)
    2. Considered a variant of Smith–Lemli–Opitz syndrome
    3. Biochemical abnormality of excess 7-dehydrocholesterol and low cholesterol identified in the liver tissue
8. Homozygosity for the W151X stop mutation in the delta7-sterol reductase gene (DHCR7) causing a lethal form of Smith–Lemli–Opitz syndrome (Löffler et al. 2000).
9. Maternal *ABCA1* genotype is associated with severity of Smith–Lemli–Opitz syndrome and with viability of patients homozygous for null mutations (Lanthaler et al. 2013).
10. The p.Phe174Ser mutation is associated with mild forms of Smith–Lemli–Opitz syndrome (Tucci et al. 2016).
11. Correlation between the 7DHC levels and the clinical severity of patients compared the plasma 7DHC levels to the severity score in the 165 patients in whom both values were available (Waterham and Hennekam 2012): Severity score and 7DHC levels correlated with one another, but this was less pronounced in patients who had a combination of a nonsense mutation and missense mutation compared to patients who had two missense mutations.

12. Genotype–phenotype correlations (Witsch-Baumgartner et al. 2000).
    1. Four classes of mutations: nonsense and splice-site mutations resulting in putative null alleles, missense mutations in the transmembrane domains (TM), mutations in the fourth cytoplasmic loop (4 L), and mutations in the C-terminal ER domain (CT).
    2. All but one of the tested missense mutations reduced protein stability. Concentrations of the cholesterol precursor 7-dehydrocholesterol and clinical severity scores correlated with mutation classes.
    3. The mildest clinical phenotypes were associated with TM and CT mutations, and the most severe types were associated with 0 and 4 L mutations.
    4. Most homozygotes for null alleles had severe SLOS; one patient had a moderate phenotype.
    5. Homozygosity for 0 mutations in DHCR7 appears compatible with life, suggesting that cholesterol may be synthesized in the absence of this enzyme or that exogenous sources of cholesterol can be used.
13. Additional related human syndromes resulting from impaired cholesterol synthesis (Kelly 2000; Porter 2002; Herman and Kratz 2012; Kanungo et al. 2013).
    1. Desmosterolosis
        1. Autosomal recessive inheritance.
        2. Caused by mutations in 24-dehydrocholesterol reductase (*DHCR24*) gene (1p31.1-p33).
        3. Elevated plasma desmosterol.
        4. Report of a female infant with a lethal syndrome of macrocephaly, thick alveolar ridges, gingival nodules, cleft palate, total anomalous pulmonary venous drainage, ambiguous genitalia, short limbs, and generalized osteosclerosis was found to have markedly increased tissue levels of desmosterol.
        5. Another report of a child with microcephaly, short stature, and delays in speech and psychomotor development was found to have an increased plasma level of desmosterol and markedly increased levels of desmosterol in cultured lymphoblasts.
        6. Intellectual disability.
        7. Midline facial defects.
        8. Relative macrocephaly.
        9. Microcephaly.
        10. Hypoplastic to agenesis of corpus callosum.
        11. Spastic contractures.
        12. Hydrocephalus.
        13. Dilated ventricles.
        14. Absent septum pellucidum.
        15. Mildly effaced gyral pattern and incomplete opercularization.
        16. Failure to thrive.
    2. Lathosterolosis
        1. Autosomal recessive
        2. Caused by mutations in *SC5DL* gene (11q23.3)
        3. Microcephaly
        4. Bitemporal narrowing
        5. Neural tube defects
        6. Congenital cataracts
        7. Intrauterine and postnatal growth retardation
        8. Seizures
        9. Intellectual disability
    3. X-linked dominant chondrodysplasia punctata type 2 (CDPX2) (Conradi–Hünermann syndrome)
        1. Caused mutations in *EBP* gene (Xp11.22-11.23)
        2. Typically in females with a variable combination of bilateral and asymmetric shortening of long bones; punctate calcification of epiphyses, trachea, and larynx; segmental cataracts; and patches of ichthyotic skin that typically follow the lines of Blaschko
        3. Lethal to males early in gestation
        4. Characteristic craniofacial appearance with frontal bossing, midface hypoplasia, flat nasal bridge, and midline orofacial defects

5. Agenesis or hypoplasia of corpus callosum
6. Congenital cataracts, microphthalmia, and microcornea
7. Sensorineural hearing loss
8. Tethered cord
9. Dandy–Walker malformation
10. Cervical myelopathy
11. Normal intelligence in females

4. CHILD syndrome (*c*ongenital *h* emidysplasia with *i* chthyosiform erythroderma/nevus and *l*imb *d* efects)
   1. X-linked dominant inheritance
   2. Caused by mutations in *NSDHL* gene (Xq28)
   3. Cutaneous and bony abnormalities similar to CDPX2
   4. Report of a patient with classic CHILD syndrome
      1. Manifests the characteristic sterol abnormality of CDPX2
      2. Carries a mutation creating a stop codon in the same sterol-Δ^8-isomerase associated with CDPX2
   5. Sensorineural hearing loss
   6. Normal intelligence in females
   7. One-sided cerebral hypoplasia with cortical polymicrogyria, ventriculomegaly, absent corpus callosum, and ipsilateral cerebellar dysplasia with completely normal contralateral side of the brain
5. Greenberg dysplasia (hydrops-ectopic calcification-moth-eaten skeletal dysplasia)
   1. Autosomal recessive inheritance
   2. A lethal skeletal dysplasia characterized by hydrops fetalis, short-limbed dwarfism, postaxial polydactyly, and abnormal chondro-osseous mineralization
   3. Radiologic abnormalities
      1. Moth-eaten-appearing long bones
      2. Ectopic epiphyseal calcification
      3. Laryngeal and tracheal calcification
      4. Platyspondyly
   4. Steroid-Δ^{14}-reductase deficiency
6. Antley–Bixler syndrome (Opitz et al. 2002)
   1. Autosomal recessive
   2. Caused by mutations in *POR* gene (1q11.2)
   3. A skeletal abnormality syndrome primarily affecting head and limbs
   4. Also known as multisynostotic osteodysgenesis with long bone fractures
   5. A high incidence of genital ambiguity, an anomaly unlikely due to the *FGFR2* mutation, suggesting possible disordered steroidogenesis in early pregnancy
   6. Elevated two primary precursors of steroid hormones, pregnenolone, and progesterone, as are the classical diagnostic metabolites for 17- and 21-hydroxylase deficiencies, suggesting attenuated steroid hydroxylation (including 17,20-lyase activity) at least in the form not associated with *FGFR2* mutations (Shackleton et al. 2004)
   7. Severe craniosynostosis
   8. Brachycephaly with high broad forehead and midface hypoplasia/choanal atresia
   9. Hydrocephalus
   10. Arnold–Chiari malformation
   11. Intellectual disability
7. CK syndrome
   1. X-linked intellectual disability
   2. Caused by mutations in *NSDHL* gene (Xq28)
   3. Mild to severe intellectual disability in males
   4. Microcephaly
   5. CNS malformation
   6. Seizures
   7. Hypotonia
   8. Dysphasia/speech delay
   9. Behavioral problems
   10. Possible psychopathology in carrier females
8. Mevalonic aciduria
   1. Autosomal recessive

2. Caused by mutations in *MVK* gene (12q24)
3. Severe failure to thrive
4. Developmental delay
5. Mild to severe intellectual disability
6. Progressive cerebellar atrophy
7. Growth retardation
8. Persistence of open fontanelle including third fontanelle
9. Cerebellar ataxia
10. Hypotonia/myopathy
11. Cataracts
12. Shortened lifespan

9. Sterol C4 methyl oxidase deficiency
   1. Autosomal recessive
   2. Caused by mutations in *SC4MOL* gene (4q32-q34)
   3. Developmental delay
   4. Microcephaly
   5. Congenital cataracts
   6. Possible psychopathology (as a result of skin findings)

Clinical Features

1. Variable clinical and biochemical phenotype (Ryan et al. 1998).
2. General.
   1. Postnatal growth retardation
   2. Failure to thrive
   3. Feeding difficulties requiring gavage feeding in many cases
   4. Abnormal intestinal motility
      1. Pyloric stenosis
      2. Vomiting
      3. Gastroesophageal reflux
   5. Feeding intolerance
   6. Gastrointestinal irritability
   7. Allergy
   8. Initial hypotonia/later hypertonia
   9. Recurrent otitis media and pneumonias
   10. Photosensitivity
   11. Adrenal insufficiency uncommon
3. Craniofacial features.
   1. Congenital microcephaly: very common
   2. Metopic prominence and bitemporal narrowing
   3. Capillary hemangioma over the glabella
   4. Eyes
      1. Epicanthal folds
      2. Ptosis (more than 50% of patients, often with asymmetrical or unilateral ptosis)
      3. Congenital cataracts
      4. Optic nerve hypoplasia
   5. Broad nasal bridge and short nasal root with anteverted nares
   6. Micrognathia
   7. Oral
      1. Cleft lip/palate
      2. High-arched/narrow hard palate
      3. Broad/ridged alveolar ridges
      4. Redundant sublingual tissues
      5. Long philtrum
   8. Low-set and posteriorly rotated ears
4. CNS anomalies.
   1. Global psychomotor retardation
   2. Microcephaly (almost universal finding)
   3. Agenesis/hypoplasia of corpus callosum
   4. Cerebellar hypoplasia
   5. Enlarged ventricles
   6. Decreased size of frontal lobes
   7. Pituitary lipoma
   8. Cerebellar hypoplasia with hypoplasia or aplasia of the vermis
   9. Holoprosencephaly sequence (5% of cases)
   10. Seizures
5. Limb anomalies.
   1. Bilateral or unilateral postaxial polydactyly in the hands or feet
   2. Short/proximally placed thumb
   3. Short first metacarpals
   4. Hypoplastic thenar eminences
   5. Subtle "zigzag" alignment of the phalanges of the index finger
   6. Characteristic Y-shaped cutaneous syndactyly of the second-third toes
6. Genital anomalies.
   1. Male (range from normal to the appearance of complete sex reversal) (Nowaczyk and Irons 2012)
      1. External genitalia: normal, hypospadias, female appearing, or ambiguous.

2. Internal genitalia: gonads varying from normal testes to ovotestes to normal ovaries or missing gonads; sex reversal including blind vaginal pouch and rudimentary or bicornuate uterus.
3. Up to 25% of individuals with SLOS have a 46,XY karyotype with a female genital phenotype.
4. Hypospadias or bilateral cryptorchidism occurs in 50% of males with SLOS.

2. Female
1. Hypoplasia of labia minora
2. Hypoplasia of labia majora

7. Congenital heart defects (about 50% of cases) (Lin et al. 1997).
1. Endocardial cushion defect (AV canal)
2. Septal defect
3. Hypoplastic left heart syndrome
4. Patent ductus arteriosus
5. Aortic coarctation
6. Anomalous pulmonary venous return
7. Hypertrophic cardiomyopathy
8. Hypertension

8. Renal anomalies (about 25% of cases).
1. Renal hypoplasia/aplasia with oligohydramnios sequence
2. Horseshoe kidney
3. Renal cortical cysts
4. Hydronephrosis
5. Renal ectopia
6. Ureteral duplication
7. Fetal lobation
8. Hypoplastic bladder and ureters

9. Adrenal anomalies.
1. Adrenal hyperplasia
2. Adrenal hypoplasia

10. Respiratory tract anomalies.
1. Laryngomalacia
2. Tracheomalacia
3. Sleep apnea
4. Abnormal pulmonary lobation
5. Pulmonary hypoplasia

11. Gastrointestinal/hepatic anomalies.
1. Pyloric stenosis (prominent clinical problem)
2. Poor feeding/sucking
3. Gastroesophageal reflux
4. Constipation
5. Malrotation
6. Hirschsprung disease
7. Cholestatic liver disease

12. Skin.
1. Photosensitivity
2. Cutis marmorata
3. Dry skin/eczema

13. Behavioral disorders.
1. Hypersensitivity with tactile defensiveness (oral, hands, and feet)
2. Unusual hyperresponsivity to auditory and visual stimuli
3. Aggressiveness and self-injury
4. Severe sleep disturbance
5. Autistic behavior

14. Prognosis.
1. Many survive to adulthood.
2. Many affected children died in the first year from failure to thrive and infections.

15. So-called Smith–Lemli–Opitz syndrome type II (Curry et al. 1987), a lethal syndrome resembling the original Smith–Lemli–Opitz syndrome.
1. Autosomal recessive disorder
2. Multiple congenital anomalies with male pseudohermaphroditism and frequent early lethality
3. Lethal in the newborn period from internal malformations
4. Most 46,XY "males" with severe hypogenitalism or female-appearing external genitalia
5. Same sterol pattern in most patients
6. Differences in severity between type I and type II Smit–Lemli–Opitz syndrome: due to severity of the mutations according to subsequent molecular genetic studies
7. Possibility of genetic heterogeneity of the Smith–Lemli–Opitz syndrome

16. A lethal multiple congenital anomaly syndrome of polydactyly, sex reversal, renal hypoplasia, and unilobular lungs described in three cases (Donnai et al. 1986).
17. Clinical criteria for the revised severity score (revised Bialer score) by Kelly and Hennekam (2000). The severity score is obtained based on categories of cerebral,

ocular, oral, skeletal, and genital defects identified. Based on the severity score, Smith–Lemli–Opitz syndrome phenotype can be divided into three categories: mild (<20), classical (20–50), and severe (>50). Severity score can be correlated with biochemical parameters and provides a basis for establishing a genotype–phenotype correlation.

1. Brain
    1. Score 1: seizures; qualitative MRI abnormality
    2. Score 2: major CNS malformations; gyral defects
2. Oral
    1. Score 1: bifid uvula or submucous cleft
    2. Score 2: cleft hard palate or median cleft lip
3. Acral
    1. Score 0: non-Y-shaped minimal toe syndactyly
    2. Score 1: Y-shaped 2–3 toe syndactyly; clubfoot; upper or lower polydactyly; other syndactyly
    3. Score 2: any two of the above
4. Eye
    1. Score 2: cataract; frank microphthalmia
5. Heart
    1. Score 0: functional defects
    2. Score 1: single-chamber or vessel defects
    3. Score 2: complex cardiac malformation
6. Kidney
    1. Score 0: functional defect
    2. Score 1: simple cystic kidney disease
    3. Score 2: renal agenesis; clinically important cystic disease
7. Liver
    1. Score 0: induced hepatic abnormality
    2. Score 1: simple structural abnormality
    3. Score 2: progressive liver disease
8. Lung
    1. Score 0: functional pulmonary disease
    2. Score 1: abnormal lobation; pulmonary hypoplasia
    3. Score 2: pulmonary cysts; other major malformations
9. Bowel
    1. Score 0: functional GI disease
    2. Score 1: pyloric stenosis
    3. Hirschsprung disease
10. Genitalia
    1. Score 1: simple hypospadias
    2. Score 2: ambiguous or female genitalia in a 46,XY; frank genital malformation in a 46,XX

Diagnostic Investigations

1. Diagnostic biochemical hallmarks of the syndrome
    1. Low serum cholesterol levels (10% of patients with DHCR7 deficiency have normal levels of cholesterol).
    2. Markedly elevated serum levels of 7-dehydrocholesterol (cholesta-5,7-dien-3beta-ol; 7DHC), precursor of cholesterol. However, up to 25% of reports of RSH/SLO in the literature may describe genetic conditions other than RSH/SLO with 7-DHC-emia (Cunniff et al. 1997).
    3. Cholesterol precursors 7-DHC and 8-DHC are important biomarkers of the level of functioning in SLOS, especially regarding cognitive abilities (Thurm et al. 2016).
2. DHCR7 enzyme assay
3. Analysis of sterol biosynthesis in cultured cells
4. Use of patient-derived iPSCs (induced pluripotent stem cells), a new discovery, to model neural deficits in SLOS, a rare autosomal recessive, multiple malformations, and intellectual disability syndrome (Francis et al. 2016; Wen et al. 2016)
5. Aberrant MRI findings (Lee et al. 2013)
    1. Observed in 96% SLOS patients, with abnormalities of the septum pellucidum the most frequent (76%) finding.
    2. Abnormalities of the corpus callosum were found in 69% patients.
    3. Other findings
        1. Cerebral atrophy
        2. Cerebellar atrophy
        3. Colpocephaly
        4. White matter lesions
        5. Arachnoid cysts

6. Dandy–Walker variant
7. Type I Chiari malformation

6. *DHCR7* mutation testing
   1. Sequence analysis.
   2. Targeted mutation analysis.
   3. Seven most frequent mutations described to date, representing two-thirds of the mutation in analyzed alleles (Jira et al. 2003).
      1. IVS8-1 G > C (31.5%)
      2. T93M (11.2%)
      3. R404C (10.7%)
      4. W151X (6.4%)
      5. V326L (6.3%)
      6. R352W (3.2%)
      7. E448K (3.2%)
   4. SLOS patients who are heterozygous/homozygous for one pathogenic mutation and only one parent carrying that mutation are candidates for DHCR7 gene (partial) deletions (Lanthaler et al. 2015).

Genetic Counseling

1. Recurrence risk: carrier frequency (2%, a reasonable estimate for risk assessment) is relatively high (Porter 2008).
   1. Patient's sibs: 25%
   2. Patient's offspring: not increased
2. Prenatal diagnosis.
   1. Prenatal screening as part of routine triple-marker screen for Down syndrome and neural tube defects: abnormally low maternal serum level of unconjugated estriol observed in pregnancies affected with Smith–Lemli–Opitz syndrome (Bradley et al. 1999; Schoen et al. 2003).
   2. Second trimester ultrasonography (Goldenberg et al. 2004).
      1. Nuchal edema
      2. Renal malformation
      3. Polydactyly
      4. Ambiguous genitalia
      5. Cerebral malformation
      6. Cardiac malformation
      7. Intrauterine growth retardation
   3. A successful first-trimester prenatal diagnosis of SLO by showing elevated levels of 7-DHC in direct analysis of a chorionic villus biopsy (Sharp et al. 1997). The result was confirmed by demonstration of 7-DHC accumulation in cultured cells (skin fibroblasts, CV cells) under modified growth conditions and by the biochemical examination of fetal brain.
   4. Prenatal diagnosis (Jezela-Stanek et al. 2006) can be established by:
      1. Detection of elevated 7-dehydrocholesterol concentrations (Abuelo et al. 1995) or SLOS-causing mutations in the DHCR7 gene by analysis in chorionic villus samples or amniocytes.
      2. Amniotic fluid sterol analysis: accurate prenatal diagnosis of RSH/SLOS is possible by sterol analysis of AF and CV specimens (Kratz and Kelley 1999; Haas et al. 2013).
      3. Serial measurements of estriol, pregnanetriol, 7-dehydropregnanetriol, and 8-dehydroestriol concentrations in maternal urine samples obtained between 9 and 20 weeks of gestation.
   5. Preimplantation genetic diagnosis has been made for SLOS with successful blastomere diagnosis with mutations in the *DHCR7* gene, allowing transfer of mutation-free embryos and successful pregnancies (Liss et al. 2008).
   6. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require molecular genetic testing; prior identification of the disease-causing mutations in the family is necessary (Nowaczyk 2013).
3. Management (Porter 2000; Jira et al. 2003; Svoboda et al. 2012).
   1. The mainstay of SLOS treatment (Kelly et al. 2015).
      1. Adequate dietary cholesterol intake.
      2. Cholesterol supplementation increases plasma and tissue cholesterol levels and often decreases 7DHC and 8DHC levels via feedback inhibition of the 3-hydroxy-3-methylglutaryl-coenzyme

A (HMG-CoA) reductase (Svoboda et al. 2012).
3. Patients are encouraged to consume high-cholesterol foods (e.g., egg yolks, whipped cream, and butter fat) or take pharmaceutical-grade cholesterol, administered at a dose of 20–300 mg/kg/day (Svoboda et al. 2012).
4. Educational interventions.
5. Behavioral management.

2. Therapeutic trials using dietary supplementation of cholesterol (Irons et al. 1997).
   1. Used to treat complications related to the biochemical disturbance. Clinical benefits of this therapy are limited by the presence of developmental problems.
   2. Currently, most patients being treated with pharmaceutical-grade cholesterol suspended in either soybean oil or Ora-Plus syrup or alternatively with egg yolks (Linck et al. 2000): increases plasma cholesterol and decreases plasma 7-dehydrocholesterol in Smith–Lemli–Opitz syndrome.
   3. Multiple benefits of dietary cholesterol supplementation (Elias et al. 1997).
      1. Improved nutrition and growth
      2. Decreased irritability
      3. Increased alertness
      4. Increased sociability
      5. Decreased self-abusive and aggressive behavior
      6. Decreased tactile defensiveness
      7. Decreased photosensitivity
      8. Decreased infections
      9. Improved hearing
      10. Improved muscle tone and strength
   4. Use of bile acids shown to have no clear benefit.
3. An alternative therapeutic strategy of treating with simvastatin (an oral HMG-CoA reductase inhibitor) (Jira et al. 2000) for a median period of 2 years with impressive overall biochemical effect.
   1. A decrease of 7DHC and 8DHC
   2. An increase of cholesterol
   3. Promising clinical improvement
4. A placebo-controlled trial of simvastatin therapy in Smith–Lemli–Opitz syndrome (Wassif et al. 2016).
   1. Relatively safe in patients with SLOS
   2. Improves the serum dehydrocholesterol-to-total sterol ratio and significantly improves irritability symptoms in patients with mild to classic SLOS
5. Fresh frozen plasma, which contains cholesterol-rich lipoproteins, used to provide cholesterol supplementation in very sick patients and the fetuses (Porter 2000).
6. Antenatal treatment of SLOS by cholesterol supplementation is feasible and results in improvement in fetal plasma cholesterol levels and fetal red cell volume. SLOS may be added to the growing list of human genetic disorders for which prenatal diagnosis is available and therapeutic intervention may be possible (Irons et al. 1999).
7. Management of SLOS during pregnancy (Ellingson et al. 2014).
   1. Serial monitoring of cholesterol and 7DHC levels with dietary intervention to increase exogenous cholesterol and decrease the accumulation of potentially toxic cholesterol precursors.
   2. A cholesterol-loading diet, including lean meats, cheese, and eggs, was recommended beginning at approximately 29 weeks of gestation.
   3. Serial fetal ultrasounds were performed due to concern for intrauterine growth restriction, heart defects, or other anomalies associated with either SLOS or toxicity due to cholesterol precursors crossing the placenta.

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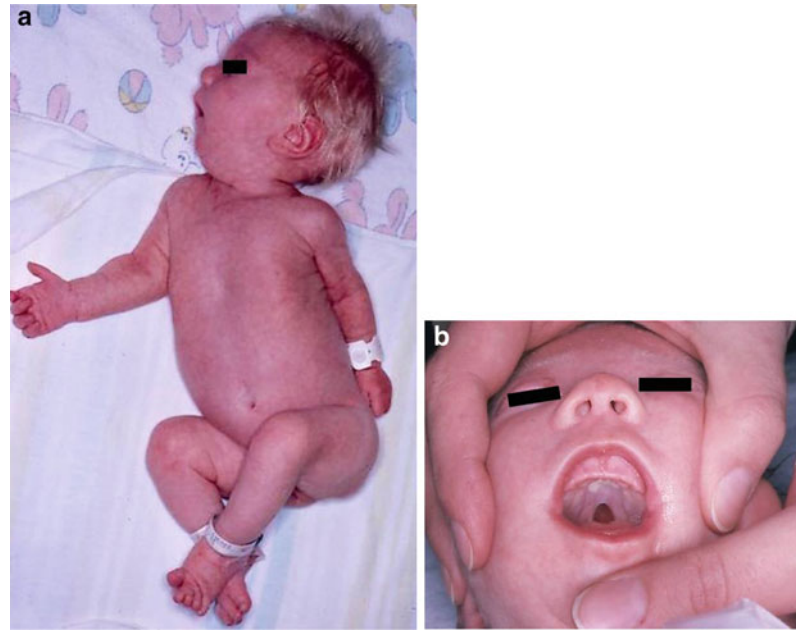

Fig. 1 (**a**, **b**) An infant (**a**) with Smith–Lemli–Opitz syndrome showing failure to thrive, ptosis, cleft palate (**b**), thick alveolar ridge, upturned nares, micrognathia, transverse palmar crease, and syndactyly between the second and third toes

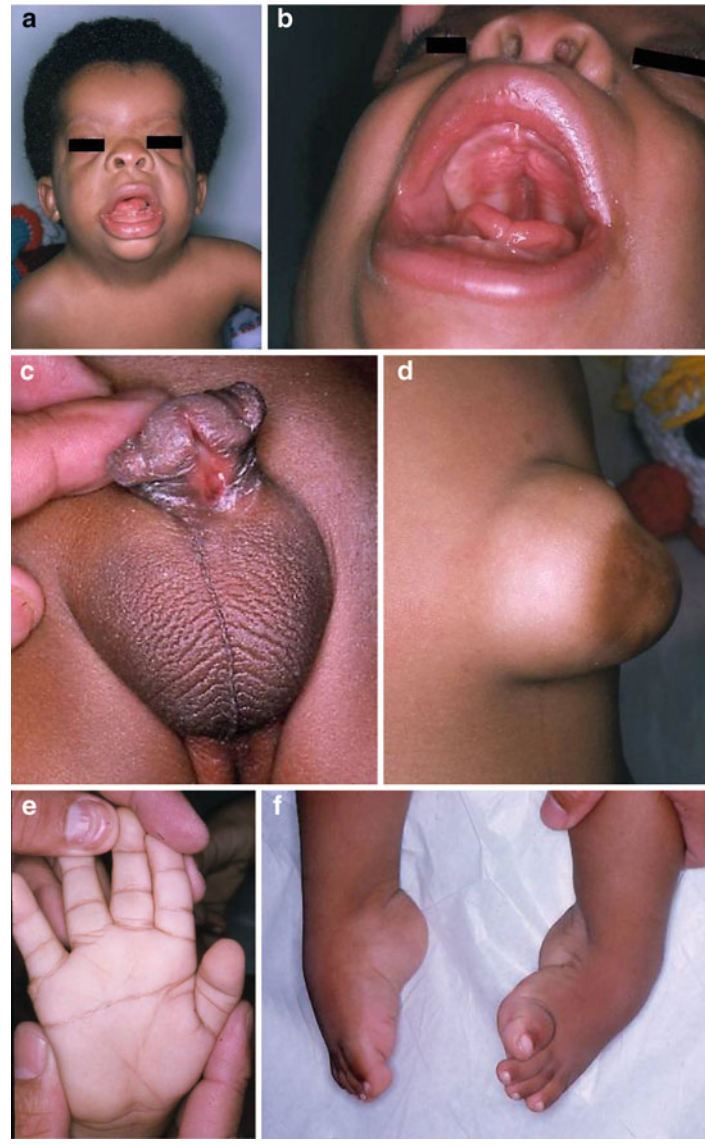

Fig. 2 (**a**–**f**) A boy (**a**, **b**) with Smith–Lemli–Opitz syndrome showing characteristic facial features (epicanthal folds, ptosis of the eyelids, broad nose with upturned nares, and thick alveolar ridges), ambiguous genitalia (hypospadias) (**c**), umbilical hernia (**d**), transverse palmar crease (**e**), and talipes equinovarus (**f**)

Smith-Magenis Syndrome

Contents

Smith-Magenis syndrome (SMS) is a complex multiple congenital anomaly and mental retardation syndrome caused by an interstitial deletion of chromosome 17p11.2.

Synonyms and Related Disorders

Chromosome 17p11.2 deletion syndrome

Genetics/Basic Defects

1. Inheritance
    1. Autosomal dominant inheritance in virtually all cases of SMS occurring de novo
    2. Rare familial chromosome complex rearrangements leading to deletion (17)(p11.2) and SMS
2. Caused by an interstitial deletion of 17p11.2 in the majority of cases (Smith et al. 1986; Straton et al. 1986; Elsea et al. 1997; Potocki et al. 2003)
    1. A common deletion size observed in the majority of patients, derived from nonallelic homologous recombination between low-copy repeat gene clusters during either maternal or paternal gametogenesis
    2. Either smaller- or larger-sized deletions in about 20–25% of patients
3. Considered a contiguous gene syndrome (Greenberg et al. 1991)
    1. Haploinsufficiency of multiple functionally unrelated genes located in close proximity is responsible for the phenotype (Juyal et al. 1996).
    2. Deletion of a common interval spanning an estimated 4–5 Mb in majority of patients.
4. Sterol regulatory element-binding protein 1 (SREBF1) has been mapped to 17p11.2 within the SMS critical region (Chen et al. 1996). Therefore, the patients are hemizygous for the gene encoding SREBP1 leading to hypercholesterolemia.
5. Rare nondeletion cases (Potocki et al. 2003; Truong et al. 2010)
    1. Report of additional patients without a microdeletion, each harboring a mutation in *retinoic acid-induced 1* gene (*RAI1*), which maps within the SMS critical region (Slager et al. 2003).
    2. *RAI1* mutations: the second most frequent molecular etiology with this gene being located in the SMS locus at 17p11.2 (Dubourg et al. 2014).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_219

3. Haploinsufficiency of *RAI1* results in developmental delay, mental retardation, sleep disturbance, self-abusive behaviors, and most features commonly seen in SMS (Seranski et al. 2001).
4. Although *RAI1* is the primary gene responsible for most features of SMS, other genes within 17p11.2 contribute to the variable features and overall severity of the syndrome (Girirajan et al. 2006).
5. *MYO15* clearly associated with a specific phenotypic feature (sensorineural hearing impairment) in a patient with SMS who harbored a recessive mutation on the nondeleted allele (Liburd et al. 2001).

Clinical Features

1. Infantile hypotonia (Smith et al. 2010)
2. Feeding difficulties
3. Failure to thrive
4. Developmental delay
5. Distinctive craniofacial features (Chen et al. 1996; Allanson et al. 1999)
    1. Brachycephaly
    2. Broad square-shaped face
    3. Prominent forehead
    4. Synophrys
    5. Epicanthal folds
    6. Upslanted palpebral fissures
    7. Deep-set eyes
    8. Broad nasal bridge
    9. Marked midfacial hypoplasia
    10. Short full-tipped nose with reduced nasal height
    11. Micrognathia in infancy changing to relative prognathia with age
    12. Distinctive appearance of the mouth, with fleshy everted upper lip with a "tented" appearance
6. Otolaryngologic anomalies
    1. Speech delay
    2. Hoarse voice
    3. Velophalangeal insufficiency
    4. Tracheobronchial problems
7. Ocular anomalies
    1. Iris anomalies
    2. Microcornea
    3. Retinal detachment
8. Skeletal abnormalities (Spilsbury and Mohanty 2003)
    1. Short stature
    2. Scoliosis
    3. Brachydactyly
    4. Flat feet
9. Dermatological features (Guérin-Moreau et al. 2015)
    1. Skin features secondary to self-injurious behavior, such as bites, abrasions, dystrophic scars, limited spots of hyperkeratosis, anomalies of the nails, and whitlows, were found in the majority of patients.
    2. Acral pachydermia and fissured plantar keratoderma: common.
    3. Xerosis: constant and associated with extensive keratosis pilaris in the majority of patients.
    4. Dermatofibromas: frequent in older patients.
    5. Dense and shiny hair with an unusual hairline.
    6. Eyelash trichomegaly and heavy brows as well as folliculitis on the back: common.
10. Immune complex-mediated autoimmunity: adult onset of multiple autoimmune disorders (Yang et al. 2014)
    1. Systemic lupus erythematosus
    2. Antiphospholipid antibody syndrome
    3. Autoimmune hepatitis
11. Characteristic neurobehavioral phenotype (Dykens et al. 1997; Smith et al. 1998a, b; Willekens et al. 2000; Boddaert et al. 2004)
    1. Mental retardation (most patients in moderate range)
    2. Speech delay
    3. Signs of peripheral neuropathy
    4. Inattention
    5. Hyperactivity
    6. Maladaptive behaviors including frequent outbursts and temper tantrums
    7. Attention seeking
    8. Mimics attention deficit hyperactivity disorder (Gnanavel 2014)
    9. Impulsivity

10. Distractibility
11. Disobedience
12. Aggression
13. Toileting difficulties
14. Decreased sensitivity to pain
15. Self-injurious behaviors
    1. Self-hitting
    2. Self-biting
    3. Skin picking
    4. Inserting foreign objects into body orifices
    5. Yanking fingernails and/or toenails (onychotillomania)
16. Stereotypic behaviors (Dykens and Smith 1998)
    1. Specific to SMS
       1. Spasmodic upper-body squeeze or "self-hug"
       2. Hand licking and page flipping ("lick and flip")
    2. Additional stereotypes
       1. Mouthing objects or insertion of hand in mouth
       2. Teeth grinding
       3. Body rocking
       4. Spinning or twirling objects
17. Significant sleep disturbance (Smith et al. 1998b) potentially due to circadian rhythm abnormalities of melatonin (Potocki et al. 2000, 2003; De Leersnyder et al. 2001a)

12. Other features (Greenberg et al. 1996)
    1. Cardiac defects
    2. Renal and urinary tract abnormalities
    3. Thyroid function abnormalities
    4. Cleft lip/palate
    5. Hearing loss
    6. Seizures
    7. Immune function abnormalities, especially low IgA

Diagnostic Investigations

1. Cytogenetic studies for detection of an interstitial deletion of 17p11.2
    1. G-banded karyotype: may not detect small deletion especially when the indication of cytogenetic study is other than SMS
    2. Molecular cytogenetic analysis by FISH using a DNA probe specific for the SMS critical region
2. Molecular genetic testing of RAI1, the only gene known to account for the majority of features in SMS: available only on a clinical basis
3. Blood chemistry
    1. Hypercholesterolemia (Smith et al. 2002)
    2. Hypertriglyceridemia
    3. Qualitative immunoglobulins
    4. Thyroid function tests
4. Molecular analysis using single-nucleotide polymorphism array (Yang et al. 2014)
    1. A de novo 3.8-Mb deletion (breakpoints, chr17:16,660,721-20,417,975), resulting in haploinsufficiency for TACI (transmembrane activator and CAML interactor).
    2. The data are consistent with potential loss of function for the BAFF (B-cell-activating factor) receptor TACI as a contributing factor to human autoimmune phenomena.
5. Renal ultrasound for possible renal and urologic anomalies
6. Echocardiogram for possible cardiac defects
7. Radiography of the spine for scoliosis and other vertebral anomalies
8. EEG for clinical seizures
9. MRI (Maya et al. 2014) and PET imaging (Boddaert et al. 2004)
    1. Periventricular heterotopia
    2. Ventriculomegaly
    3. Hypoplasia of the cerebellar vermis
    4. Thin corpus callosum
    5. Thin brain stem
    6. A significant decrease of gray matter concentration in the insula and lenticular nuclei
    7. A significant hypoperfusion in the same regions
10. Diagnostic strategies (Elsea and Girirajan 2008)
    1. Fluorescent in situ hybridization (FISH): classical methods used to detect the SMS 17p11.2 microdeletion (90% of cases).

2. Molecular identification (sequence analysis) of a mutation in *RAI1* (remaining 10% of cases).
3. Whole genome chromosome microarray studies (CGH) will also identify 17p11.2 deletion involving *RAI1*.
4. Multiplex ligation-dependent probe amplification (MLPA) and real-time quantitative PCR are the newer cost-effective and high-throughput technologies.

Genetic Counseling

1. Recurrence risk (Smith et al. 2010).
   1. Patient's sib (Elsea and Girirajan 2008)
      1. Less than one percentage if parental chromosome analysis is normal, taking account of possible presence of parental germ line mosaicism
      2. An increased risk, provided a parent carries a chromosome rearrangement and dependent upon the specific chromosome rearrangement or if mosaicism for either a deletion (Zori et al. 1993) or *RAI1* mutation is present in either parent (mosaicism in a parent of an affected child is estimated at 3–5%)
   2. Patient's offspring
      1. Unlikely to have offspring due to severe phenotype
      2. Theoretically, a 50% risk of having offspring with SMS
2. Prenatal diagnosis: available for pregnancies at risk using a combination of routine cytogenetic studies and FISH.
   1. Amniocentesis
   2. CVS
3. Preimplantation genetic diagnosis may be available for families in which the disease-causing deletion or mutation has been identified.
4. Management.
   1. Early childhood intervention programs
   2. Special education
      1. Speech and language
      2. Physical and occupational
      3. Sensory integration
   3. Vocational training in later years.
   4. Psychotropic medications to increase attention and decrease hyperactivity.
   5. Behavioral modification.
   6. Administration of β_1-adrenergic antagonist and melatonin helps to manage hyperactivity, enhances cognitive performance, and reduces sleep disorders (de Leersnyder 2001b).
   7. Psychosocial support for the family.

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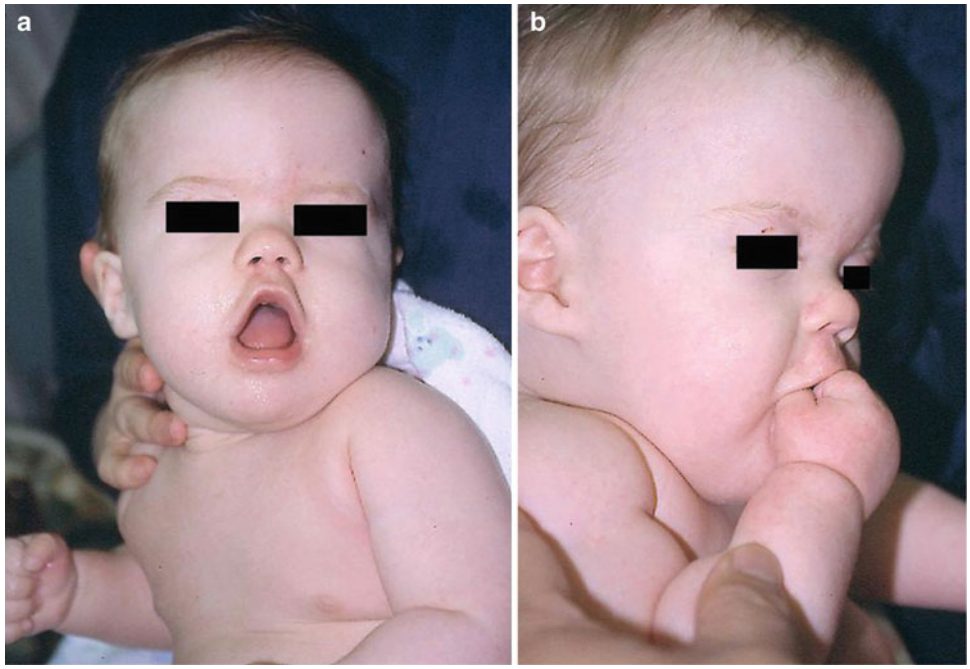

Fig. 1 (**a**, **b**) An infant with Smith-Magenis syndrome (**a**, **b**) showing prominent forehead, broad square-shaped face, synophrys, short full-tipped nose, and fleshy everted upper lip with a "tented" appearance. Chromosome analysis showed an interstitial deletion of 17p11.2

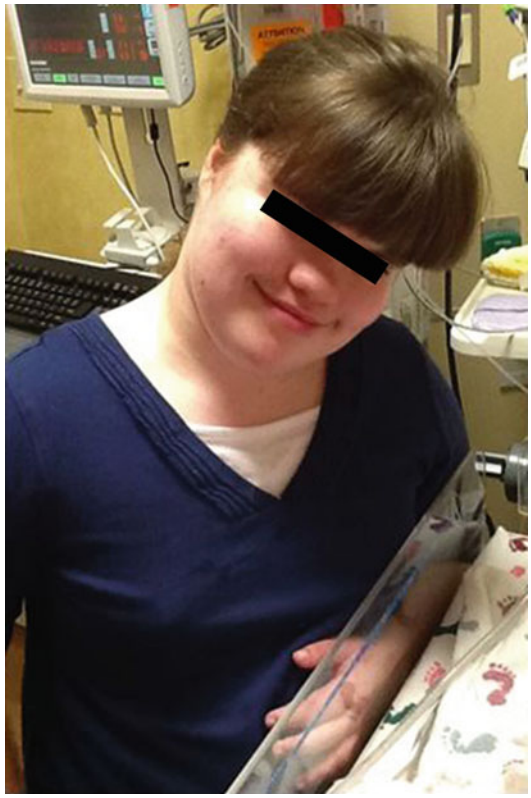

Fig. 2 Previous infant, now 16-year-old, was 4′10″ and ambulatory. She loves computer (changes pictures and knows command, search, and test-out with simple letters). However, she has behavior problems (difficult to handle, outburst, impulsive, anger, bite people, and seek attention) (Courtesy of Dr. Gerald Whitton)

Sotos Syndrome

Contents

Sotos syndrome was described by Sotos et al. (1964) in 1964 and is relatively common among overgrowth syndromes. It is also known as cerebral gigantism (Abraham and Snodgrass 1969).

Synonyms and Related Disorders

Cerebral gigantism; Malan syndrome (Sotos syndrome 2)

Genetics/Basic Defects

1. Inheritance: genetically heterogeneous (Boman and Nilsson 1980; Visser and Matsumoto 2003).
    1. Sporadic in majority of cases (>98%)
    2. Autosomal dominant inheritance reported in a few families (Hansen and Friis 1976; Winship 1985; Scarpa et al. 1994; Donnelly et al. 2011)
        1. Full penetrance
        2. Extremely variable phenotype
    3. Autosomal recessive inheritances postulated in some families
2. Discovery of human *n*uclear receptor *S*ET *d*omain-containing protein 1 (*NSD1*) gene (Hőglund et al. 2003).
    1. Report of a patient with Sotos syndrome who had t(5;8)(q35;q24.1) (Imaizumi et al. 2002).
    2. Discovery of a partial genomic sequence homologous to mouse *NSD1* near the breakpoint by constructing a BAC/PAC/cosmid contig covering the breakpoint.
    3. Human *NSD1* gene was subsequently isolated and characterized.
3. Molecular defect.
    1. A report of a child with Sotos phenotype and a de novo balanced translocation [46, XX,t(5;15)(q35;q22)] suggests a relationship between genetic material at 5q35 or 15q22 and the expression of an autosomal dominant gene (Maroun et al. 1994).
    2. The major cause of Sotos syndrome: haploinsufficiency of the *NSD1* gene (Kurotaki et al. 2002) at 5q35, because the majority of patients had either a common microdeletion including *NSD1* or a truncated type of point mutation in *NSD1*.
    3. *NSD1* gene mutations and deletions (Kamimura et al. 2003; Rio et al. 2003).
        1. Japanese patients (66%)
            1. Point mutations (48.5%)
            2. Deletions (18.2%)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. British patients (78%)
    1. Point mutations (70%)
    2. Large deletions (8%)
4. Size of the deletion correlates with severity of the phenotype.
5. Preferential paternal origin of microdeletions caused by prezygotic chromosome or chromatid rearrangements in Sotos syndrome (Miyake et al. 2003).
6. Mutations in *NSD1* are responsible for Sotos syndrome, but are not a frequent finding in other overgrowth phenotypes (Türkmen et al. 2003).
7. At least 10% of patients with clinical features of Sotos syndrome do not carry abnormalities in *NSD1* (Tatton-Brown and Rahman 2007).
    1. To date, 26 patients with Sotos-like overgrowth features have been described with either microdeletions encompassing the Nuclear Factor I-X gene (NFIX) at 19p13.2, point mutations, or small intragenic deletions (Malan et al. 2010; Yoneda et al. 2012; Priolo et al. 2012; Klaassens et al. 2014).
    2. *NFIX* mutations affecting the DNA-binding domain cause a peculiar overgrowth syndrome (Malan syndrome) (Gurrieri et al. 2015).
    3. Novel mutations of *NFIX* gene causing Marshall–Smith syndrome or Sotos-like syndrome (Martinez et al. 2015).
    4. Malan syndrome (Sotos syndrome 2) in two patients with 19p13.2 deletion encompassing NFIX gene and novel NFIX sequence variant (Jezela-Stanek et al. 2016).
8. Two siblings with Sotos features without mutations in NSD1 and detected a homozygous frameshift mutation in the *APC2* gene by whole-exome sequencing, which resulted in the loss of function of cytoskeletal regulation in neurons (Almuriekhi et al. 2015).

4. Patient with Dup(5)(q35.2-q35.3) reciprocal to the common Sotos syndrome deletion (Žilina et al. 2013).
    1. Some reciprocal genomic events, such as dup(5q35.2-q35.3), can result in opposite phenotypic outcome.
        1. Deletions in this locus lead to Sotos syndrome characterized by childhood overgrowth with advanced bone age, craniofacial dysmorphic features including macrocephaly, and learning difficulties, while duplications have been proposed to manifest in opposite phenotype related to growth.
        2. 5q35.2-q35.3 duplication phenotype: short stature since the birth, microcephaly, brachydactyly, delayed bone age, mild to moderate intellectual disability, and mild facial dysmorphism.
    2. Clinical presentation of three new cases with 5q35 microduplication, encompassing *NSD1* gene, outlining a novel syndrome characterized by microcephaly, short stature, developmental delay, and in some cases delayed bone maturation, without any typical facial or osseous anomalies (Novara et al. 2014).
5. No satisfactory explanation for the overgrowth.

Clinical Features

1. Prenatal and postnatal overgrowth (major clinical features)
    1. Large for gestational age at birth
    2. Excessive growth velocity, particularly in the first 3–4 years
    3. Advanced bone age by 2–4 years over chronological age during childhood
    4. Large hands and feet
    5. Excessive heights in some adult patients
2. Performance
    1. Developmental retardation
    2. Mental deficiency of varying degree
    3. Lack of fine motor control
    4. Difficulties in neonatal adaptation and/or feeding
3. Characteristic craniofacial appearance (Cole and Hughes 1990; Allanson and Cole 1996)
    1. Dolichocephalic large head
    2. Prominent forehead

3. Ocular hypertelorism
4. Downslanting of the palpebral fissures
5. High-arched palate
6. Premature teeth eruptions
7. Pointed chin (prominent mandible)

4. CNS manifestations
   1. Hypotonia
   2. Seizures
   3. Clumsy gait
   4. Mildly enlarged ventricles
   5. Increased subarachnoid spaces
   6. Agenesis/hypoplasia of the corpus callosum
   7. Agenesis of the septal pellucidum
   8. Hypoplasia/atrophy of the cerebellar vermis
   9. Large cisternal magna
   10. Abnormal Sylvian fissure
5. Neoplasms (3.9%) (Cohen 1999)
   1. Benign tumors
      1. Multiple hemangiomas
      2. Osteochondroma
      3. Large hairy nevus
      4. Giant-cell granulomas of the mandible
   2. Malignant tumors
      1. Wilms tumor
      2. Neuroblastoma
      3. Hepatocellular carcinoma
      4. Epidermoid carcinoma of the vagina
      5. Small-cell carcinoma of the lung
6. Other features
   1. Severe connective tissue laxity, manifesting as redundant skin, joint hypermobility, vesicoureteric reflux, and aortic dilatation in four patients with novel truncating mutations in *NSD1* (Hood et al. 2016)
   2. Strabismus
   3. Pes planus
   4. Kyphoscoliosis
   5. Asymmetric leg length
   6. Syndactyly
   7. Congenital heart defects (Noreau et al. 1998)
      1. Septal defects
      2. Persistent ductus arteriosus
      3. Ebstein malformation
   8. Functional megacolon
   9. Urinary anomalies
      1. Hypoplastic kidney
      2. Hydronephrosis
      3. Vesicoureteric reflux
   10. Recurrent hernias
   11. Abnormal dermatoglyphics
7. Social difficulties and neuropsychiatric disorders (Sarimski 2003)
   1. Social difficulties
      1. Emotional immaturity
      2. Poor motor control
      3. Temper tantrums
      4. Good social skills in some patients
   2. Neuropsychiatric disorders (Mouridsen and Hansen 2002)
      1. Intellectual impairment
      2. Learning disabilities
      3. Language impairments
      4. Behavioral disorders
8. Differential diagnosis (Tatton-Brown et al. 2015): classified into two groups (Cole and Hughes 1994)
   1. Group 1: relatively easy to distinguish because of other specific associated features.
      1. Constitutional gigantism (alone)
      2. Marfan syndrome (please see the chapter on "▶ Marfan Syndrome")
      3. Neurofibomatosis (please see the chapter on "▶ Neurofibromatosis 1")
      4. Beckwith–Wiedemann syndrome (please see the chapter on "▶ Beckwith-Wiedemann Syndrome")
      5. Marshall–Smith syndrome
      6. Adrenogenital and gonadal secreting tumors
      7. Klinefelter syndrome (please see the chapter on "▶ Klinefelter Syndrome")
      8. Acromegaly
   2. Group 2: the syndromes in this group cause more difficulties.
      1. Ruvalcaba–Myhre–Smith (Bannayan–Riley–Ruvalcaba) syndrome: characterized by macrocephaly, vascular malformations, hamartomatous polyps of the distal ileum and colon, pigmented macules on the shaft of the penis, lipomas, and increased risk of

thyroid and breast cancer. Pathogenic variants in PTEN have been found in about 65% of cases. A somewhat similar facial gestalt in combination with overgrowth may lead to confusion with Sotos syndrome, but a detailed clinical examination and molecular genetic testing should differentiate the two conditions (please see the chapter on "▶ Bannayan-Riley-Ruvalcaba Syndrome)."

2. EZH2-related Weaver syndrome (also known as Weaver–Smith syndrome): please see the description below.
3. Simpson–Golabi–Behmel syndrome type 1 (SGBS1): this X-linked condition is also associated with pre- and postnatal overgrowth in males. However, other features of SGBS not typically found in Sotos syndrome include polydactyly, supernumerary nipples, diastasis recti, and pectus excavatum. The facial gestalt also differs between the two disorders. Mutation of GPC3 is causative.
4. Fragile X syndrome (please see the chapter on "▶ Fragile X Syndrome").
5. Benign familial macrocephaly: this autosomal dominant condition is characterized by dolicho- and/or macrocephaly in an individual who is otherwise neurologically normal. It is likely a heterogeneous condition and is usually a diagnosis of exclusion.
6. Nevoid basal cell carcinoma syndrome (NBCCS or Gorlin syndrome): characterized by the development of multiple jaw keratocysts, frequently beginning in the second decade of life, and/or basal cell carcinomas usually from the third decade onward. Most individuals have skeletal anomalies such as bifid ribs or wedge-shaped vertebrae. About 60% of individuals have a recognizable appearance with macrocephaly, bossing of the forehead, and coarse facial features. Head circumference increases above the 98th centile until age 10–18 months, but is not usually associated with global developmental delay. NBCCS is caused by germ line pathogenic variants in *PTCH* and is inherited in an autosomal dominant manner.
7. Chromosome abnormalities: a Sotos syndrome-like phenotype has been associated with 4p duplications, 19p13.2 microduplication (Lehman et al. 2012), mosaic 20p trisomy (Faivre et al. 2000), and 22q13.3 deletion syndrome.
8. Nonspecific overgrowth: many individuals with overgrowth do not fulfill the diagnostic criteria for any of the above conditions but nevertheless have other features (e.g., learning difficulties, distinctive facial features) that suggest an underlying genetic cause. Nonspecific overgrowth is likely to be a heterogeneous group of conditions with multiple causes.

9. Weaver syndrome: the major differential diagnosis (Opitz et al. 1998; Douglas et al. 2003)
    1. Seen less commonly than Sotos syndrome
    2. Caused by *NSD1* mutations in a significant number of patients
    3. Cardinal features
        1. Accelerated growth
        2. Distinctive facies with micrognathia and a deep horizontal chin crease
        3. Advanced bone age
        4. Developmental delay
    4. Additional features
        1. A hoarse low-pitched cry
        2. Metaphyseal flaring of the femurs
        3. Deep-set nails
        4. Prominent finger pads
        5. Camptodactyly

Diagnostic Investigations

1. Glucose intolerance (14%).
2. Radiography.
    1. Advanced bone age.
    2. Cephalometric radiographs: steepness of the anterior cranial base angle and

protrusion of the middle and lower face, shown in all three patients from a family (Bale et al. 1985).
3. Metacarpophalangeal pattern profile analysis (Butler et al. 1988): the mean hand profile contained a major peak in the proximal phalangeal area and a smaller peak in the metacarpal area, while the distal hand bones were relatively short.

3. CNS lesions by CAT scan and/or MRI of the brain (Schaefer et al. 1997; Gusmão Melo et al. 2000).
   1. Ventricles
      1. Ventriculomegaly
      2. Prominent trigone of the lateral ventricles
      3. Prominent occipital horn
   2. Extracerebral fluid
      1. Increased supratentorial space
      2. Increased posterior fossa space
   3. Midline anomalies
      1. Persistent cavum septum pellucidum
      2. Persistent cavum vergae
      3. Cavum velum interpositum
      4. Macrocisterna magna
      5. Agenesis of corpus callosum
      6. Hypoplasia (thinning) of corpus callosum
   4. Migration abnormalities
   5. Periventricular leukomalacia
   6. Macrocerebellum
   7. Open operculum
4. Cytogenetic testing.
   1. Most affected individuals do not have a cytogenetic abnormality.
   2. Rare cytogenetic abnormality such as a translocation involving 5q35 results in Sotos syndrome (Kurotaki et al. 2003).
5. DNA analysis: NSD1 abnormalities, such as truncating mutations, missense mutations in functional domains, partial gene deletions, and 5q35 microdeletions encompassing NSD1, are identifiable in the majority (49%) of Sotos syndrome cases (Tatton-Brown and Rahman 2007).
   1. Intragenic sequence analysis/mutation scanning
   2. Deletion/duplication analysis
      1. 5q35 microdeletion analysis/*NSD1* whole gene deletion analysis
      2. *NSD1* exonic/multiexonic gene deletions

Genetic Counseling

1. Recurrence risk (Tatton-Brown and Rahman 2007)
   1. Patient's sib
      1. Most individuals with Sotos syndrome are the result of de novo mutations.
      2. No affected siblings of unaffected parents have been reported, indicating that the incidence of germ line mosaicism must be low.
      3. Therefore, the recurrence risk of unaffected parents approximates to the population risk, which is estimated to be about 1:15,000.
   2. Patient's offspring: a 50% risk as for other autosomal dominant conditions
2. Prenatal testing and preimplantation genetic diagnosis of Sotos syndrome (Tatton-Brown et al. 2015)
   1. Ultrasonography in the third trimester (Chen et al. 2002; Chen 2012).
      1. Macrocephaly
      2. Ventriculomegaly
      3. Hypoplasia of the corpus callosum
      4. An enlarged cisterna magna
      5. Overgrowth
      6. Unilateral hydronephrosis
      7. Polyhydramnios
   2. Prenatal diagnosis possible by molecular mutation analysis of fetal DNA obtained from amniocytes or CVS of previously identified disease-causing *NSD1* gene: available on a clinical basis.
   3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified.
3. Prenatal findings and the genetic diagnosis of fetal overgrowth disorders (Chen 2012)

1. Simpson–Golabi–Behmel syndrome
    1. Macrosomia
    2. Polyhydramnios
    3. Elevated maternal serum α-fetoprotein (MSAFP)
    4. Cystic hygroma
    5. Hydrops fetalis
    6. Increased nuchal translucency
    7. Craniofacial abnormalities
    8. Visceromegaly
    9. Renal anomalies
    10. Congenital diaphragmatic hernia
    11. Polydactyly
    12. A single umbilical artery
2. Beckwith–Wiedemann syndrome
    1. Macrosomia
    2. Polyhydramnios
    3. Macroglossia
    4. Omphalocele
    5. Placentomegaly
    6. A long umbilical cord
    7. Echogenic kidneys
    8. Pancreatic cystic dysplasia
4. Management:
    1. No specific therapy exists.
    2. Supportive management for cardiac abnormalities, seizures, renal problems, and scoliosis
    3. Referral to appropriate specialist for learning/behavior/speech difficulties.

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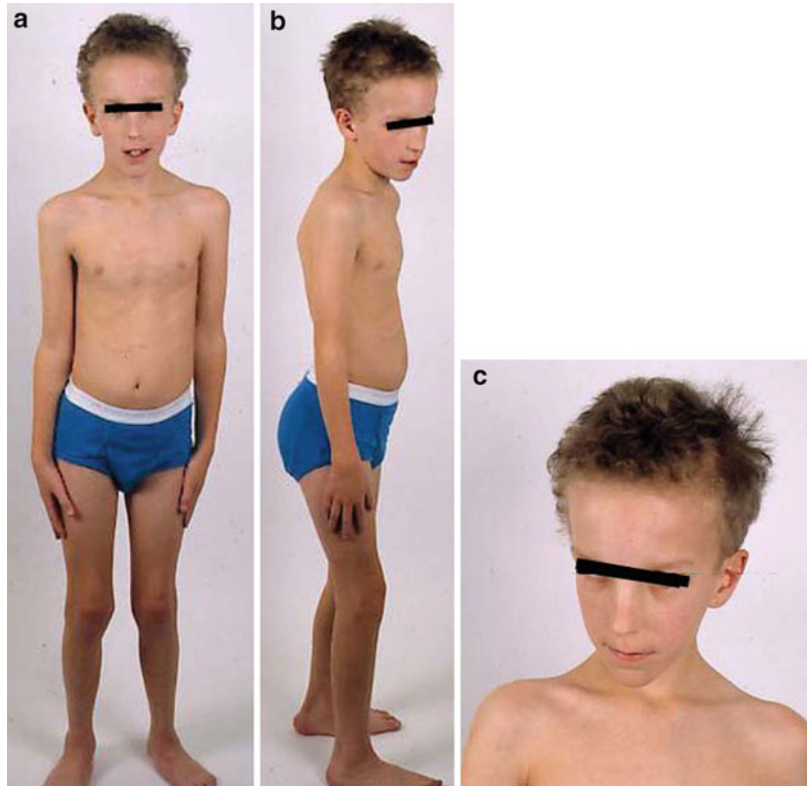

Fig. 1 (**a**–**c**) A child with Sotos syndrome showing excessive growth, a large dolichocephalic head, prominent forehead, downslanting palpebral fissures, and a pointed chin

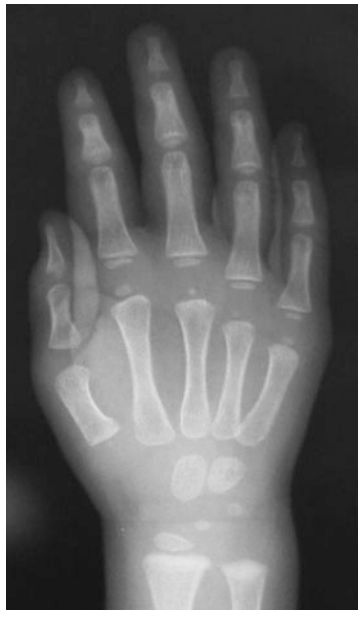

Fig. 2 The radiograph of the hand from a 20-month-old, showing advanced bone age (3 years)

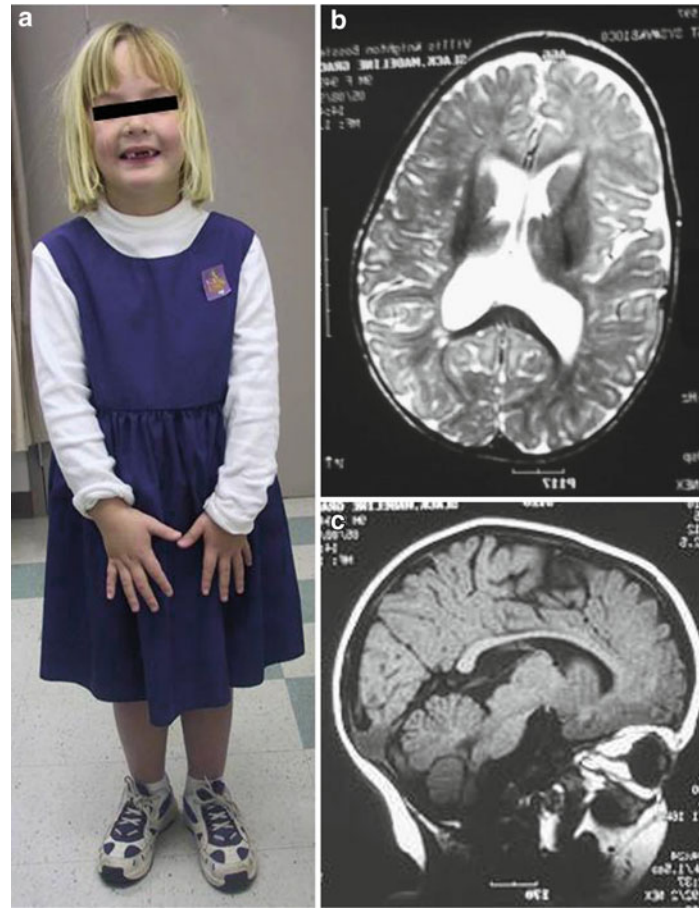

Fig. 3 (**a**–**c**) A 5-year-old girl (**a**) with Sotos syndrome showing gigantism, large head, prominent forehead, large hands and feet, and MRI findings of enlarged subarachnoid spaces, mild ventriculomegaly, thinning of the corpus callosum, and mild polymicrogyria (**b**, **c**)

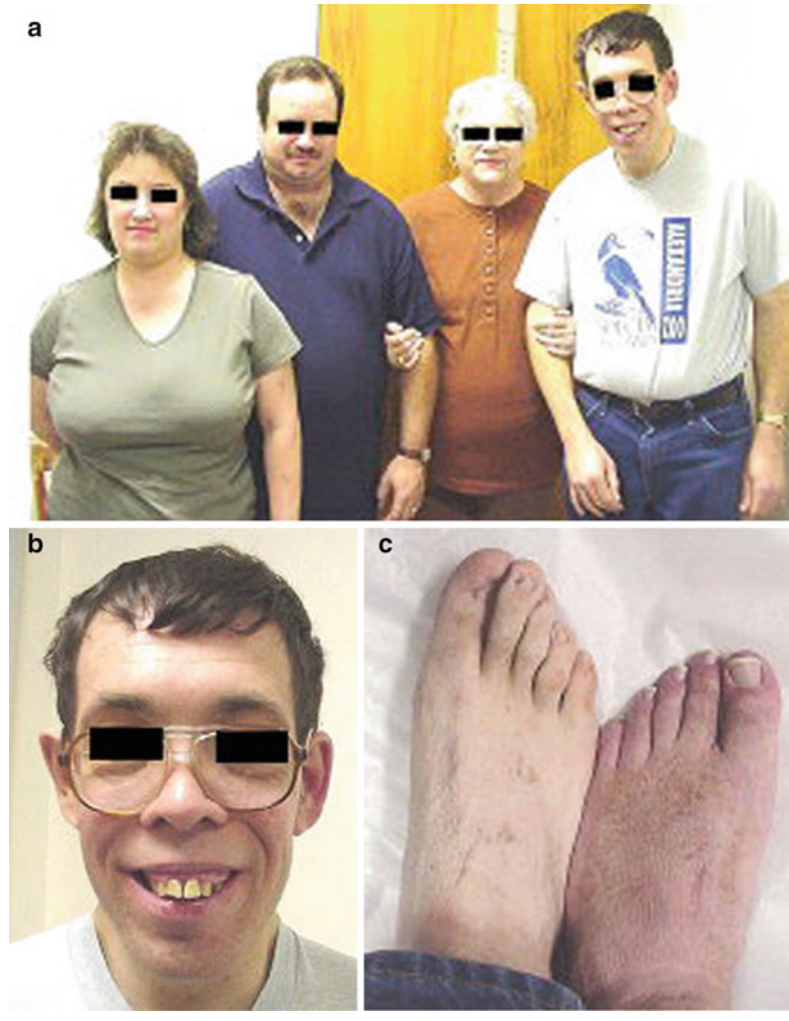

Fig. 4 (**a**–**c**) An adult with Sotos syndrome showing excessive height (compared with other family members) (**a**); prominent forehead, hypertelorism, and a pointed chin (**b**); and large hands and feet (**c**) (compared to normal adult). Chromosome analysis by FISH showed duplicated 4p15.2 and deleted 4q32. Both parents have normal chromosomes

Fig. 5 (**a**–**c**) A 2-year-old girl with Sotos syndrome has excessive height, weight, and head circumference, advanced bone age, and delayed development. The skull is characterized by dolichocephaly, frontal bossing, and deep-set eyes. Molecular study showed two variants of unknown significance: c.1515 T > C (p.N505N) and c.1515 T > C (p.L1956P). There were no apparent deletions or duplications within the coding region of NSD1

Spinal Muscular Atrophy

Contents

Spinal muscular atrophy (SMA) is a disorder characterized by degeneration of lower motor neurons and occasionally bulbar motor neurons, leading to progressive limb and trunk paralysis as well as muscular atrophy. It is a clinically and genetically heterogeneous group of neuromuscular diseases. It is the second most common lethal autosomal recessive disorder after cystic fibrosis in Caucasian populations with an overall incidence of 1 in 10,000 live births and a carrier frequency of approximately 1 in 50 (Biros and Forrest 1999).

Synonyms and Related Disorders

Adult SMA; Arthrogryposis multiplex congenita-SMA; Congenital axonal neuropathy; Dubowitz disease; Kugelberg-Welander disease; Werdnig-Hoffman disease

Genetics/Basic Defects

1. Inheritance
    1. Autosomal recessive in most cases (SMA1, SMA2, SMA3) (Crawford and Pardo 1996)
    2. Autosomal dominant in both juvenile and adult form, representing 2% of infantile and about 30% of adult SMA (Pearn 1978)
    3. X-linked infantile spinal muscular atrophy (Xp11.3-q11.2) (Dressman et al. 2007)
2. Caused by mutation or deletion of *survival motor neuron-1* (*SMN1*) (Lefebvre et al. 1995)
3. Mutation in all three forms (SMA1, SMA2, and SMA3) mapped to chromosome 5q13 (SMA critical region) (Roy et al. 1995; Brahe and Bertini 1996)
4. SMN deletions
    1. High frequency of *SMN* deletions in SMA patients (92.8%) provides a direct and accurate genetic test for:
        1. Diagnostic confirmation of SMA
        2. Prenatal prediction of SMA
    2. Homozygous deletion of *SMN* observed in:
        1. Atypical forms of SMA associated with congenital heart defects
        2. Arthrogryposis
        3. Some cases of congenital axonal neuropathy
        4. Some patients affected with adult form of SMA
    3. Rare cases of homozygous *SMN* exon 7 deletion or conversion reported in

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asymptomatic relatives of haploidentical type II or III SMA patients
4. Absence of deletion of the *SMN* gene or linkage to chromosome 5q in (Zerres et al. 1997):
    1. SMA associated with diaphragmatic involvement
    2. SMA with olivopontocerebellar atrophy
    3. Autosomal dominant form of SMA
    4. Amyotrophic lateral sclerosis
    5. Post-polio syndrome
5. Molecular-phenotype correlation (Lorson et al. 2010; MacKenzie 2010)
    1. Phenotype of SMA associated with disease-causing mutations of the *SMN* gene spans a continuum without a clear delineation of subtypes.
    2. The severity of the SMA phenotype inversely correlated with:
        1. *SMN2* copy number: The greater the *SMN2* copy number (both in infants and children with spinal muscular atrophy and in mouse models), the milder the disease.
        2. The level of full-length SMN protein produced by *SMN2* (~10–15% compared with *SMN1*).

Clinical Features

1. Variability of clinical features and severity (Arnold et al. 2015):
    1. The predominant clinical features of SMA: muscle weakness and atrophy attributed to motor neuron dysfunction and loss.
    2. Weakness: usually symmetric and proximally predominant.
    3. The spectrum of severity: ranges from mild proximal limb weakness noticed in adulthood to severe generalized weakness with respiratory failure in the neonatal period.
    4. Lower limbs: more involved than upper limbs, and bulbar and respiratory weakness usually occurs in patients with more severe limb weakness.
    5. Onset and progression of weakness: distinct from many other motor neuron disorders in that there is usually a presymptomatic period in all but the most severe cases (type 0), followed by rapidly progressive functional loss and a later relatively static phase with slow progression.
2. Existing classification system based on age of onset of symptoms, useful for prognosis and management (Tsao 2013):
    1. Congenital axonal neuropathy (Korinthenberg et al. 1997)
        1. Prenatal onset of SMA
        2. Decreased fetal movement
        3. Maternal polyhydramnios
        4. Severe muscle weakness (hypotonia)
        5. Absence of movement
        6. Joint contractures
        7. Facial diplegia
        8. Ophthalmoplegia
        9. Respiratory failure requiring immediate endotracheal intubation and ventilation
        10. Death from respiratory failure within days
    2. Arthrogryposis multiplex congenita-SMA (Burglen et al. 1996)
        1. Prenatal onset of SMA
        2. Decreased fetal movement
        3. Maternal polyhydramnios
        4. Breech presentation
        5. Severe muscular weakness (hypotonia)
        6. Arthrogryposis multiplex congenita
        7. Absence of movement except for extraocular and facial movement
        8. Death from respiratory failure before 1 month of age
    3. SMA1 (acute spinal muscular atrophy, Werdnig-Hoffman disease) (Byers and Banker 1961; Thomas and Dubowitz 1994)
        1. Represents about 30% of all SMA cases
        2. Onset before 6 months of age
        3. The most severe form with fatal outcome
        4. Severe generalized muscular weakness (hypotonia)
        5. Lack of motor development

6. Mild joint contractures at the knees and rarely at the elbows
7. Most severely affected neonates:
    1. Difficulty in sucking and swallowing
    2. Abdominal breathing
8. Facial muscles spared completely with a bright, normal expression
9. Ocular muscles and the diaphragm not involved until late in the course of the disease
10. Fasciculation of the tongue seen in most but not all cases
11. Intercostal paralysis with severe collapse of the chest: the rule
12. Affected children unable to sit without support
13. Absence of tendon reflexes (areflexia)
14. Normal intelligence
15. Usually die within 2 years due to the following:
    1. Feeding difficulty
    2. Breathing difficulty

4. SMA2 (chronic infantile spinal muscular atrophy, Dubowitz disease)
    1. Represent about 45% of SMA cases
    2. Onset between 6 and 12 months
    3. The intermediate form (a more slowly progressive generalized disease with a variable prognosis)
    4. Poor muscle tone at birth or within first 2 months of life
    5. Slow attainment of motor milestones
        1. Not sitting independently by age 9–12 months
        2. Not standing by 1 year of age
    6. Frequent tongue fasciculation and atrophy
    7. Common finger trembling and general flaccidity
    8. Diminished or absent deep tendon reflexes
    9. Intact sensation
    10. Loss of the ability to sit independently by the mid-teens
    11. Slow or arrest of clinical progression
    12. Severe scoliosis if untreated
    13. Defect in respiratory ventilation
    14. Highly variable life expectancy, ranging up to adult life in some cases
5. SMA3 (juvenile spinal muscular atrophy, Kugelberg-Welander disease) (Kugelberg and Welander 1956)
    1. Represents about 8% of all SMA cases
    2. Childhood onset after 12 months (usually after 18 months to 30 years of life)
    3. The mild chronic form
    4. Motor milestones
        1. Ability to walk but frequent fall on walking
        2. Trouble walking upstairs and downstairs at age 2–3 years
    5. Muscle weakness
        1. Proximal muscle weakness associated with muscle atrophy
        2. Legs more severely affected than the arms
    6. Normal sensation
    7. No evidence of upper motor neuron involvement
    8. Hypertrophy of the calves in about 25% of cases
    9. Prognosis generally correlates with the maximum motor function attained.
    6. SMA4 (adult SMA)
        1. Adult onset (after 20 or 30 years of age)
        2. Muscle weakness (after 30 years of age)
        3. Clinical features similar to those described for SMA3 with evidence of lower motor neuron involvement
            1. Tongue fasciculations
            2. Muscle atrophy
            3. Depressed deep tendon reflexes
            4. Normal sensation

3. Dubowitz classification of childhood SMA (Dubowitz 1995):
    1. Type 1: severe (variable)
    2. Type 2: intermediate (variable)
    3. Type 3: mild (variable)
    4. Type 4.0: normal
4. Subtypes of childhood SMA (Munsat 1991; Nicole et al. 2002; Carre and Empey 2015):
    1. Type 0
        1. Age of onset: prenatal

2. Clinical presentations
    1. Most severe
    2. Lack of fetal movement
    3. Arthrogryposis
    4. Joint contractures
    5. Fatal at birth unless respiratory/medical support is available.
2. Type I
    1. Age of onset: birth to 6 months
    2. Clinical presentations
        1. Severe generalized muscle weakness and hypotonia at birth
        2. Motor milestones: never sit alone
        3. Death from respiratory failure in less than 2 years
3. Type II
    1. Age of onset: 6–12 months
    2. Clinical presentations
        1. Motor milestones: able to sit, unable to walk or stand without aid
        2. Death: >2 years
4. Type III
    1. Age of onset: after 18 months
    2. Clinical presentations
        1. Milder form
        2. Motor milestones: can stand and walk unaided but lose ambulation as disease progresses
        3. Death: adult
5. Type IV
    1. Age of onset: adolescence to adulthood
    2. Clinical presentations: like type III, but rarely diagnosed

5. Consider diagnosis of SMA in infants presenting with the following clinical features:
    1. During neonatal period
        1. Severe hypotonia
        2. Absent movement
        3. Contractures, usually of a mild degree
        4. Evidence of anterior horn cell (i.e., lower motor neuron) involvement
            1. Tongue fasciculations
            2. Absence of deep tendon reflexes
        5. Respiratory failure
        6. Variable cranial nerve involvement usually apparent late in the course
            1. Ophthalmoplegia
            2. Facial diplegia
    2. After neonatal period
        1. Poor muscle tone
        2. Symmetric muscle weakness
            1. Sparing the ocular muscles
            2. Involving the facial muscles and diaphragm late in the course of the disease
        3. Delayed acquisition of motor skills
        4. Evidence of anterior horn (i.e., lower motor neuron) involvement
            1. Tongue fasciculations (seen in only 65% of patients)
            2. Absence of deep tendon reflexes
        5. Normal reaction to sensory stimuli
        6. Normal intelligence
6. Natural history (Lorson et al. 2010; MacKenzie 2010):
    1. Clinical features of the disease are caused by specific degeneration of α-motor neurons in the spinal cord, leading to muscle weakness, atrophy, and, in the majority of cases, premature death.
    2. Most afflicted infants and children, while largely neurologically and completely cognitively intact, grow progressively weaker over time, with many ultimately succumbing to respiratory failure at a young age.
    3. The natural history of SMA has been altered over the past several decades, primarily through supportive care measures, but an effective treatment does not presently exist.
7. Spinal muscular atrophy not linked to *SMN* gene (Wang et al. 2007; Savas et al. 2014):
    1. Scapuloperoneal spinal muscular atrophy
        1. Inheritance (gene locus): autosomal dominant (gene mapped on 12q24.1–q24.31)
        2. Clinical presentations
            1. Congenital absence of muscles
            2. Progressive weakness of scapuloperoneal and laryngeal muscles
    2. Pontocerebellar hypoplasia with spinal muscular atrophy (Barth 1993)
        1. Inheritance (gene locus): autosomal recessive (*VRK1*)
        2. Clinical presentations
            1. Onset at 0–6 months
            2. Cerebellar and brainstem hypoplasia

3. Absent dentate nucleus
4. Neuronal loss in basal ganglia
5. Cortical atrophy

3. X-linked infantile spinal muscular atrophy with arthrogryposis
   1. Inheritance (gene locus): X-linked (gene mapped on Xp11.3–q11.2)
   2. Clinical presentations
      1. Onset at birth or infancy
      2. Contractures
      3. Death before 2 years of age
4. Spinal muscular atrophy with respiratory distress type 1 (Grohmann et al. 2003)
   1. Inheritance (gene locus): autosomal recessive (gene mapped on 11q13.2–q13.4)
   2. Clinical presentations
      1. Onset within the first 3 months of age
      2. Eventuation of the right or both hemidiaphragms
      3. Finger contractures
      4. Pes equinus foot deformities
5. Congenital SMA with predominant lower limb involvement (Fleury and Hageman 1985)
   1. Inheritance (gene locus): autosomal dominant or sporadic (*DYNC1H1*)
   2. Clinical presentations
      1. Arthrogryposis
      2. Weakness, especially distal lower limbs early
      3. Nonprogressive but severe disability
6. Congenital SMA with predominant upper limb involvement (Darwish et al. 1981; Hageman et al. 1993)
   1. Inheritance (gene locus): unknown
   2. Clinical presentations
      1. Arthrogryposis
      2. Weakness, especially distal upper limbs early
      3. Nonprogressive

Diagnostic Investigations

1. Increased serum creatine phosphokinase (CK) activity in about half of the patients with type III SMA
2. Electromyography (EMG)
   1. During voluntary effort
      1. Spontaneous discharge activity in resting muscle
      2. Increased amplitude
      3. Prolonged duration of motor unit potentials
   2. Severe denervation commonly found in older patients
   3. Nerve conduction velocity
      1. Generally considered normal (Emery 1971)
      2. Some decrease in velocity in severe case
3. Muscle histology (Emery 1971)
   1. Denervation changes with small groups of atrophic muscle fibers associated with markedly hypertrophied fibers.
   2. Small angular fibers randomly intermixed with normal-sized fibers.
   3. Atrophic fibers arranged in groups
      1. Usually of uniform fiber type based on the myosin ATPase reaction
      2. Considered as an extensive collateral reinnervation of previously denervated muscle fibers by sprouts from surviving motor neurons
   4. In SMA type III, but not in infantile SMA (type I or II)
      1. Markedly hypertrophic fibers
      2. Excessive variation in fiber size
      3. Internal nuclei
      4. Observation of degenerative changes with necrosis and regenerative fibers associated with proliferative interstitial connective tissue
         1. Interpreted as “pseudomyopathic” changes.
         2. Usually found in patients with high serum levels of CK activity suggesting the presence of a myopathic process secondary to neurogenic process.
         3. These pseudomyopathic changes not observed in other human neurogenic diseases suggest that they can be specific to the molecular mechanism resulting in or associated with juvenile SMA.

4. Neuropathologic features found at autopsy of SMA patients
    1. Loss of the large anterior horn cells of the spinal cord (most striking feature)
    2. Severe degree of central chromatolysis in the remaining surviving motor neurons, appearing as large ballooned cells without stored substances
    3. Other anterior horn cells
        1. Pyknotic
        2. Presence of occasional figures of neuronophagia associated with astrogliosis
        3. Small anterior roots
5. Algorithm of diagnostic tests for a patient suspected to have SMA (D'Amico et al. 2011)
    1. Homozygous SMN1 deletion detected: confirm 5q SMA diagnosis
    2. Homozygous SMN1 deletion not detected
        1. Creatine kinases dosage and electrophysiological tests such as electromyography (EMG), and nerve conduction study, should be performed. If EMG suggests a motor neuron disease, then further testing for SMN mutations should be pursued.
        2. SMN1 gene copy number testing using multiplex ligation-dependent probe amplification (MLPA) or real-time PCR.
        3. If the patient has a single *SMN1* copy, it is mandatory to sequence the coding region of the undeleted allele to identify the second causative mutation, generally subtle sequence variations, including point mutations, insertions, and deletions.
        4. However, in about one third of patients with a typical clinical picture and a single SMN1 copy, the second mutation is not found in *SMN1*/*SMN2* coding region. This finding is more common in type III SMA and might be due to the presence of deep intronic mutations, unidentified so far. Finally, sequence analysis of SMN1 gene is suggested also in those patients who have a typical clinical picture, two *SMN1* copies, and are born to consanguineous parents or originate from genetic isolates. Indeed, rare patients homozygous for *SMN1* subtle mutations have been occasionally reported.
        5. Conversely, in a patient with two *SMN1* copies, SMA diagnosis, related to SMN1 mutations, is virtually excluded, and other motor neuron disorders such as spinal muscular atrophy with respiratory distress (SMARD1), X-linked spinal muscular atrophy, distal SMA, and juvenile amyotrophic lateral sclerosis should be considered.
        6. If the electrophysiological examination excludes a motor neuron disease, the child should be reexamined and must receive additional diagnostic testing considering other disorders.
6. Molecular diagnosis of SMA (Prior and Russman 2011)
    1. Molecular testing for homozygous deletion or mutation of the *SMN1* gene allows efficient and specific diagnosis. In combination with loss of *SMN1*, patients retain variable numbers of copies of a second similar gene, *SMN2*, which produces reduced levels of the survival motor neuron (SMN) protein that are insufficient for normal motor neuron function (Arnold et al. 2015).
    2. The following relatively simple DNA tests enable confirmation of a suspected clinical diagnosis of SMA or prediction of the outcome of a pregnancy in families with a history of SMA (Biros and Forrest 1999).
        1. SSCP analysis
        2. PCR followed by restriction enzyme digestion
    3. Mutation analysis of *SMN1* available on clinical basis.
        1. Used to detect deletion of exons 7 and 8 of *SMN1*
        2. Homologous deletions of exon 7 of *SMN1* in 95% of cases with clinical diagnosis of SMA (Ogino et al. 2002)
        3. Compound heterozygotes for deletion of *SMN1* exon 7 and an intragenic mutation of *SMN1* in 2–5% of patients with a clinical diagnosis of SMA
    4. Sequence analysis of all *SMN1* exons and intron/exon borders available on clinical basis.

1. Used to identify the intragenic *SMN1* mutations present in the 2–5% of patients who are compound heterozygotes
2. Limitations
    1. Cannot determine whether the point mutation is in the SMN1 gene or the SMN2 gene, unless one of these genes is absent
    2. Does not detect exonic duplications
    3. Cannot detect deletions of whole exons if more than one SMN gene copy is present

5. Duplication analysis to determine *SMN2* copy number.
    1. *SMN2* copy number ranges from 0 to 5
    2. Quantitative PCR: currently used for accurate determination of *SMN2* copy number
6. SMA carrier testing (gene dosage analysis) available clinically.
    1. Mutation analysis not reliable for carrier detection since it does not quantitate the number of *SMN1* gene copies.
    2. A PCR-based dosage assay (called SMA carrier testing or *SMN* gene dosage analysis) allows for the determination of the number of *SMN1* gene copies, thus permitting highly accurate carrier detection.
    3. Dosage analysis to differentiate carriers from non-carriers (Zeesman et al. 2002).
7. Linkage analysis available on clinical basis.
    1. Available to families in which direct DNA testing is not informative
    2. May be used for confirmation of carrier testing results and prenatal testing results
8. UBA1 sequence analysis for X-linked infantile spinal muscular atrophy (Baumbach-Reardon et al. 2012)

7. Newborn screening: An effective technology exists for newborn screening of SMA (Prior et al. 2010).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive inheritance: 25%
        2. Autosomal dominant inheritance: not increased unless a parent is affected
        3. X-linked recessive inheritance (Baumbach-Reardon et al. 2012): If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
    2. Patient's offspring: only milder forms of SMA likely to reproduce
        1. Autosomal recessive inheritance
            1. All offspring: carriers
            2. Recurrence risk not increased unless the spouse is affected or a carrier (Carre and Empey 2015)
        2. Autosomal dominant inheritance: 50%
        3. X-linked recessive inheritance (Baumbach-Reardon et al. 2012): Males with a severe phenotype do not generally survive; males with milder phenotypes will pass the disease-causing mutation to all of their daughters and none of their sons.
2. Prenatal diagnosis (Matthijs et al. 1998; Stewart et al. 1998; Baumbach-Reardon et al. 2012; Carre and Empey 2015)
    1. Possible to detect fetuses at 25% risk when the disease-causing *SMN* mutations in both parents are known
    2. Mutation analysis on fetal DNA obtained from CVS or amniocentesis
    3. Prenatal diagnosis cannot predict the clinical outcome in terms of severity, because the number of copies of *SMN2* is not specific to each SMA subtype: two copies of *SMN2* can be present in either SMA type 1 or type 2 (Feldkötter et al. 2002)
    4. Linkage analysis
        1. Many diagnostic laboratories still perform linkage analysis in addition to direct SMN^T mutation analysis in families where the previously affected child lacks both copies of SMN^T, since there are people in the normal population who lack both copies of SMN^T but not clinically affected.

2. The only option available to the families where no deletion has been observed but the clinical findings are consistent with 5q SMA.
5. Preimplantation genetic diagnosis: available clinically for families in which the disease-causing mutations have been identified in an affected family member

3. Management (Iannaccone 2007; Sendtner 2010)
   1. Treat and prevent complications of weakness and maintain quality of life.
   2. Several organ systems affected by weakness.
      1. Respiratory (restrictive lung disease)
         1. Noninvasive ventilation support using new technology for patients with sufficient orofacial muscle strength. Long-term ventilatory support is not usually considered.
         2. A new awareness of the importance of identifying sleep-disordered breathing.
         3. A new multidisciplinary approach to standard of care.
      2. Gastrointestinal (dysphagia): feeding gastrostomy for children with difficulty in sucking and swallowing
      3. Orthopedic (progressive deformities)
         1. Orthosis to allow to sit upright rather than be bedridden
         2. Option of surgical repair for the severe scoliosis
   3. Therapy development.
      1. Previous therapy approaches have focused on upregulation of SMN expression from a second SMN (*SMN2*) gene that gives rise to low amounts of functional SMN protein.
      2. Drug development to target disease-specific mechanisms at cellular and physiological levels is in its early stages, as the pathophysiological processes that underlie the main disease symptoms are still not fully understood.
      3. Human-induced pluripotent stem cell technology for generation of large numbers of human motor neurons could help to fill this gap and advance the power of drug screening.
      4. In parallel, advances in oligonucleotide technologies for engineering *SMN2* pre-mRNA splicing are approaching their first clinical trials, whose success depends on improved technologies for drug delivery to motor neurons.
      5. If this obstacle can be overcome, this could boost therapy development, not only for SMA but also for other neurodegenerative disorders.
   4. Future treatment approaches (Tisdale and Pellizzoni 2015).
      1. Results from ongoing clinical trials are eagerly awaited, and evidence of therapeutic benefit would favor the implementation of universal newborn screening, in turn allowing both earlier diagnosis and therapeutic intervention and possibly improved clinical outcome.
      2. It is anticipated that continuing progress in SMA research will strongly affect not only this devastating disease of childhood, but also other neurodegenerative conditions of the motor system.

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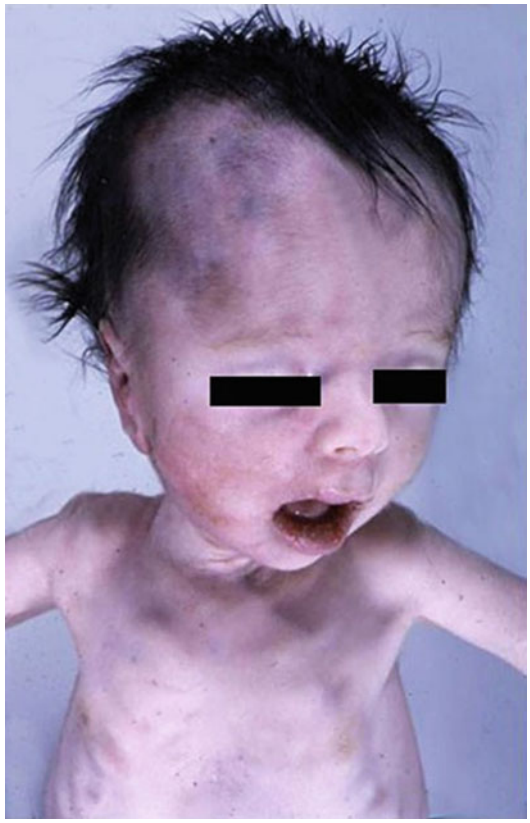

Fig. 1 A 2 1/2-week-old white male died of respiratory failure associated with congenital spinal muscular atrophy (Werdnig-Hoffman disease). There was generalized muscle atrophy including respiratory muscle

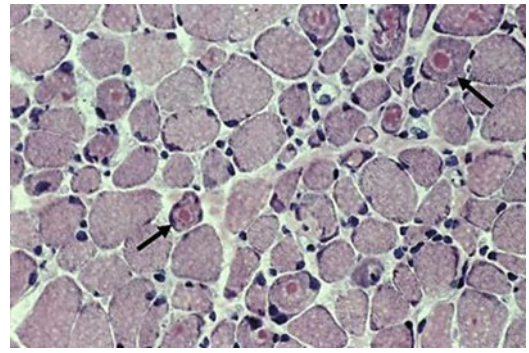

Fig. 3 Residual muscle seen in a 14-year-old female with spinal muscular atrophy showed chronic denervative change with presence of scattered target fibers (*arrows*) (H & E ×400)

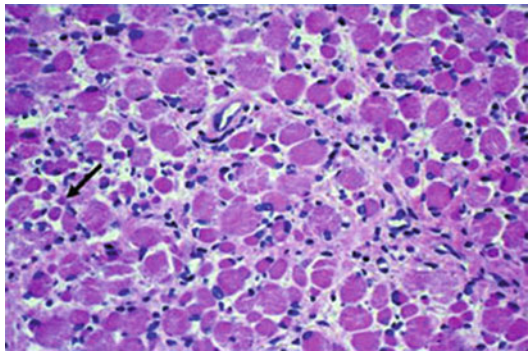

Fig. 2 Quadriceps muscle showed many exceedingly atrophic muscle fibers which tend to be in groups (*arrow*). No degenerative muscle fibers were present (H & E, ×100)

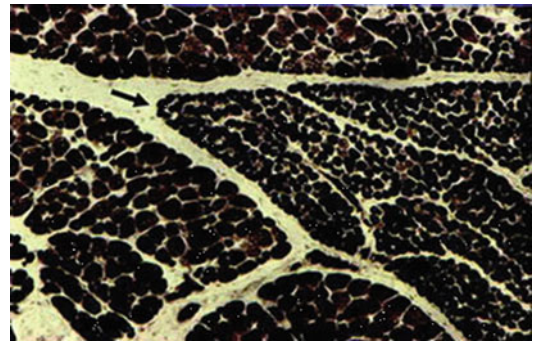

Fig. 4 Biopsy of quadriceps muscle from a 10-month-old girl with spinal muscular atrophy showed a group atrophy involving several entire fascicles (*arrow*). Both type I (*light-stained*) and type II (*dark-stained*) fibers were affected. This was accompanied by an enervative phenomenon (the large muscle fibers all stain pale) (Myosin ATPase, at 9.4, ×50)

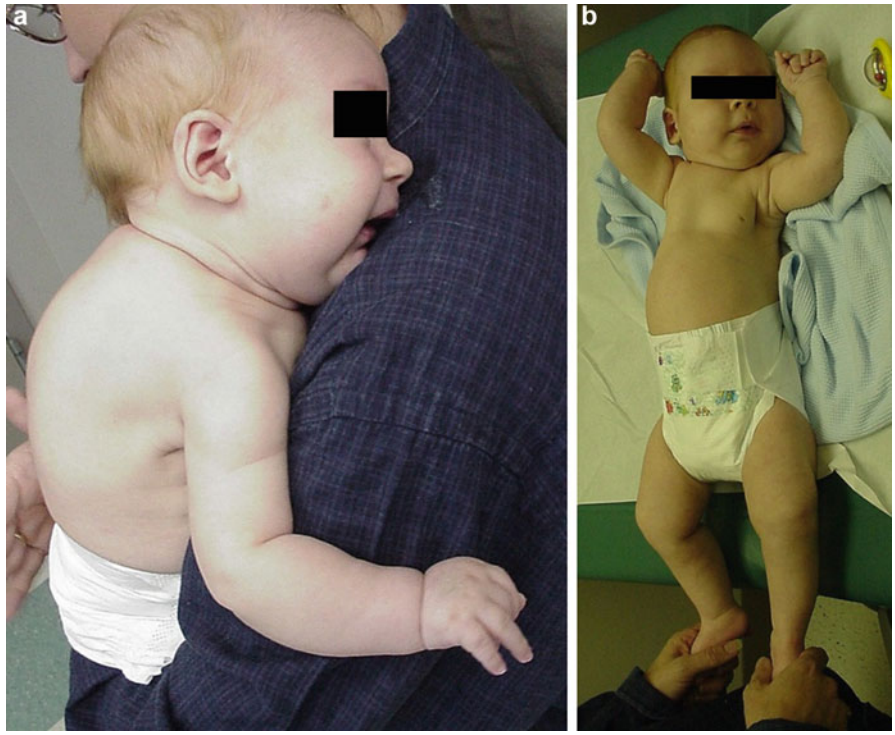

Fig. 5 A 3-month-old infant boy with Werdnig-Hoffman disease showing generalized hypotonia (**a**). He had a small chest with diaphragmatic breathing (**b**), fasciculation of the tongue, and absence of deep tendon reflexes. Molecular genetic analysis revealed homozygous exon 7 deletion and homozygous exon 8 deletion for the survival motor neuron genes (*SMN*)

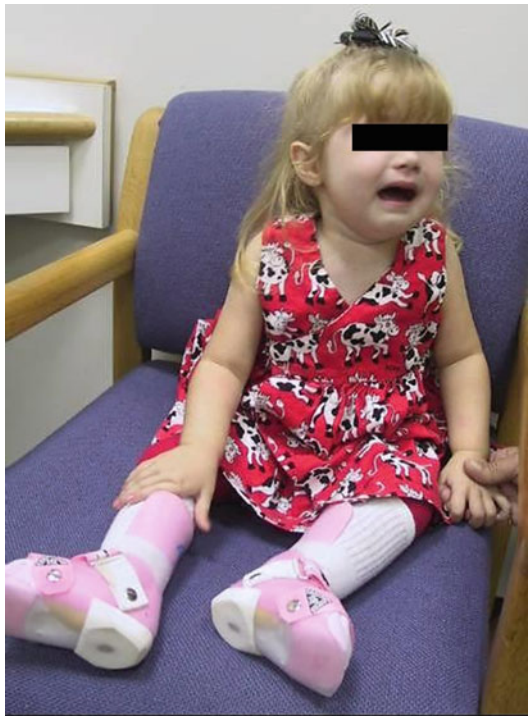

Fig. 6 A 27-month-old girl with SMA1. She could not stand holding or independently and had foot drops, absence of deep tendon reflexes, and muscle weakness. She was confined to a wheelchair. Molecular genetic analysis revealed homozygous exon 7 deletion and homozygous exon 8 deletion for the *SMN* gene

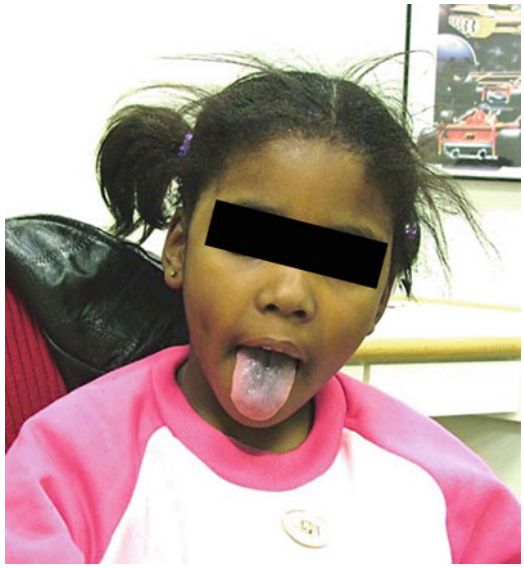

Fig. 7 A 5-year-old girl with SMA showing tongue fasciculation

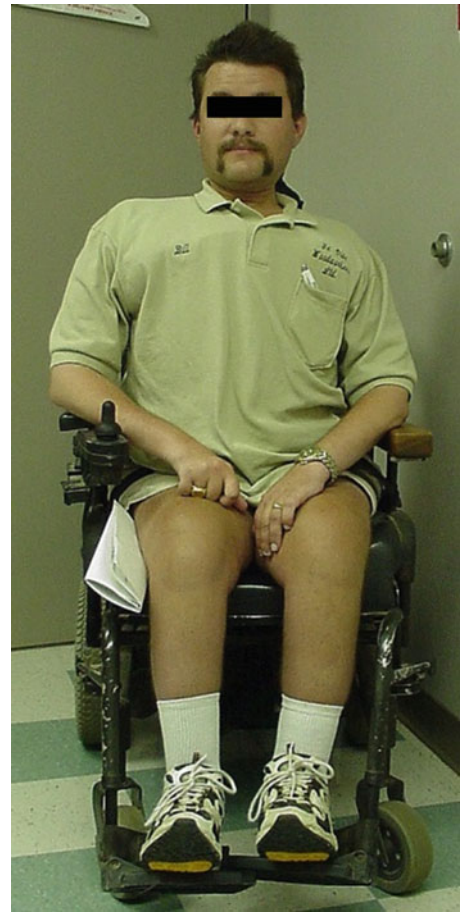

Fig. 8 A 30-year-old man with Kugelberg-Welander disease showing muscle weakness and had been confined to a wheelchair for some time. He had trouble standing and began to walk at 6 years of age. Molecular genetic diagnosis revealed homozygous exon 7 deletion and homozygous exon 8 deletion

Fig. 9 This 22-month-old boy was evaluated for spinal muscular atrophy. He never pulls himself up and stands alone. He used his hands to move his legs. Physical examination showed slightly atrophic lower leg muscles and absent knee jerks. Molecular genetic analysis (Athena Diagnostics) identified zero copy of the survival motor neuron gene 1 (*SMA1*), confirming the clinical diagnosis of spinal muscular atrophy in this patient, and three copies of *SMN2*. An increased number ($\geq$3 copies) of *SMN2* gene copies may be associated with a less severe phenotype of SMA. Conversely, fewer ($\leq$2) *SMN2* gene copies may be associated with a severe phenotype of SMA. *SMA2* genes are able to produce a protein identical to that of the *SMN1* gene but at a reduced (10–20 %) capacity

Spondyloepiphyseal Dysplasia

Contents

Spondyloepiphyseal dysplasia (SED) refers to a group of disorders with primary involvement of the vertebrae and epiphyseal centers resulting in a short-trunk disproportionate dwarfism. Two major types (congenita and tarda) will be discussed here.

Synonyms and Related Disorders

SED congenita; SED tarda

Genetics/Basic Defects

1. Genetic basis of SED
    1. SED congenita
        1. Autosomal dominant inheritance (Diamond 1970)
        2. Spondyloepiphyseal dysplasia congenita gene mapped to chromosome 12q13
        3. Gonadal mosaicism reported
        4. Advanced paternal age recognized as a risk factor
    2. SED tarda
        1. X-linked recessive inheritance (Bannerman et al. 1971; Heuertz et al. 1995)
            1. Most common
            2. The gene mapped to Xp22.12-p22.31
        2. Autosomal recessive inheritance
        3. Autosomal dominant inheritance
2. Molecular basis of SED (Lee et al. 1989; Cole et al. 1993; Chan et al. 1995)
    1. SED congenita
        1. Caused by mutations in *COL2A1* gene, which encodes the α1(II) chain of type II collagen. The gene was mapped on chromosome 12.
        2. The mutations result in abnormal type II collagen, which is the major collagen of nucleus pulposus of the spine, hyaline cartilages, fibrocartilages, and vitreous humor of the eyes.
        3. Other skeletal dysplasias affected by collagen II abnormalities.
            1. Autosomal forms of SED tarda
            2. Achondrogenesis type II
            3. Hypochondrogenesis
            4. Kniest dysplasia
            5. Stickler dysplasia
            6. Spondylometaepiphyseal (Strudwick) dysplasia
    2. SED tarda, X-linked form (Gedeon et al. 1999, 2001; Christie et al. 2001;

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Grunebaum et al. 2001; Savarirayan et al. 2003; Choi et al. 2009)

1. Caused by mutations in *SEDL* (SED late) gene (designated "sedlin"), now called *TRAPPC2* (trafficking protein particle complex 2) gene, mapped on Xp22.12-p22.31.
2. *SEDL* gene encodes a protein of 140 amino acids with a role in vesicular transport.
3. Over 30 novel mutations affecting the *SEDL* gene recognized: the most common type of *SEDL*-gene disruption being deletion, representing 50% of identified mutations (Savarirayan et al. 2003).

Clinical Features

1. SED congenita
    1. Clinical features present at birth.
    2. Short newborn with disproportionately shortened trunk.
    3. Delayed motor development.
    4. Short neck.
    5. Cervical myelopathy resulting from atlantoaxial instability (Reardon et al. 1994), odontoid hypoplasia, and spinal cord compression, often presenting at age 5–10 years.
        1. Delayed motor development
        2. Decreased endurance
        3. Progressive motor weakness
        4. Hypotonia
        5. Sleep apnea
        6. Alterations in respiration
        7. Pyramidal tract signs (spasticity, hyperreflexia, Babinski sign, and clonus)
    6. Respiratory insufficiency may develop secondary to thoracic dysplasia (Naumoff 1977).
    7. Barrel-shaped chest with pectus carinatum deformity.
    8. Protuberant abdomen.
    9. Spine abnormalities.
        1. Lumbar lordosis
        2. Thoracic kyphoscoliosis evident in adolescence
    10. Hip abnormalities.
        1. Hip flexion contractures
        2. Coxa vara
            1. An almost universal finding
            2. Varying severity
            3. Progressive
            4. Associated progressive hip dislocation if ligamentous laxity present
        3. The delayed ossification of the capital femoral epiphysis predisposing the hip to deformation with flattening, lateral extrusion, hinge abduction, and premature osteoarthritis
    11. Knee abnormalities.
        1. Valgus alignment of the knees often associated with overgrowth of the medial femoral condyle
        2. Rare genu varum
    12. Other clinical features.
        1. Gait problems often attributed to hip and knee deformities
        2. Clubfeet (talipes equinovarus) present in some patients
        3. Ocular anomalies
            1. Myopia and retinal detachment (>50%): important clinical findings in many patients
            2. Cataracts
            3. Buphthalmos secondary glaucoma and strabismus
            4. Clear corneas
        4. Deafness
        5. Cleft palate
        6. Abdominal or inguinal hernias
    13. A cause of lethal neonatal dwarfism (Macpherson and Wood 1980)
2. SED tarda
    1. X-linked recessive form
        1. Normal appearance at birth
        2. Variable age of onset
            1. Hip and trunk features appearing around 4 years of age.
            2. Diagnosis not recognized until the adolescent years in some patients.
        3. Only males are affected.
        4. Mild disproportionate trunk shortening.

5. Barrel-shaped chest.
6. Atlantoaxial instability secondary to odontoid hypoplasia.
7. Progressive joint and back pain with osteoarthritis commonly involving hip, knee, elbows, and shoulder joints.
8. Hip involvement.
    1. Hip pain or stiffness presenting around the first or second decade of life.
    2. Changes mimic bilateral Legg-Calve-Perthes disease.
    3. Varying degrees of coxa magna, flattening, extrusion, and subluxation.
    4. Osteoarthritis of the hip, a common sequela.
9. Kyphoscoliosis.
10. Lumbar lordosis.
11. Epiphyseal involvement.
    1. Primarily in the shoulders, hips, and knees
    2. Symmetrical and bilateral
12. Rare association with nephrotic syndrome.
13. Craniofacial appearance, vision, and hearing not affected in X-linked SED tarda.
14. Normal intelligence.
15. Normal life span.

2. Autosomal recessive form
    1. Onset between the ages of 4 and 10 years.
    2. Short stature.
    3. Waddling gait.
    4. Disproportionately short trunk.
    5. Accentuated spinal curvatures.
    6. Restricted mobility of the hip joints.
    7. Hip pain becomes worse with increasing age.
3. Autosomal dominant form
    1. Clinical features identical to those in the recessive form of SED tarda
    2. Hip pain and waddling gait noted after the fourth year of life
    3. Mild shortness of the trunk
    4. Progressive hip changes causing considerable discomfort

Diagnostic Investigations

1. Radiography
    1. SED congenita (Spranger and Langer 1970, 1974; Kozlowski et al. 1977)
        1. A generalized delay in the development of ossification centers
            1. Absent epiphyseal centers of the distal femur and proximal tibia, os pubis, calcaneus, and talus, which are usually present at birth
            2. Femoral heads usually not visible on radiographs until patients are aged 5 years
            3. Femoral capital epiphyses: flattened and irregular in shape when they appear on radiographs
        2. Vertebral abnormalities
            1. Varying degrees of platyspondyly
            2. Oval, trapezoid, or pear-shaped vertebrae resulting from posterior wedging of vertebral bodies.
            3. Incompletely fused ossification centers of the vertebral bodies.
            4. End-plate irregularities and intervertebral disk space narrowing become obvious with an increased anteroposterior diameter of the vertebral bodies in adolescents and young adults.
            5. Exaggerated lumbar lordosis.
            6. Progressive kyphoscoliosis developing in late childhood.
            7. Odontoid hypoplasia or os odontoideum leading to atlantoaxial instability: common.
        3. Pelvic abnormalities
            1. Short and small iliac crests with horizontal acetabular roofs and delayed ossification of the pubis
            2. Small iliac bones with lack of normal flaring of the iliac wings
            3. Deep acetabular fossae appearing empty due to the severely retarded ossification of femoral heads
            4. Varying severity of coxa vara
            5. Delayed ossification of the femoral head predisposing hip to deformation

with flattening, lateral extrusion, hinge abduction, and premature osteoarthritis

4. Tubular bone abnormalities
    1. Delayed ossification centers of the distal femur and proximal tibia leading to flattening and irregularity
    2. Genu valgum usually present with overgrowth of the medial femoral condyle
    3. Relatively short and broad long tubular bones
    4. Presence of some metaphyseal flaring especially in the region of the distal femur and proximal and distal humerus
    5. Delayed or disorganized ossification of carpal and tarsal centers with occasional extra epiphyses

2. SED tarda, X-linked recessive form (Langer 1964; MacKenzie et al. 1996)
    1. Radiographic changes usually apparent in children older than 4–6 years (not evident at birth).
    2. Changes suggestive of atlantoaxial instability, platyspondyly, kyphoscoliosis, and epiphyseal involvement similar to those seen in patients with SED congenita.
    3. Predominantly affecting the spinal vertebral bodies and epiphyses during skeletal growth.
    4. A mound of bone ("donkey hump") typically present in the central and posterior portions of the superior and inferior end plates on lateral radiographs in patients with X-linked recessive type of SED tarda (not features of the autosomal dominant or recessive types of SED tarda). However, absence of ossification at the upper and lower anterior margins of the vertebral bodies is considered to be the distinctive radiographic feature.
    5. Symmetric epiphyseal involvement primarily in the shoulders, hips, and knees.
    6. Delayed ossification predisposing the weight-bearing joints of the lower extremities to deformation and premature osteoarthritis.
    7. Changes in the hip (dysplastic changes of femoral heads and neck) mimic bilateral Legg-Calve-Perthes disease.
    8. Presence of varying degrees of coxa magna, flattening, extrusion, and subluxation.
    9. Minor skeletal changes in carrier women with X-linked recessive SED tarda in a six-generation kindred from Arkansas (Whyte et al. 1999).
        1. Subtle abnormal shape of the pelvis and knees
        2. Premature occurrence of degenerative changes in the spine leading to frequent complaint of arthralgia in the middle age

3. SED tarda, autosomal recessive form
    1. Irregular upper and lower plates of the vertebral bodies
    2. Anteriosuperior ossification defects of some vertebrae
    3. Less frequent findings
        1. Additional ossification defects of the anterioinferior edges of the vertebral bodies
        2. Anterior protrusion of central portions of the vertebral bodies
    4. Femoral heads
        1. Well-developed capital femoral epiphyses in the younger child
        2. Progressive flattening and destruction of the femoral heads with advancing age
        3. Milder abnormalities in the knee joints
        4. Small and irregular carpal bones
        5. Slightly short and irregular metacarpals and phalanges in some patients

4. SED tarda, autosomal dominant form
    1. Accentuated dorsal flattening of the vertebral bodies in the younger patient
    2. Platyspondyly with a rectangular shape of the vertebral bodies in the older patient
    3. Mild and slowly progressive deformities of capital femoral epiphyses and knee epiphyses

4. Slightly short phalanges and metacarpals with narrowing of the joint spaces
2. MRI (Parikh 2013)
   1. To delineate cord compression due to C1-C2 instability
   2. To evaluate severe spinal deformities prior to surgical intervention
   3. To evaluate the condition of the epiphyseal centers prior to reconstructive procedures
3. CT scan (Parikh 2013)
   1. To assess the configuration of bones and joints prior to surgical intervention
   2. To reconstruct three-dimensional images for help in surgical planning of severe cases
4. Hip arthrography (Parikh 2013)
   1. To document congruity of the femoral head or hinged abduction
   2. To evaluate severe varus deformity of the femoral neck
5. Laboratory features of SED congenita
   1. Fine metachromatic inclusions in the peripheral lymphocytes
   2. Normal urinary excretion of acid mucopolysaccharides including keratosulfate
   3. Histopathology (Yang et al. 1980)
      1. Mildly disorganized physis (epiphyseal growth plate).
      2. Chondrocytes containing PAS-positive cytoplasmic inclusions.
      3. Ultrastructurally, the inclusions correspond to the accumulations of finely granular material in dilated cisterns of rough endoplasmic reticulum.
6. Molecular genetic analysis
   1. Mutations in *COL2A1* gene in SED congenita
   2. Mutation in *SEDL* gene in X-linked recessive SED tarda (Tiller and Hannig 2011)
      1. Sequence analysis clinically available
      2. Mutation types
         1. Deletions
         2. Splice mutations
         3. Missense mutations
         4. Nonsense mutations
      3. Detected in >80% of affected males with X-linked spondyloepiphyseal dysplasia tarda
      4. Molecular genetic testing in new patients relied largely on mutation screening by sequencing the entire coding region.
      5. Carrier testing of at-risk female relatives available once the mutation has been identified in the proband

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Spondyloepiphyseal dysplasia congenita (autosomal dominant): recurrence risk low unless presence of parental gonadal mosaicism
      2. Spondyloepiphyseal dysplasia tarda, X-linked
         1. The risk to sibs depends on the carrier status of the mother.
         2. When the mother is a carrier: a 25% risk of having an affected brother; a 25% risk of having an unaffected brother; a 25% risk of having a carrier sister; a 25% risk of having a non-carrier sister.
         3. When the mother is not a carrier: The risk to sibs is low (the risk of gonadal mosaicism in mothers not yet known).
      3. Spondyloepiphyseal dysplasia tarda, autosomal recessive: 25%
      4. Spondyloepiphyseal dysplasia tarda, autosomal dominant: low unless a parent is affected
   2. Patient's offspring
      1. Spondyloepiphyseal dysplasia congenita, autosomal dominant
         1. When the spouse is not affected: 50% of offspring will be affected.
         2. When the spouse is also affected with spondyloepiphyseal dysplasia congenita: 50% of offspring are heterozygous and affected; 25% are homozygous, which is ordinarily fatal in the first few months of life, and 25% are unaffected.

2. Spondyloepiphyseal dysplasia tarda
    1. Autosomal recessive form: recurrence risk to offspring low unless the spouse is a carrier
    2. Autosomal dominant form: 50%
3. Spondyloepiphyseal dysplasia tarda, X-linked recessive
    1. None of the sons of an affected male will be affected.
    2. All daughters of an affected male are carriers.

2. Prenatal diagnosis
    1. Prenatal ultrasound at 20 weeks of gestation (Turner et al. 2010): shortening of all fetal long bones, bowing of femora and humeri, clubfeet, and small thoracic cage.
    2. Molecular genetic diagnosis on fetal DNA from amniocytes or CVS available in families at risk for SED congenita, provided the disease-causing mutation (*COL2A1*) is identified in the proband.
    3. Molecular genetic diagnosis on fetal DNA from amniocytes or CVS possible in families at risk for X-linked SED tarda, provided the disease-causing mutation (*SEDL*) is identified in the proband.
    4. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member.
3. Management (Parikh 2013)
    1. SED congenita
        1. Supportive care including psychosocial support
        2. Tracheostomy/ventilator support for severe respiratory difficulties to maintain adequate ventilation (Harding et al. 1990; Augenstein et al. 1996)
        3. Posterior atlantoaxial fusion for patients with signs and symptoms of atlantoaxial instability measuring 8 mm or more or myelopathy
        4. Brace for scoliosis initially
        5. Posterior spinal fusion for severe scoliosis or for patients resistant to bracing
        6. Surgical correction for hip and knee abnormalities
        7. Surgical correction of equinovarus deformities unmanageable by physical therapy or serial casting
    2. SED tarda, X-linked type
        1. Supportive care
            1. Avoid activities and occupations that place undue stress on the spine and weight-bearing joints to prevent premature arthritis.
            2. Chronic pain management.
            3. Psychosocial support for the patient and family.
        2. Bracing for scoliosis
        3. Posterior spinal fusion for severe scoliosis
        4. Posterior stabilization for atlantoaxial instability
        5. Valgus or valgus-extension intertrochanteric osteotomy to improve hip congruity
        6. Total joint arthroplasty for osteoarthritis in adulthood
        7. Management of hip dysplasia
            1. Acetabular augmentation if the acetabulum is insufficient to contain the enlarged femoral head (coxa magna)
            2. May require hip replacement

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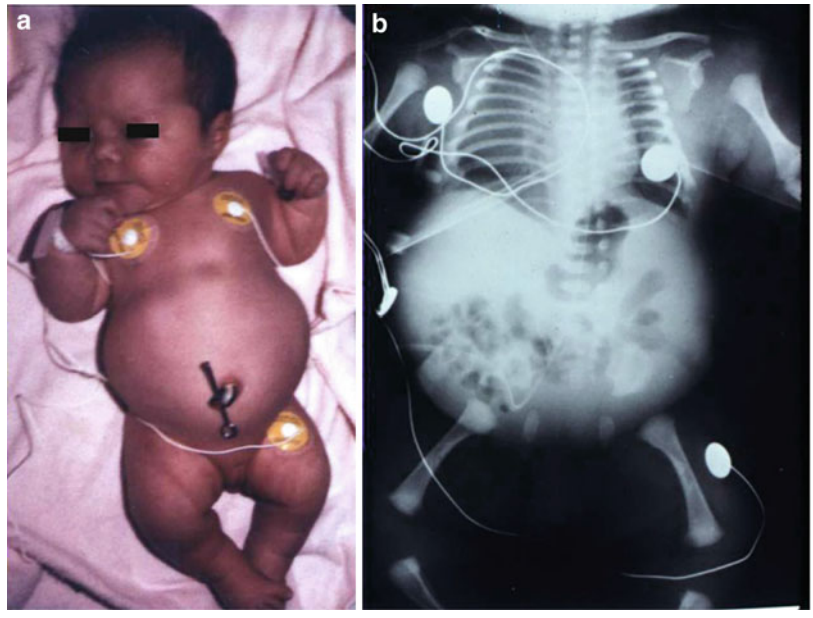

Fig. 1 (**a**, **b**) A neonate with SED congenita showing moderately shortened limbs, short trunk, and large head. Radiograph shows small oval vertebral bodies, reniform ilia, and moderately shortened limb bones

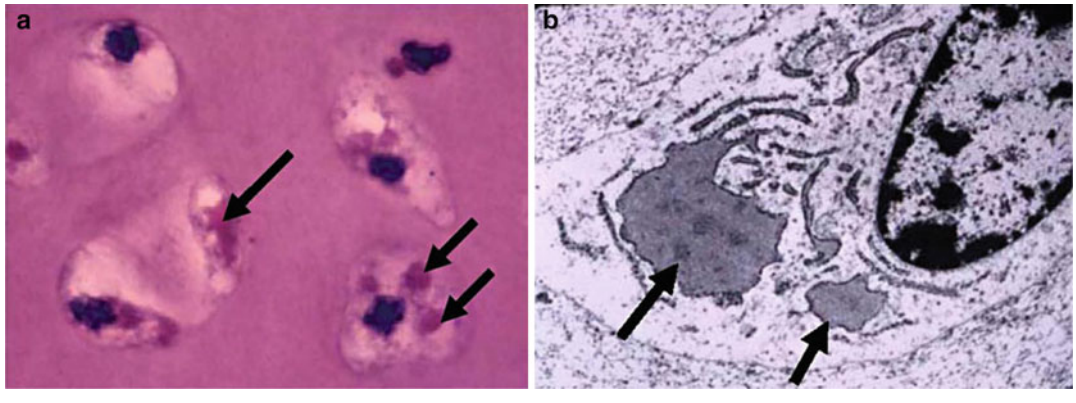

Fig. 2 (**a**, **b**) Photomicrograph of a neonate with SED congenita shows frequent presence of cytoplasmic inclusions in the chondrocytes of resting cartilage and the zone of proliferation. The cytoplasmic inclusion is a dilated rough endoplasmic reticulum containing finely granular material

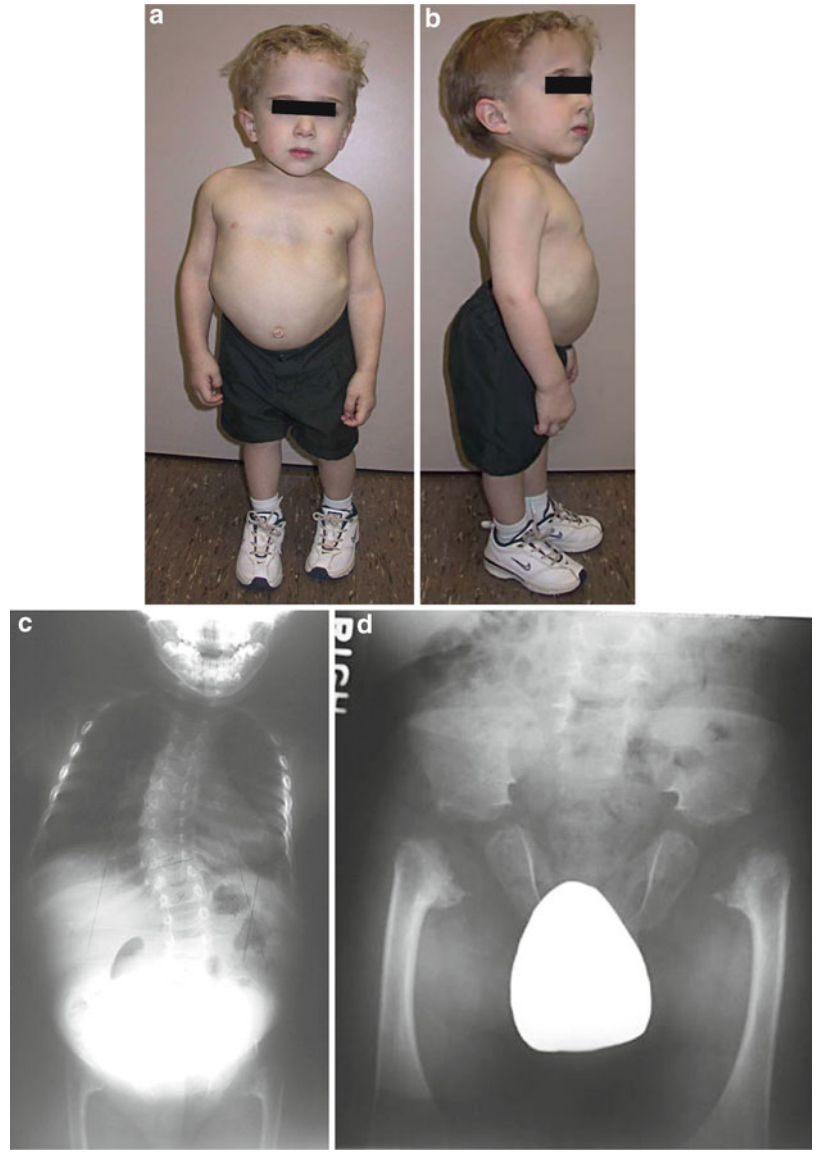

Fig. 3 (**a**–**d**) A boy with SED congenita showing short trunk, short, broad chest with pectus excavatum, globoid abdomen, and hyperlordosis. Radiographs showed lack of ossification of the femoral epiphysis, short femoral neck, generalized platyspondyly, and thoracolumbar scoliosis

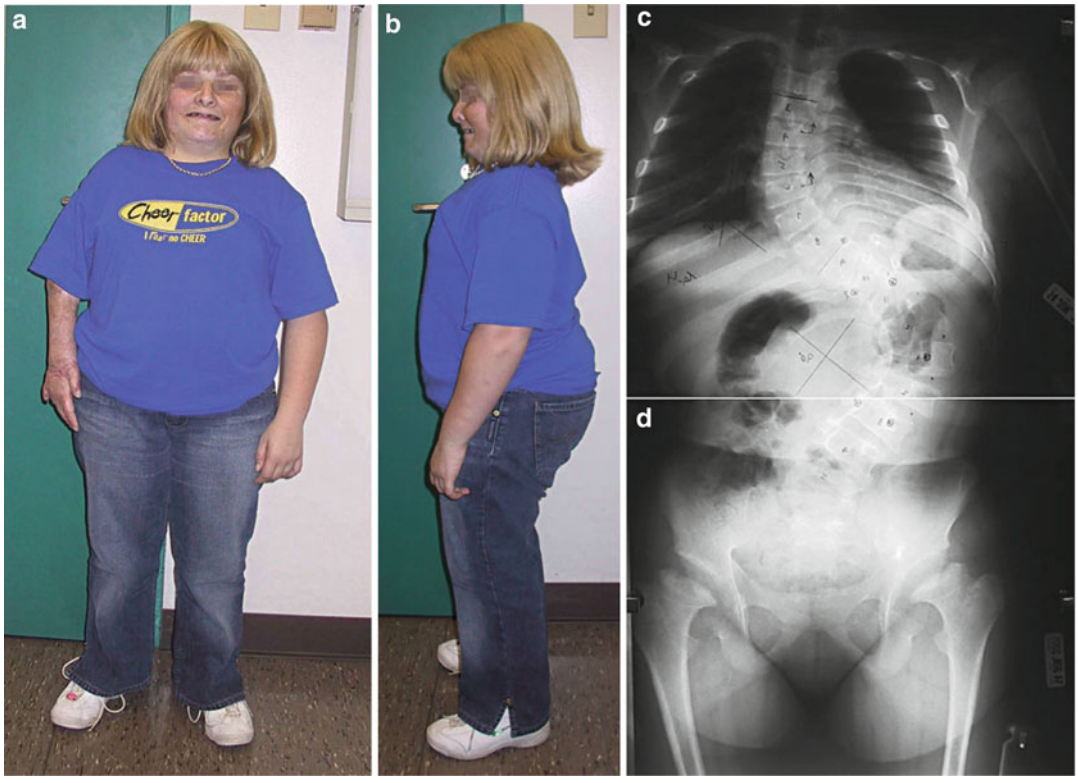

Fig. 4 (**a**–**d**) An adult with SED showing short-trunk dwarfism. Radiographs showed flat vertebral bodies, severe scoliosis, and retarded ossification of femoral head and neck

Fig. 5 (**a–d**) A 9-year-old boy with spondyloepiphyseal dysplasia tarda showing kyphosis. The spinal radiographs showed anterior body projection, widening of vertebral body spaces, and lumbar kyphosis. Femoral epiphysis was poorly developed (flat epiphyses) and acetabular sockets were not well formed

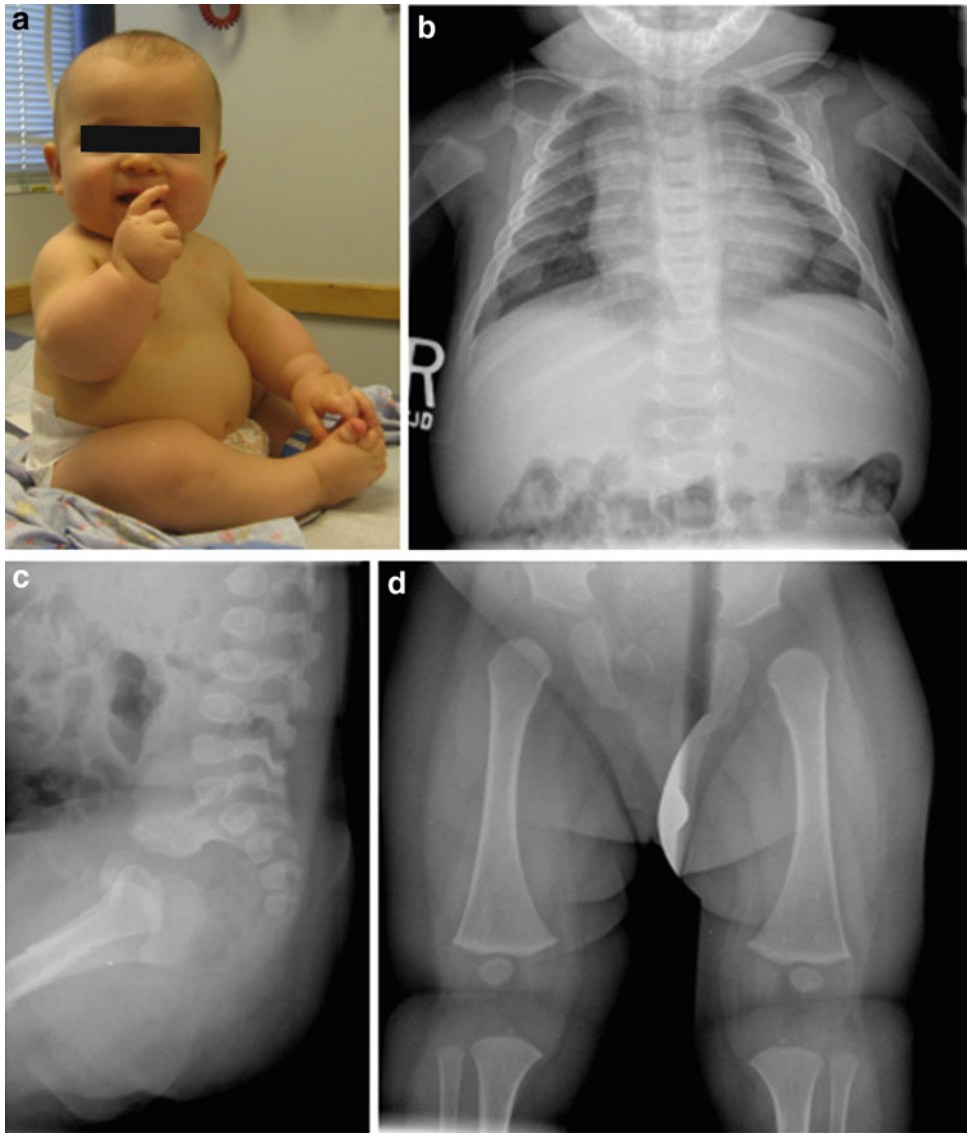

Fig. 6 (**a**–**d**) This 9-month old boy (**a**) was evaluated for short stature (height age of approximately 4 months). Skeletal survey (**b**–**d**) showed markedly delay epiphyseal development and ovoid appearance of the thoracic and lumbar vertebrae with anterior tonguing of L1, suggesting spondyloepiphyseal dysplasia congenita. DNA sequencing revealed a c.2965C>T transition in exon 43 of the *COL2A1* gene. This change converts a codon for arginine (CGT) to a codon for cysteine (TGT). The patient is heterozygous for this mutation. This exact change has previously been reported as a *COL2A1* mutation in a patient with spondyloepiphyseal dysplasia (Chan et al. 1993) (Courtesy of Dr. Susonne Ursin)

Stickler Syndrome

Contents

In 1965, Stickler et al. (1965) described a family with progressive myopia, retinal detachment and blindness, and premature degenerative changes in various joints. The disorder was subsequently termed "hereditary arthroophthalmopathy" (Herrmann et al. 1975a, b) or "hereditary progressive arhroophthalmopathy" (Popkin and Polomeno 1974). The incidence is estimated to be about 1 in 10,000 (Admiraal et al. 2002).

Synonyms and Related Disorders

Hereditary arhroophthalmopathy; Hereditary progressive arhroophthalmopathy; Wagner-Stickler syndrome

Genetics/Basic Defects

1. Inheritance (Robin et al. 2014)
    1. Autosomal dominant.
        1. Stickler syndrome caused by heterozygous mutation of COL2A1, COL11A1, or COL11A2 is inherited in an autosomal dominant manner.
        2. Autosomal dominant (Hall 1974) with wide variation in expression and virtually complete penetrance (Popkin and Polomeno 1974).
        3. Wagner-Stickler syndrome: a hereditary progressive arthroophthalmopathy with an autosomal dominant pattern of inheritance (Liberfarb et al. 1981).
    2. Autosomal recessive: Stickler syndrome caused by biallelic mutation of COL9A1, COL9A2, or COL9A3 is inherited in an autosomal recessive manner.
2. Association of the Stickler syndrome with following collagen gene mutations (Richards et al. 2013):
    1. Stickler syndrome type 1: *COL2A1* gene mutations (Hoornaert et al. 2010).
        1. Observed in membranous or type 1 vitreous phenotype (afibrillar phenotype).
        2. The presence of vitreous anomalies, retinal tears or detachments, cleft palate, and a positive family history were shown to be good indicators for a COL2A1 defect.
        3. Stickler syndrome type 1 is predominantly caused by loss-of-function mutations in the COL2A1 gene as >90% of the mutations were predicted to result in nonsense-mediated decay.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. A report on a familial apparently balanced reciprocal translocation t(12;15)(q13;q22.2) which disrupts *COL2A1* and causes type 1 Stickler syndrome, in a mother and two of her children (Dupont et al. 2013).
5. Different mutations of the *COL2A1* gene were associated with similar phenotypes, but with different degrees of expressivity. Retinal detachment was the most serious complication (Kondo et al. 2016).

2. Stickler syndrome type 2: *COL11A1* gene mutations (Richards et al. 2010).
   1. Observed in beaded or type 2 vitreous phenotype.
   2. Stickler syndrome type 2 (Marshall syndrome).
      1. Marshall syndrome associated with a splicing defect at the COL11A1 locus (Griffith et al. 1998)
      2. More severe facial features (short nose, midfacial flattening)
      3. High myopia
      4. Less risk of retinal detachment
      5. Moderate hearing impairment
   3. Some mutations in *COL11A1* have been classified as Marshall syndrome, but as demonstrated by Annunen et al. (1999), the short nose, anteverted nares, midfacial hypoplasia, and flat nasal bridge that are common in cases of Marshall syndrome with *COL11A1* mutations are also often present in young individuals with mutations in *COL2A1*, making differential diagnosis based on facial phenotypes difficult (Marjava et al. 2007).
   4. Recently, recessive mutations in the *COL11A1* gene have been demonstrated to result in fibrochondrogenesis, a much more severe skeletal dysplasia, which is often lethal.
   5. Some mutations in *COL11A1* are recessive (associated with unusually profound hearing loss), modified by alternative splicing and result in type 2 Stickler syndrome rather than fibrochondrogenesis.
3. Stickler syndrome type 3: *COL11A2* gene mutations.
   1. *COL11A2* gene has been localized to 6p22 to 6p21.3 (Brunner et al. 1994)
   2. Cause nonocular Stickler syndrome type 3 (Iwasa et al. 2015).
      1. Stickler-like facial features
      2. Mild-to-moderate deafness
      3. Normal eyes (Sirko-Osadsa et al. 1998)
   3. Also found in patients with a recessively inherited variant denoted as otospondylomegaepiphyseal dysplasia (OSMED)
   4. Also cause autosomal dominant nonsyndromic deafness (DFNA13) (McGuirt et al. 1999)
4. Rare recessive forms of Stickler syndrome exist that are due to mutations in genes encoding type 9 collagen.
   1. Stickler syndrome type 4: *COL9A1* mutations – vitreous syneresis with an optically empty vitreous due to progressive gel liquefaction (Van Camp et al. 2006)
   2. Stickler syndrome type 5: *COL9A2* mutations
   3. Autosomal recessive Stickler syndrome due to a loss-of-function mutation in the *COL9A3* gene (Faletra et al. 2014)
5. *LOXL3*, encoding lysyl oxidase-like 3, is mutated in a family with autosomal recessive Stickler syndrome (Alzahrani et al. 2015).

3. Stickler syndrome has been subclassified on the basis of vitreoretinal phenotype (Snead 1996).
   1. Type 1 families with a characteristic congenital vitreous anomaly show linkage without recombination to markers at the *COL2A1* locus.
   2. Type 2 families with different congenital vitreoretinal phenotypes are not linked to *COL2A1*.
4. Type 11 collagenopathies (Spranger 1998):
   1. On the basis of molecular studies, three type 11 collagenopathies have been defined: Stickler syndrome type 2 and dominant

and recessive otospondylomegaepiphyseal dysplasia (OSMED) (Vikkula et al. 1995; Van Steensel et al. 1997).
2. Stickler syndrome 1 and Kniest dysplasia are type 2 collagenopathies with considerable clinical and radiographic overlap.
3. Inborn errors of cartilage collagen formation lead to a family of genetically heterogeneous but pathogenetically related and hence phenotypically similar disorders. The type 11 collagenopathies are part of this family.

5. Genotype-phenotype correlations: difficult to predict the severity of the phenotype on the basis of genotype (Liberfarb et al. 2003).
   1. Type 1 Stickler syndrome.
      1. Ocular Stickler syndrome with mutations in *COL2A1* (chromosome locus: 12q13.11-q13.2).
      2. Families with Sticklers syndrome type 1 have a characteristic congenital vitreous anomaly and are linked without recombination to markers at the COL2A1 locus (Richards et al. 1996).
      3. The presence of vitreous anomalies, retinal tears or detachments, cleft palate, and a positive family history were shown to be good indicators for a *COL2A1* defect (Hoornaert et al. 2010).
   2. Type 2 Stickler syndrome.
      1. Ocular Stickler syndrome with mutations in *COL11A1* (chromosome locus: 1p21).
      2. Families with the type 2 variety have a different vitreoretinal phenotype and are not linked to the *COL2A1* gene (Richards et al. 1996).
   3. Type 3 Stickler syndrome: nonocular Stickler syndrome with mutations in *COL11A2* (chromosome locus: 6p21.3).
   4. Early onset of high myopia with vitreous abnormalities may serve as a key indicator of Stickler syndrome, while the existence of mandibular protrusion in pediatric patients may be an efficient indicator for the absence of mutations in *COL2A1* and *COL11A1* (Wang et al. 2016).

Clinical Features

1. Considerable clinical variability within families and between families (Zlotogora et al. 1992; Stickler et al. 2001), explainable in part by locus and allelic heterogeneity
2. Ocular features (Spallone 1987)
   1. Myopia.
      1. Congenital
      2. Nonprogressive
      3. Of high degree
   2. Abnormalities of vitreous formation and gel architecture.
      1. Pathognomonic of Stickler syndrome
      2. A prerequisite for diagnosis
      3. Vitreous anomalies
         1. Characteristic congenital "membranous" vitreous anomaly (type 1 phenotype) in type 1 Stickler syndromes
         2. Sparse and irregularly thickened bundles of fibers throughout the vitreous cavity (type 2 phenotype) in type 2 Stickler syndrome
   3. Retinal detachment.
      1. The most serious ophthalmologic complication
      2. Mainly occurs in the second decade of life (Vilaplana et al. 2015)
   4. Cataracts: mainly developing in the fourth decade of life (Vilaplana et al. 2015). However, congenital glaucoma has been reported in a 1-month-old boy (Shenoy and Mandal 2013).
   5. Ectopia lentis.
   6. Strabismus.
   7. Open-angle glaucoma.
   8. No ocular abnormalities in Stickler syndrome type 3.
3. Hearing impairment (Nowak 1998; Admiraal et al. 2002; Acke et al. 2012)
   1. Considerable variability (Jacobson et al. 1990).
   2. Common occurrence.
   3. Sensorineural hearing loss predominates, but also conductive hearing loss, especially in children and patients with a palatal defect, may occur.

4. The distinct disease-causing collagen genes are associated with a different prevalence of hearing impairment, but still large phenotypic variation exists.
5. Conductive hearing impairment.
    1. Resulting from recurrent otitis media
    2. Secondary to cleft palate
6. Sensorineural hearing impairment.
    1. Type 1 Stickler syndrome with mutations in the *COL2A1* gene
        1. Occurring in 50–60%
        2. Typically mild-to-moderate degrees
        3. Predominantly affecting higher frequencies
        4. No tangible progression beyond presbycusis
    2. Type 2 Stickler syndrome (Marshall syndrome) with the mutations in the *COL11A1* gene
        1. Occurring in 80–100%
        2. More severely affected
        3. Starting at a younger age or congenital in origin
        4. Showing progression
    3. Type 3 Stickler syndrome with mutations in the *COL11A2* gene
        1. A typical feature
        2. Hundred percent penetrance
        3. Mild-to-moderate impairment
        4. Nonprogressive when accounted for presbycusis
        5. Showing different audiometric configurations
4. Associated anomalies
    1. Orofacial anomalies
        1. Facial bone hypoplasia
            1. Flat midface.
            2. Depressed nasal bridge.
            3. Maxillary hypoplasia.
            4. Mandibular hypoplasia (Pierre-Robin anomaly/sequence): 51% of the patients presenting with Robin sequence features had been diagnosed with the Stickler syndrome (Antunes et al. 2012).
        2. High arched/cleft palate
        3. Bifid uvula
        4. Abnormal teeth
        5. Malocclusion
    2. Generalized musculoskeletal abnormalities
        1. Arthropathy (Lewkonia 1992)
            1. Joint hyperextensibility
            2. Enlarged joints
            3. Premature osteoarthritis
            4. Progressive joint degeneration (85%) (Popkin and Polomeno 1974)
        2. Slender extremities
        3. Long fingers
        4. Hypotonia
        5. Relative muscle hypoplasia
        6. Kyphosis
        7. Scoliosis
        8. Pectus carinatum
        9. Accessory carpal ossicles
        10. Hip dislocation
        11. Coxa valga
        12. Genu valga
        13. Talipes equinovarus
    3. Mitral valve prolapse (Liberfarb and Goldblatt 1986)
5. Intelligence: normal
6. Clinical features seen in different types of Stickler syndrome (Li and Thorne 2010)
    1. Type 1
        1. Ocular
            1. Myopia
            2. Vitreoretinal degeneration
            3. Cataracts
            4. Retinal detachment
        2. Musculoskeletal
            1. Mild degenerative changes
            2. Hypermobility
        3. Auditory: Normal to slight hearing impairment
        4. Craniofacial: cleft palate
        5. Possibility of a potential occurrence of seizures among the clinical manifestations of Stickler syndrome type 1, suggesting the presence of a continuous neurological spectrum in some individuals harboring heterozygous mutations in *COL2A1* (Savasta et al. 2015)
    2. Type 2
        1. Ocular

1. Congenital nonprogressive myopia
2. Cataracts

2. Musculoskeletal
1. Mild degenerative changes
2. Hypermobility

3. Auditory: early-onset sensorineural hearing loss
4. Craniofacial: cleft palate

3. Type 3
1. Ocular: none
2. Musculoskeletal: early-onset osteoarthritis
3. Auditory: high-tone sensorineural hearing loss
4. Craniofacial: Pierre-Robin sequence

7. Differential diagnosis (Snead and Yates 1999; Bowling et al. 2000)
1. Wagner hereditary vitreoretinal degeneration
1. Consisting solely of ocular abnormalities
1. Myopia
2. Vitreous degeneration
3. Preretinal avascular membranes
4. Retinal degeneration and thinning

2. No increased risk of retinal detachment or systemic abnormalities

2. Weissenbacher-Zweymüller syndrome and otospondylomegaepiphyseal dysplasia (OSMED)
1. Pierre-Robin sequence
2. Snub nose
3. Proximal limb shortening resolved by adulthood
4. Dumbbell-shaped femora and humeri
5. Coronal vertebral clefts
6. Sensorineural hearing loss
7. No eye abnormalities
8. *COL11A2* mutations
9. Appears to represent the same entity as nonocular Stickler syndrome

3. Erosive vitreoretinopathy (Brown et al. 1994)
1. Autosomal dominant eye disorder
2. Phenotype resembling Wagner syndrome but lacking any systemic abnormalities
3. Condition mapped to 5q13-q14 suggesting it may be an allelic variant of Wagner syndrome (Brown et al. 1995)

4. Marshall syndrome (Marshall 1958)
1. Autosomal dominant disorder
2. Clinical phenotype
1. Cataracts
2. Myopia
3. Abnormal vitreous
4. Midfacial hypoplasia
5. Congenital deafness

3. Associated with *COL11A1* mutation in a family affected with Marshall syndrome

5. Kniest dysplasia
1. Ocular abnormalities
1. Severe myopia
2. Vitreous veils
3. Perivascular lattice
4. Retinal detachment
5. Cataracts

2. Systemic findings
1. Short trunk dwarfism
2. Kyphoscoliosis
3. Deafness
4. Depressed nasal bridge
5. Cleft palate

6. Spondyloepiphyseal dysplasia
7. Marfan syndrome
8. Goldmann-Farve syndrome
1. A rare recessively inherited condition
2. Ocular abnormalities
1. Night blindness
2. Retinal detachment
3. Pigmentary chorioretinal degeneration
4. Vascular sheathing in the fundus

9. Jansen syndrome
1. Ocular abnormalities similar to Wagner syndrome
2. Absent systemic abnormalities

10. Congenital retinoschisis
1. A sex-linked recessive trait
2. Usually occurring in emmetropic or hyperopic patients
3. Membrane-like structures in midvitreous

Diagnostic Investigations

1. Audiologic and otologic testing for hearing loss (Jacobson et al. 1990)
2. Audiometric analysis (Acke et al. 2012, 2016)
    1. Regular auditory follow-up is strongly advised, particularly because many Stickler patients are visually impaired.
    2. A mild and predominantly high-frequency sensorineural hearing loss (SNHL) in type 1 Stickler patients, which is characterized by an early onset and is nonprogressive compared with normal age-specific hearing thresholds. The absence of otoacoustic emissions is a frequent finding and is probably inherent to the impact of a *COL2A1* mutation in the inner ear.
    3. In type 2 patients, the audiogram demonstrates mild-to-moderate low- and mid-frequency SNHL and moderate-to-severe high-frequency SNHL. This hearing loss has an early onset as well, and seems to be nonprogressive in adult age.
3. Vitreous slit-lamp biomicroscopy can distinguish between patients with *COL2A1* mutations and those with dominant negative mutations in *COL11A1*, who produce a different "beaded" vitreous phenotype (Richards et al. 2000)
4. Radiographic features
    1. The most common specific roentgenographic findings (Bennett and McMurray 1990)
        1. Coxa valga
        2. Widening of femoral neck
        3. Acetabular protrusio
        4. Chondrolysis
        5. Avascular necrosis
        6. Premature arthritic changes
    2. Generalized spondyloepiphyseal dysplasia
    3. Flattening of the epiphyses
    4. Narrowing of the diaphyses
    5. Flaring or widening of the metaphyses
    6. Wedging of the tubular bones
    7. Anterior maxillary and mandibular underdevelopment
5. CT scan studies in type 1 Stickler syndrome (Kaissi et al. 2013)
    1. Anterolateral ossification of the anterior longitudinal spinal (Forestier disease)
    2. Platyspondyly
    3. Extensive endplate sclerosis and anterior spurring associated with giant osteophytes formation
    4. Schmorl's nodes associated with narrowing of the intervertebral disc spaces
    5. Development of vertebral scalloping along the lower lumbar vertebrae
    6. Extensive hyperostosis of the anterior longitudinal spinal ligaments, resulting in the characteristic radiographic finding of a Bamboo-like spine resembling ankylosing spondylitis
    7. The overall spine pathology is compatible with severe premature spine degeneration overwhelmed by diffuse hyperostosis
    8. Femoral anteversion of the hips secondary to significant acetabulo-femoral dysplasia
    9. Internal rotation of both knees
    10. Epiphyseal fragmentations associated with trochlear dysplasia
6. Ocular histopathologic findings (Blair et al. 1979)
    1. Total retinal detachment with marked folding
    2. Disorganization of the retina
    3. A preretinal membrane
7. A novel strategy for screening families with type 1 Stickler syndrome due to *COL2A1* nonsense mutations, using a modified RNA-based protein truncation test (Freddi et al. 2000)
8. Rapid determination of *COL2A1* mutations in individuals with Stickler syndrome: Analysis of potential premature termination codons (Wilkin et al. 2000)
9. Nonocular Stickler syndrome with a novel mutation in *COL11A2* diagnosed by massively parallel sequencing in Japanese hearing loss patients (Iwasa et al. 2015)

10. Clinically available molecular genetic testing for mutations affecting different genes (*COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, *COL9A3*) (Robin et al. 2014)
    1. Sequence analysis
    2. Deletion/duplication analysis
11. Targeted next-generation sequencing is an efficient and cost-effective molecular tool in the genetic diagnosis of Stickler syndrome, whereas the more standardized whole-exome sequencing might be an alternative approach (Acke et al. 2014)

Genetic Counseling

1. Recurrence risk (Robin et al. 2014)
    1. Variable clinical expression of Stickler syndrome may complicate the genetic counseling (Faber et al. 2000).
        1. Exercise caution on assuming a de novo mutation: radiographic studies and clinical examination of the parents including formal testing of hearing and vision
        2. Mutation search whenever possible
        3. Uncertainty in predicting clinical consequences of inheriting a mutation
    2. Patient's sib
        1. Autosomal dominant inheritance (COL2A1, COL11A1, COL11A2-related Stickler syndrome)
            1. A 50% risk if a parent has Stickler syndrome
            2. A low recurrence risk if the parents are clinically affected and the disease-causing mutation not identified
        2. Autosomal recessive inheritance (*COL9A1*): a 25% risk
    3. Patient's offspring
        1. Autosomal dominant: a 50% risk
        2. Autosomal recessive: risk not increased unless the spouse is a carrier
    4. Mosaicism in Stickler syndrome (Stevenson et al. 2012)
        1. A family with two clinically affected sibs with Stickler syndrome who have clinically unaffected parents.
        2. Both sibs have a novel heterozygous mutation in exon 26 of *COL2A1* (c.1525delT); this results in a premature termination codon downstream of the mutation site.
        3. One parent was found to have low level mosaicism in DNA extracted from whole blood.
        4. This scenario encourages consideration of molecular testing in seemingly unaffected parents for recurrence risks and potential screening for mild age-related manifestations.
2. Prenatal diagnosis (Robin et al. 2014)
    1. Ultrasonographic demonstration of Pierre-Robin sequence as a part of Stickler syndrome (Soulier et al. 2002)
    2. Mutation analysis on amniocytes or CVS cells in at-risk families with known mutations
    3. Linkage analysis of the 3′VNTR polymorphism on the involved gene (*COL2A1*) using amniocytic DNA (Lisi et al. 2002)
    4. Preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family
3. Management (Bowling et al. 2000; Wilkin et al. 2001)
    1. Early evaluation of at-risk patients for the development of the following complications
        1. Retinal tears
        2. Retinal detachment
        3. Cataracts
        4. Glaucoma
    2. Long-term monitoring
    3. Cleft palate repair with appropriate feeding techniques
    4. Corrective lenses for myopia
    5. Avoid contact sports which may lead to retinal detachment
    6. Laser photocoagulation of vitreoretinopathy as preventive treatment for retinal detachment (Leiba et al. 1996)
    7. Surgical repair of retinal detachments and remove cataracts with possible lens implantation

8. The primary surgery should be vitrectomy combined with scleral buckling and silicone oil tamponade (Alshahrani et al. 2015)
9. Glaucoma management
10. Corrective treatment for strabismus
11. Hearing aids for hearing loss
12. Speech therapy
13. Symptomatic treatment for arthropathy
    1. Joint pain management
    2. Appropriate splints for strengthening and stabilizing lax joints
    3. Braces or aids to assist daily activities
    4. Hydrotherapy or other physical therapy modalities to increase range of motion, endurance, and strength
    5. Low-dose steroids along with methotrexate and hydroxychloroquine: The patients responded to treatment and there was significant improvement in their joint symptoms (Dhaon et al. 2015)
14. Management for mitral valve prolapse
    1. Antibiotics prophylaxis
    2. Beta-blocker for symptomatic patients
15. Use of external distractors and the role of imaging prior to mandibular distraction in infants with isolated Pierre-Robin sequence and Stickler syndrome (Mingo et al. 2016)

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Fig. 1 A 32-year-old female with Stickler syndrome having severe myopia, retinal detachment, cleft palate, sensorineural hearing loss, mitral valve prolapse, hyperextensible joints, and severe degenerative joint disease

Sturge-Weber Syndrome

Contents

Sturge-Weber syndrome (SWS) comprises of vascular malformations of the central nervous system and the port-wine stain or nevus flammeus of the face in a trigeminal nerve distribution. The syndrome is also known as encephalotrigeminal angiomatosis (King and Schwarz 1954). The incidence is estimated to be approximately 1 in 50,000 (Sturge 1879; Parkes Weber 1922; Thomas-Sohl et al. 2004).

Synonyms and Related Disorders

Encephalofacial or encephalotrigeminal angiomatosis; Leptomeningeal vascular malformation (angioma); Port-wine stains

Genetics/Basic Defects

1. Genetics:
   1. A sporadic, nonfamilial disease
   2. Uncertain inheritance: only a few familial clusters of the syndrome reported; most of these have not exhibited the clear-cut autosomal dominant inheritance pattern.
   3. Proposed to represent a genetically mosaic condition. Lesions in the Sturge-Weber syndrome result from somatic mutations in affected areas, such as the port-wine stain or leptomeningeal angioma, but not in blood or normal skin (Huq et al. 2002).
   4. A potential role of fibronectin in the pathogenesis of Sturge-Weber syndrome. The gene expression findings in fibroblast (Comi et al. 2003) supported the hypothesis of a somatic mutation underlying the disorder.
   5. A novel synonymous mutation (c.1229G > A) (p.K420K) of RASA1 was identified in a Chinese patient with sporadic Sturge-Weber syndrome (Zhou et al. 2011): Further study is needed.
2. Basic defect: caused by residual embryonal blood vessels and their secondary effects on surrounding brain tissue.
3. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ* (Shirley et al. 2013; Nakashima et al. 2014).
4. Angiomas are well documented in SWS and are thought to arise from a mutation in the guanine nucleotide-binding protein G (q) subunit alpha (GNAQ) which mediates signals between G-protein coupled receptors and

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downstream processes. The finding of an angiomatous meningioma in SWS suggests a common pathway may be involved in the aberrant vascular proliferation of both conditions (Ahmed and Prayson 2015).

5. Pathophysiology: Neurologic dysfunction of the syndrome results from secondary effects of residual embryonal blood vessels on surrounding brain tissue:
   1. Hypoxia
   2. Ischemia
   3. Venous occlusion
   4. Thrombosis
   5. Infarction
   6. Vasomotor phenomenon
   7. Seizures
6. Factors contributing to epileptogenesis (Pinto et al. 2016):
   1. Decreased brain tissue perfusion due to abnormal venous drainage
   2. Anoxic injury contributing to cerebral calcification
   3. Breakdown of the blood–brain barrier
   4. Presence of developmental cortical malformations

Clinical Features

1. Variable natural history of the disease (Oakes 1992; Mirowski et al. 1999)
2. Three cardinal features (Comi 2003):
   1. Capillary malformation (port-wine stain, cutaneous angioma) in the upper trigeminal neural distribution
      1. Involves the ophthalmic branch of the trigeminal nerve, in particular, the upper eyelid and supraorbital region
      2. May extend into the maxillary and mandibular regions
      3. May be associated with soft tissue and bony overgrowth
      4. May be hidden in scalp or mouth
      5. May be absent in the forme fruste of Sturge-Weber syndrome
   2. Ocular abnormalities (Celebi et al. 2000; Mantelli et al. 2016):
      1. Usually ipsilateral to the port-wine stain, involving the eyelid, anterior chamber, cornea, choroid, and retina
      2. Glaucoma (60%) (Cibis et al. 1984): unilateral and is associated with the presence of an ipsilateral port-wine stain
      3. Buphthalmos
      4. Vascular malformations of the conjunctiva, episclera, choroids, and retina
      5. Rare choroidal hemangioma and nevus of Ota (Celebi et al. 2000)
   3. Leptomeningeal vascular malformation (angioma):
      1. May be unilateral (more common) or bilateral
      2. Usually ipsilateral to port-wine stain
      3. Capillary and venous anomalies of leptomeninges
      4. No correlation between the size of facial and CNS malformations
      5. Encephalotrigeminal angiomatosis with intracranial calcification (Alonso et al. 1979)
3. CNS manifestations:
   1. Seizure/epilepsy (75–90% of cases) (Arzimanoglou and Aicardi 1992)
   2. Bilateral intracranial calcification (15%) (Boltshauser et al. 1976)
   3. Mental retardation present in approximately 50% of cases
   4. Contralateral hemiplegia or hemisensory deficits
   5. Contralateral homonymous hemianopsia (impaired vision in half of the visual field)
   6. Headaches
   7. Developmental delay
   8. Learning disorders
   9. Attention deficit hyperactivity disorder
   10. Predictors of cognitive functions in children with Sturge-Weber syndrome (Bosnyák et al. 2016):
      1. The early trajectory of cognitive changes in children with unilateral Sturge-Weber syndrome is highly variable.
      2. Children with improving IQ likely undergo effective unimpeded functional reorganization.

3. Early onset, frequent seizures, and interictal epileptiform abnormalities on EEG likely interfere with this process resulting in poor cognitive functions.

11. Uncontrolled seizures, mental subnormality, visual handicap, and cosmetic disfiguration were the major impediments in life (Jagtap et al. 2012).

4. In a child with developmental delay presenting with seizures, macrocephaly, presence of port-wine stains on the body and imaging features of subcortical "tram-track"-like pattern of calcifications, parenchymal volume loss, enlarged choroid plexus, and calvarial hyperostosis are diagnostic of Sturge-Weber syndrome (Ragupathi et al. 2014).
5. Soft tissue and skeletal overgrowth (60–83%) (Greene et al. 2009):
   1. Often exhibit localized cutaneous growths, either pyogenic granuloma or fibrovascular nodules
   2. Do not combine venous, lymphatic, or arterial anomalies in an extremity, although simple diffuse venous varicosities have been seen
   3. Often erroneously diagnosed as having either Klippel-Trenaunay syndrome (extremity capillary-lymphatico-venous malformation with overgrowth)
   4. Parkes Weber syndrome (extremity capillary-arteriovenous malformation with overgrowth): Right-sided hemihypertrophy resulting from right-sided congenital spastic hemiplegia with a morbid condition of the left side of the brain revealed by radiogram (Parkes Weber 1922)
6. Long-term outcome in adults (Sujansky and Conradi 1995a, b; Arzimanoglou et al. 2000):
   1. Distribution of port-wine stain
      1. Cranial: 98%
      2. Extracranial: 52%
   2. Glaucoma (60%)
   3. Seizures (83%)
   4. Neurologic deficit (65%)
   5. Developmental delay usually associated with seizures
      1. With seizures: 43%
      2. Without seizures: 0%
   6. Presence of behavior and emotional problems
      1. With seizures: 85%
      2. Without seizures: 58%
   7. Require special education
      1. With seizures: 71%
      2. Without seizures: 0%
   8. Employability
      1. With seizures: 46%
      2. Without seizures: 78%
   9. Normal fertility
   10. Indications of progressive nature
      1. Increasing duration of seizures and postictal deficits
      2. Increase in atrophy or of calcified lesions or both
7. Classification of encephalofacial angiomatosis of Sturge-Weber syndrome (Roach 1992; Sudarsanam and Ardern-Holmes 2014; Mukherjee et al. 2015):
   1. Type I (both facial and leptomeningeal angioma, possible glaucoma) (classic Sturge-Weber syndrome).
   2. Type II (facial angioma alone, without evident endocranial involvement); may have glaucoma.
   3. Type III (isolated leptomeningeal-brain angioma): usually no glaucoma. Very few cases of Sturge-Weber syndrome type III have been reported (Pascual-Castroviejo et al. 1993).
8. Neurocutaneous syndromes (Chao 1959; Figueiredo et al. 2016):
   1. Autosomal dominant:
      1. NF1 (please see the chapter on "► Neurofibromatosis 1")
      2. NF2 (please see the chapter on "► Neurofibromatosis 2").
      3. Hereditary hemorrhagic telangiectasia: an inherited systemic vascular dysplastic disorder correlated with multiple mucocutaneous telangiectasias, recurrent nasal and gastrointestinal bleeding episodes, and large arteriovenous malformations of the lungs, liver, and/or brain.
      4. Tuberous sclerosis complex (please see the chapter on "► Tuberous Sclerosis").

5. Von Hippel-Lindau disease (please see the chapter on "► Von Hippel-Lindau Disease").
6. Hypomelanosis of Ito (please see the chapter on "► Hypomelanosis of Ito").

2. Autosomal recessive:
   1. Pseudoxanthoma elasticum: a connective tissue disorder that causes mineralization of elastic skin fibers, eyes, cardiovascular system, and digestive system.
   2. Xeroderma pigmentosum (XP): a disorder identified by photosensitivity, pigmentary transformation, premature aging of the skin, and development of malignant tumors as a result of cellular hypersensitivity to ultraviolet (UV) radiation due to an error in DNA repair. Patients with XP have been divided into eight complementation groups.
   3. Ataxia telangiectasia (please see the chapter on "► Ataxia-Telangiectasia").
3. X-linked:
   1. Fabry disease (deficiency of α-galactosidase A (a-Gal A) activity): Early manifestations include corneal and lenticular opacities, skin lesions, acroparesthesias, hypohidrosis, and gastrointestinal symptoms.
   2. Incontinentia pigmenti (please see the chapter on "► Incontinentia Pigmenti").
4. Sporadic:
   1. Sturge-Weber syndrome
   2. Wyburn-Mason Syndrome (retinoencephalofacial angiomatosis): characterized by arteriovenous malformations that affect the retina, visual pathways, midbrain, and facial structures

Diagnostic Investigations

1. Radiography:
   1. Asymmetric skull
   2. Double contour curvilinear following "gyriform" patterns of intracranial calcifications: Pathognomonic for Sturge-Weber syndrome (Boltshauser et al. 1976):
      1. Classic "tram-line," "tram-track," or "trolley-track" intracranial calcifications:
         1. Considered pathognomonic prior to modern neuroimaging
         2. Often a late finding
         3. May not be present initially
      2. Distribution:
         1. In the subcortical region, primarily in the parietal and occipital regions
         2. Unilateral (80%) or bilateral (20%)
2. EEG to evaluate seizure activities: The most consistent EEG finding was a unilateral reduction of background amplitude in the waking record (Brenner and Sharbrough 1976).
3. Angiographic findings:
   1. Lack of superficial cortical veins
   2. Nonfilling dural sinuses
   3. Abnormal, tortuous vessels
4. Ultra-widefield fluorescein angiography: first documentation of retinal vein-to-vein anastomoses in Sturge-Weber syndrome (Quan et al. 2015).
5. CT scan findings (Chamberlain et al. 1989; Di Rocco and Tamburrini 2006):
   1. Intracranial dense gyriform or "tram-track" calcifications which more commonly affect the parieto-occipital cortical area and/or the choroid plexus and are usually absent in early infancy.
   2. Diffuse high attenuation of the superficial and deep white matter, presumably due to microcalcifications.
   3. Gyriform enhancement after iodinated contrast enhancement, expression of the pial angiomatosis.
   4. Brain atrophy, consequence of vascular steal phenomenon (Limotai et al. 2015) of the pial angioma on the surrounding cortical structures.
   5. Thickening of the calvarium, more frequently observed in patients with early onset symptoms as an indirect feature of loss of the brain substance.
   6. Abnormal draining veins.
   7. Enlarged ipsilateral choroid plexus.

8. Blood–brain barrier breakdown during seizures.

6. MRI findings: the gold standard imaging modality for the identification of structural brain abnormalities (Di Rocco and Tamburrini 2006):
   1. Leptomeningeal enhancement with Gd-diethyltriaminepentaacetic acid on T1-weighted images is considered one of the most important signs that help define the extent of the vascular malformation; however, its absence does not exclude the diagnosis (Elster and Chen 1990).
   2. Enlarged choroid plexus.
   3. Sinovenous occlusion.
   4. Cortical atrophy.
   5. Accelerated myelination.
7. MRI with contrast for any parturient with a port-wine nevus of the face in the ocular (trigeminal nerve) region have to rule out an intracranial vascular malformation, especially if a related seizure disorder is present (Dolkart and Bhat 1995).
8. Even though computed tomography and T1- and T2-weighted magnetic resonance imaging have great diagnostic value, magnetic resonance imaging enhanced with gadolinium-DTPA discloses the cerebral, leptomeningeal, and ocular lesions before the first evidence of neurologic abnormality (Pascual-Castroviejo et al. 1993).
9. Single-photon emission computed tomography to measure cerebral blood flow (Griffiths 1996; Pinton et al. 1997):
   1. Hyperperfusion early (before 1 year)
   2. Hypoperfusion late (after 1 year)
10. Positron emission tomography (PET) for hypometabolism.
11. Histology:
    1. Thickened and discolored leptomeninges
    2. Abnormal venous structures
    3. Calcifications (Di Trapani et al. 1982):
       1. Cerebral vessel walls
       2. Perivascular tissue
       3. Rarely within neurons

Genetic Counseling

1. Recurrence risk:
   1. Patient's sib: low
   2. Patient's offspring: low
2. Prenatal diagnosis: not been reported
3. Management (Thomas-Sohl et al. 2004; Comi 2015; Sudarsanam and Ardern-Holmes 2014; Takeoka 2015):
   1. Medical care:
      1. Medications for recurrent headaches/migraine
         1. Ibuprofen: first choice
         2. Abortive therapy with sumatriptan
         3. Preventive therapy with propranolol or nortriptyline
      2. Stimulant medication may be a safe and effective intervention for SWS children with attention issues/attention deficit hyperactivity disorder (ADHD) (Lance et al. 2014).
      3. Management of glaucoma to control the intraocular pressure and prevent progressive visual loss and blindness:
         1. Beta-blocker drops: first choice
         2. Adrenergic drops or carbonic anhydrase inhibitor drops: second choice
      4. Anticonvulsants for seizure (partial epilepsy most prevalent in children) control:
         1. Carbamazepine and oxcarbazepine: first choice (Kaplan et al. 2016)
         2. Valproate, topiramate, phenobarbital, phenytoin
      5. Strokelike episodes: aspirin
      6. Neurobehavioral problems:
         1. Methylphenidate: first choice
         2. Clonidine: second choice
         3. Dextroamphetamine or risperidone
      7. Dermatologic laser therapy for port-wine stain: Treatment of the cutaneous PWS with dye laser photocoagulation has been helpful in reducing the cosmetic blemish from the cutaneous vascular dilatation.

8. Port-wine birthmark (Comi 2015):
    1. Laser therapy of port-wine stains: a method of selection (Kowalska-Brocka et al. 2015).
    2. Treated with laser procedures beginning in infancy when the flat, pink birthmark responds best and the birthmark is smaller (Chapas et al. 2007).
    3. Early laser treatment may lessen later progression of the birthmark, which can consist of tissue hypertrophy, blebs, and complications affecting vision, airway, and swallowing.
9. Successful treatment with photodynamic therapy for Sturge-Weber syndrome-associated diffuse choroidal hemangioma (Nugent et al. 2015).

2. Anesthetic management of pediatric patients with Sturge-Weber syndrome (Khanna et al. 2015):
    1. Avoiding a rise in intracranial and intraocular pressures, vigilant intraoperative monitoring, and postoperative care are the key for conducting safe anesthesia in these children.
    2. Sevoflurane was safely used in children with seizures.
    3. For ophthalmic procedures, laryngeal mask airway can be used for airway maintenance with minimal complications in children with SWS.
3. Surgical care:
    1. Surgery (trabeculectomy) for glaucoma if medications fail to lower intraocular pressure.
    2. Drainage valve implantation, with an anterior chamber maintainer, is a good choice for treatment when surgery is done in cases with glaucoma. This method may reduce the risk of intraoperative suprachoroidal effusion and expulsive hemorrhage by stabilizing intraocular pressure within normal limits during the surgery (Celebi et al. 2000).
    3. Option of early surgery for patients with Sturge-Weber syndrome with drug-resistant epilepsy:
        1. Focal cortical resection
        2. Hemispherectomy
        3. Corpus callosotomy
        4. Vagal nerve stimulation
    4. Lesionectomy provided that the pial angioma is unilateral and the resection can be complete.
    5. Hemispherectomy:
        1. For treatment of encephalotrigeminal angiomatosis (Falconer and Rushworth 1960): All exhibited epilepsy and/or a behavioral disturbance occurring in association with an infantile hemiplegia and their epilepsy and personality conditions were improved by excision of the affected cerebral hemisphere (hemispherectomy), but not their infantile hemiplegia. All remained mentally backward, but the four who were operated on during childhood proved to be educable.
        2. One can expect excellent results if the indications for surgery are carefully analyzed and hemispherectomy is performed on an individual basis (Ito et al. 1990).
        3. Children undergoing hemispherectomy presented at a young age and had frequent seizures for approximately 1 year but are now mostly seizure-free (Kossoff et al. 2002).

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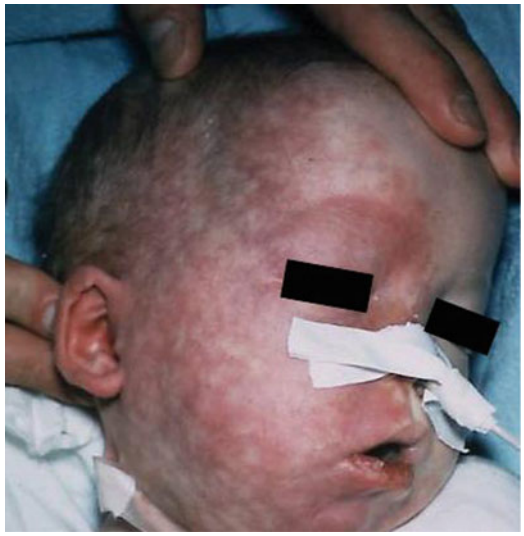

Fig. 1 An infant with Sturge-Weber syndrome showing port-wine stain primarily affecting the *right* side of the face

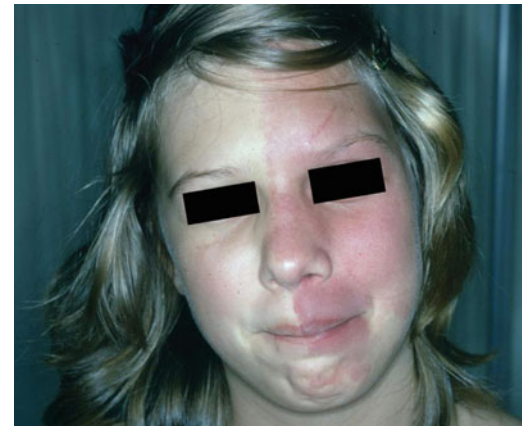

Fig. 2 A girl with typical Sturge-Weber syndrome showing port-wine stain affecting the *left* side of the face

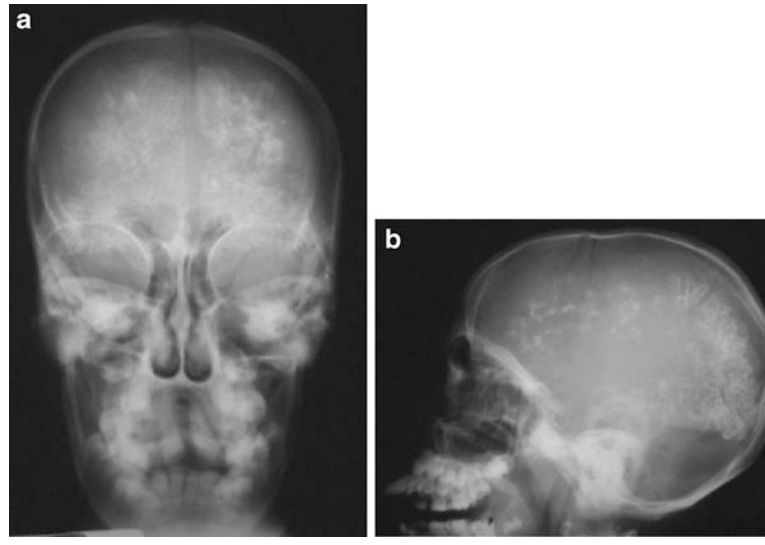

Fig. 3 (**a**, **b**) Radiographs of the skull in another patient demonstrate the typical gyriform pattern of cortical calcification

Symphalangism

Contents

Symphalangism is a rare congenital condition characterized by stiffness of the digits caused by ankylosis of the interphalangeal joints of the fingers and toes. Symphalangism was first described by Harvey Cushing in 1916 (Fig. 1).

Synonyms and Related Disorders

Cushing proximal symphalangism; Proximal symphalangism with conductive hearing loss; Multiple synostosis syndrome; Symbrachydactyly

Genetics/Basic Defects

1. Symphalangism was initially used to describe an autosomal dominant disorder affecting PIP joints of the fingers (Cushing 1919; Strasburger et al. 1965; Elkington and Huntsman 1967; Gaal et al. 1988; Castle et al. 1993)
2. Caused by mutations of the nogin (*NOG*) gene (on chromosome 17q22) in most cases of symphalangism (Polymeropoulos et al. 1995; Takahashi et al. 2001)
3. Identical mutations in *NOG* can cause either tarsal/carpal coalition syndrome or proximal symphalangism (Dixon et al. 2001)
4. Mutations in another protein, growth and differentiation factor 5 (*GDF5*): recently found to be associated with symphalangism (Seemann et al. 2005)
5. *NOG* and *CDF5* genes have been identified to be the disease-causing genes of proximal symphalangism (SYM1) (Gong et al. 1999; Seemann et al. 2005)
6. Nonhereditary symphalangism, often seen with symbrachydactyly, is reported as sporadic (Upton 2005)

Clinical Features

1. Symphalangism may involve proximal or distal interphalangeal joints, although proximal interphalangeal joint involvement is more common (Borah et al. 2006).
2. The fused phalanges cause disability or loss of hand function, including the inability to make a fist or perform activities that require fine manual dexterity (Durmus et al. 2012).
3. The diagnosis is currently applied most often to congenital stiffness of the finger joints with absence of transverse volar skin creases over

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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those joints that are fused (Flatt and Wood 1975)

4. Proximal symphalangism (Plett et al. 2008; Potti et al. 2011; Liu et al. 2014)
    1. Also called Cushing proximal symphalangism
    2. An autosomal dominant disorder
    3. Ankylosis of the PIP joints of the fingers and toes: generally affect the PIP joints of digits from the ulnar side to the radial side and finally to the thumbs
    4. Frequently associated with other bony fusions
        1. Talonavicular synostosis in the feet (Geelhoed et al. 1969)
        2. Ear ossicle (stapes) fusion leading to conductive deafness
    5. When the abnormality is more extensive, it is termed multiple synostosis syndrome (Maroteaux et al. 1972)
    6. Other clinical features
        1. Hyperopia
        2. Characteristic facies: a broad hemicylindrical nose with a lack of alar flare and a thin upper vermilion (Herrmann 1974)
        3. Absent flexion creases of the digits
        4. Shortened metacarpals and hypoplasia or aplasia of the distal phalanges in the hands and feet
5. Distal symphalangism
    1. Ankylosis or rigidity of the distal interphalangeal joints of the hands and/or feet (Poush 1991)
    2. Inheritance consistent with autosomal dominant inheritance
6. Classification of symphalangism by Flatt and Wood (1975)
    1. True symphalangism: involved digit with normal length
    2. Symbrachydactylism: short and stiff digits
    3. Symphalangism with associated anomalies
7. Associated syndromes, e.g.,
    1. Apert syndrome
    2. Poland syndrome
    3. Wassel type III polydactyly with symphalangism: thumb duplication with symphalangism (Wassel 1969; Boutros et al. 1998; Al-Aithan et al. 2005; Takagi et al. 2009; Al-Qattan 2010; Ciloglu et al. 2014)

Diagnostic Investigations

1. Radiography
1. Hallmark feature: longitudinal bony fusion across the joint
2. Involvement sites
    1. Symphalangism of the distal interphalangeal (DIP) can be seen in patients with symbrachydactyly
    2. Involvement of the metacarpophalangeal (MP) joint: extremely rare (Flatt and Wood 1975; Upton 2005)
2. Molecular genetic analysis for NOG and CDF5 genes: currently not available clinically

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal dominant inheritance: not increased unless a parent is affected
        2. Sporadic: apparently not significantly increased
    2. Patient's offspring
        1. Autosomal dominant inheritance: a 50 % risk
        2. Sporadic: apparently not significantly increased
2. Prenatal diagnosis: has not been reported
3. Management
    1. Treatment of symphalangism in adults: uniformly unsuccessful
    2. Manipulations and various arthroplasties can be applied to the fusions, but patient satisfaction is poor (Flatt and Wood 1975)
    3. Surgical intervention is rarely indicated, and physical, occupational, and exercise therapies are usually beneficial (Joshi et al. 2008)
    4. Physical therapy: considered before surgical intervention (Durmus et al. 2012)

5. Symphalangism of the hand in children: can be restored into a mobile joint by release of the collateral ligament, a dorsal capsulotomy, and postoperative physical therapy (Baek and Lee (2012)

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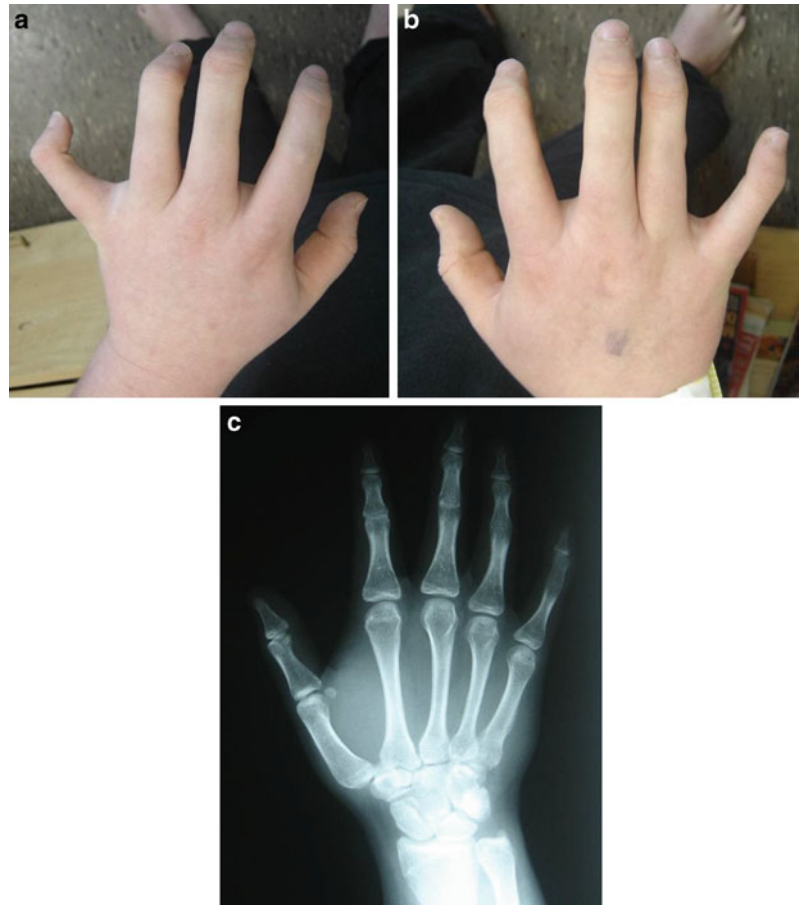

Fig. 1 (**a**–**c**) The patient was evaluated for congenital stiffness of finger joints and inability to make fists. The knuckles were smooth over the proximal interphalangeal (*PIP*) joints of the 2nd to 5th fingers of both hands. The distal phalanx motions were normal (**a**, **b**). The hand radiograph showed PIP joint ankylosis of the 3rd–5th fingers and severely reduced PIP joint space of the 2nd fingers of both hands (only the right hand is shown here) (**c**)

Tay-Sachs Disease

Contents

Tay-Sachs disease is a hereditary neurodegenerative disorder resulting from excess storage of GM2 ganglioside within the lysosomes of cells, caused by deficiency of hexosaminidase A. The incidence of the disease is estimated to be 1 in 3,600 in Ashkenazi Jews (AJ) with carrier frequency of 1 in 30 and 1 in 360,000 in other population with carrier frequency of 1 in 300. Tay-Sachs disease is the most frequently occurring sphingolipidoses.

Synonyms and Related Disorders

GM1-gangliosidosis; GM2 activator protein deficiency (GM2-gangliosidosis-AB variants); GM2-gangliosidosis; Hexosaminidase A deficiency; Sandhoff disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. Biochemical defect (Brady 2001): deficiency of the isoenzyme β-hexosaminidase A (Hex A).
3. Genetic basis.
    1. Mutations in the hexosaminidase A (*HEXA*) gene (on chromosome 15q23-q24) that codes for the subunit of the β-hexosaminidases result in the deficiency of Hex A (αβ) that results in Tay-Sachs disease.
    2. A high heterogeneity of HEXA lesions in Tay-Sachs disease (Akli et al. 1993).
    3. Over 100 different mutations have been identified in the *HEXA* gene to date.
    4. Presence of a small number of common mutations in populations where the carrier frequency is high (Sutton 2002).
        1. Ashkenazi Jews (Bach et al. 2001).
            1. Two common mutations associated with Tay-Sachs disease [a four base-pair insertion into exon 11 of the *HEXA* gene (1278insTATC) accounting for 75–80% of all mutations in this population; a splice site mutation in intron 12 (1421 + 1G → C) accounting for 15% of mutations]

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2. One mutation associated with a late-onset form of the disease (G269S in 3% of carriers)
3. The high incidence of the disease in Ashkenazi Jews is attributed predominantly to three mutations present in high frequency, while in non-Jews some two dozen mutations have been identified thus far (Gravel et al. 1991)
4. Pseudodeficiency polymorphism (R247W in 2% of carriers)

2. Pennsylvania Dutch.
   1. An intron 9 splice site mutation (1,073 + 1G → A)
   2. Pseudodeficiency allele (R247W)
3. Cajuns in Southern Louisiana: A genealogy could well trace to a single ancestral couple (Thurmon 1993).
   1. An intron 9 splice site mutations (1,073 + 1G → A)
   2. Four base-pair insertion in exon 11 (1278insTATC)
4. French Canadians in Eastern Quebec.
   1. A large (7.6 kb) deletion at the 5′ end of the gene
   2. A splice site mutation in intron 7 (805 + 1G → A)
   3. Common 4 base-pair insertion in exon 11 seen in Ashkenazi Jews (1278insTATC)

4. GM2-gangliosidosis-AB variants (Sheth et al. 2016).
   1. A rare autosomal recessive neurodegenerative disorder occurring due to deficiency of GM2 activator protein resulting from the mutation in *GM2A* gene.
   2. Children with phenotypic presentation as GM2-gangliosidosis (Tay-Sachs or Sandhoff disease) and normal enzyme activity of β-hexosaminidase A and β-hexosaminidase B in leucocytes need to be investigated for GM2 activator protein deficiency.
5. The concept of Tay-Sachs disease as the only ganglioside storage disease has expanded to two forms of gangliosidoses, GM1-gangliosidoses and GM2-gangliosidoses, and the latter into three distinct genetic disorders, Tay-Sachs disease, Sandhoff disease, and the GM2 activator protein deficiency. More recently, all three genes coding for the three proteins each responsible for distinct genetic forms of GM2-gangliosidosis – beta-hexosaminidase alpha and beta subunits and the GM2 activator protein – have been cloned, and many disease-causing mutations have been identified (Suzuki 1994).
6. Sphingolipidoses or gangliosidoses (Chen et al. 2014).
   1. Include GM1-gangliosidoses and GM2 (Tay-Sachs)-gangliosidoses, Niemann-Pick disease, Gaucher disease, Farber disease, Krabbe disease, Fabry disease, and metachromatic leukodystrophy.
   2. Each disease includes several types that are named for the lipid substrate that accumulate in each case.
   3. With the exception of X-linked recessive Fabry disease, they share a common autosomal recessive inheritance pattern and have a collective frequency of 1 in 8,000 live births.
   4. Multiple-organ dysfunction (liver, lung, spleen, heart, and lungs) is common.
   5. Since gangliosides are abundantly expressed in the central nervous system, the diseases share clinical findings, including a spectrum of early onset progressive neurodegeneration and a "cherry-red macula" from accumulation of various sphingolipid precursors or by-products within cells of the retina.

Clinical Features

1. Classic infantile acute-onset Tay-Sachs disease
   1. Natural history (Sutton 2002)
      1. Appears normal at birth
      2. Normal motor development in the first few months of life
      3. Progressive weakness and loss of motor skills beginning around 2–6 months of life

4. Followed by decreased social interaction, increased sensitivity to noise (hyperacusis), and an increased startle response to noise
5. Progressive neurodegeneration
6. Uniformly fatal: death from pneumonia usually occurring between 2 and 5 years of age

2. Clinical features
    1. Delayed development
    2. Poor feeding
    3. Lethargy
    4. Hypotonia
    5. Hyperreflexia
    6. Opisthotonos
    7. Hyperacusis
    8. A cherry-red spot on the fovea centralis of the macula, representing loss of ganglion cells in the foveal area with the remaining ones filled with the ganglioside
    9. The disappearance of the cherry-red spot in an otherwise typical patient with Tay-Sachs disease: consistent with the pathological finding of loss of retinal ganglion cells (Kivlin et al. 1985)
    10. Progressive neurodegeneration
        1. Developmental regression.
        2. Macrocephaly secondary to accumulation of storage material within the brain after about 15 months of age. There is no evidence of hepatosplenomegaly or other peripheral evidence of storage disease.
        3. Myoclonic seizures, most during the first year of life.
        4. Progressive macular degeneration leading to blindness, usually by 1 year of age.
        5. Deafness.
        6. Spasticity.
        7. Complete disability.

2. Subacute (juvenile) Tay-Sachs disease (2–18 years of age): characterized by progressive neurologic deterioration that mainly affects motor and spinocerebellar function leading to:
    1. Progressive spasticity with seizures and dementia
    2. A vegetative state by late childhood or mid-teens
3. Juvenile or subacute GM2-gangliosidosis (Maegawa et al. 2006)
    1. A group of inherited neurodegenerative diseases caused by deficiency of lysosomal beta-hexosaminidase resulting in GM2-ganglioside accumulation in brain.
    2. Clinically heterogeneous, not only in terms of age of onset and clinical features but also with regard to the course of the disease.
    3. In general, the earlier the onset of symptoms, the more rapidly the disease progresses.
    4. The Tay-Sachs and Sandhoff variants differed somewhat in the frequency of specific clinical characteristics.
    5. Speech deterioration progressed more rapidly than gait abnormalities in both the Tay-Sachs variant and Sandhoff variant groups.
    6. Among patients with the Tay-Sachs variant, the HEXA genotype showed a significant correlation with the clinical course.
4. Late-onset (adult) Tay-Sachs disease (Shapiro et al. 2008)
    1. A chronic, progressive, lysosomal storage disorder caused by a partial deficiency of beta-hexosaminidase A (HEXA) activity.
    2. Deficient levels of HEXA result in the intracellular accumulation of GM2-ganglioside, resulting in toxicity to nerve cells.
    3. Clinical picture varied between and within families and included spinocerebellar, various motor neuron, and cerebellar connection syndromes (Argov and Navon 1984).
    4. Clinical manifestations primarily involve the central nervous system (CNS) and lower motor neurons, including:
        1. Ataxia.
        2. Weakness.
        3. Spasticity.
        4. Dysarthria.
        5. Dysphagia.
        6. Dystonia.
        7. Seizures.

8. Psychosis: Psychosis is reported in 30–50% of adult-onset patients, and many are misdiagnosed with schizophrenia (MacQueen et al. 1998).
9. Mood disorders are present in more than 25% (MacQueen et al. 1998).
    1. Mania
    2. Depression
10. Cognitive decline (more than 20%).

5. The prevalence of peripheral nervous system: a predominantly axon loss polyneuropathy affecting distal nerve segments in the lower and upper extremities (27% of cases).

5. Late-onset GM2-gangliosidosis (Brett et al. 1973)
    1. Hexosaminidase A: Partial and profound deficiency
    2. Gait disturbance
    3. An exaggerated startle reaction to sound and an unusual type of cherry-red spot at the macula
    4. Optic atrophy in late stage
    5. Pathological changes: similar to Tay-Sachs disease

Diagnostic Investigations

1. Newborn screening: enzymatic diagnosis in dried blood spots on filter paper for Tay-Sachs and Sandhoff diseases (Chamoles et al. 2002).
2. Diagnosis and carrier testing (heterozygote screening) (Kaback et al. 1977).
    1. Indications for carrier testing.
        1. Fully or partially Jewish
        2. Pennsylvania Dutch
        3. Cajuns of Southern Louisiana
        4. French Canadians of Eastern Quebec
    2. Ashkenazi Jewish population screening for Tay-Sachs disease (Lew et al. 2015a).
        1. Should be offered to Ashkenazi Jewish (AJ) individuals of reproductive age in order to provide informed reproductive choice
        2. Partners of TSD carriers should be offered screening, regardless of heritage
3. Preconceptional counseling for at-risk couples.
4. Enzyme assay.
    1. Using fluorimetric study measuring activity of both Hex A and Hex B in either serum or leukocytes
    2. Decreased activity of Hex A with normal or increased activity of Hex B in carriers
    3. Limitations of serum assay
        1. Overlapping of the values between carriers and noncarriers
        2. Unreliable in pregnant women and in women taking oral contraceptives
        3. Inability to distinguish carriers of pseudodeficiency alleles from carriers of disease-causing mutations
    4. Clarification of abnormal or inconclusive results of enzyme assay by:
        1. Enzyme assay on leukocytes
        2. DNA mutation analysis for common mutations and pseudodeficiency alleles
5. In the future it would be expected that a laboratory using a single DNA-based technology could diagnose and screen for a myriad of human diseases including Tay-Sachs disease (Mahuran et al. 1990).
6. Next-generation DNA sequencing of HEXA: a step in the right direction for carrier screening (Hoffman et al. 2013).
7. Molecular genetic testing (Kaback and Desnick 2011).
    1. Targeted mutation analysis: using a panel of common *HEXA* mutations when assay of HEXA enzymatic activity is abnormal:
        1. In a symptomatic individual in order to identify the disease-causing mutations
        2. In an asymptomatic individual to evaluate for the presence of a pseudodeficiency allele
    2. Sequence analysis/mutation scanning: to identify *HEXA* mutations in an individual who:

    1. Is affected but had only one or neither mutation identified using a panel of standard mutations
    2. Has carrier-level enzymatic results but did not have a mutation identified using a panel of standard mutations
    3. Massively parallel DNA sequencing is expected to become the testing modality of choice over the coming years (Lew et al. 2015b).
3. CT scan of the brain: areas of low density in the basal ganglia and cerebral white matter
4. MRI of the brain.
    1. An increased signal in the basal ganglia and cerebral white matter on T_2-weighted images
    2. Thalamic T2 hypointensity: a diagnostic clue for Tay-Sachs disease (Güngör et al. 2016)
5. Brain imaging in late-onset GM2-gangliosidosis: Cerebellar atrophy, particularly of the vermis, was a prominent feature in all patients with normal-appearing cerebral hemispheres (Streifler et al. 1993).
6. In adults with cerebellar atrophy and signs of anterior horn disease, diagnostic considerations should include late-onset Tay-Sachs disease/GM2-gangliosidosis (Steiner et al. 2016).
7. MR spectroscopy (Aydin et al. 2005).
    1. Demonstrates an increase in myoinositol/creatine and choline/creatine ratios with a decrease in the N-acetyl aspartate/creatine ratio.
    2. The spectroscopy findings support demyelination, gliosis, and neuronal loss in the neuropathological process of Tay-Sachs disease.
8. Characteristic neuropathological findings (Kaback et al. 1993).
    1. Pathologic changes are restricted to the nervous system.
    2. Ballooning of neurons with massive intralysosomal accumulation of lipophilic membranous bodies.
    3. Nature and structure of the stored intraneuronal material : GM2-ganglioside.
    4. Ultrastructural demonstration of neuronal storage in fetal Tay-Sachs disease (Cutz et al. 1974).
    5. Abnormal cytoplasmic inclusion bodies identified in fetal spinal cord at 12 weeks and retina and spinal ganglia during 19th–22nd week of gestation (Adachi et al. 1974).
    6. Cisternae of the endoplasmic reticulum: the primary site of lipid accumulation in neurons during the fetal stage of Tay-Sachs disease (Adachi et al. 1974).
9. Chemical studies on three fetuses (Schneck et al. 1972).
    1. Absence of hexosaminidase A activities in all tissues in one fetus
    2. Increase in the percent of cerebral GM2-ganglioside
    3. Abnormal inclusion bodies seen in fetal neurons

Genetic Counseling

1. Recurrence risk.
    1. Patient's sib: 25%
    2. Patient's offspring
        1. Acute infantile form: not surviving to reproductive age.
        2. Late-onset form may reproduce: risk not increased unless the spouse is a carrier.
2. Prenatal diagnosis (Kaback and Desnick 2011) is available when HEXA enzyme assay has shown both parents to be heterozygous, and molecular genetic testing has ruled out the presence of a pseudodeficiency allele in either parent:
    1. Enzyme analysis (absence of hexosaminidase A) on cultured or uncultured amniocytes (O'Brien et al. 1971) or chorionic villus cells (Grebner and Jackson 1985).
    2. The use of MUGS (4-methylumbelliferyl-2-acetamido-2-deoxy-beta-D-glucopyranosyl-6-sulfate) as substrate for HEXA makes prenatal diagnosis by CVS

of families at risk for TSD simple, direct, and accurate (Callahan et al. 1990).

3. First-trimester prenatal diagnosis of Tay-Sachs disease (Grabowski et al. 1984): The diagnoses were based on the absence of beta-hexosaminidase A activity as determined by (1) specific enzyme assays, (2) anion-exchange chromatography, and (3) cellulose acetate gel electrophoresis.
4. DNA analysis when one of the common mutations had been identified in the family.
    1. Preferred method of prenatal diagnosis
    2. Less prone to error
5. Preimplantation genetic diagnosis (Hansis and Grifo 2001; Georgiou et al. 2014) may be available for families in which the disease-causing mutations have been identified in an affected family member.

3. Management (Desnick and Goldberg 1977).
    1. No effective treatment to alter the natural history.
    2. Primarily supportive.
        1. Provide adequate nutrition and hydration
        2. Manage infections
        3. Protect airway
        4. Control seizures
        5. Bowel management
    3. Psychologic care of carriers and affected families (Schweitzer-Miller 2001).
    4. Enzyme replacement therapy and bone marrow transplantation: not yet successful.
    5. Options to modify 25% risk of having an affected child with each pregnancy if both partners are found to be carriers (Sutton 2002).
        1. Prenatal diagnosis by amniocentesis or chorionic villus sampling
        2. Egg or sperm donation
        3. Preimplantation genetic diagnosis
        4. Adoption
    6. Coordinating adult education, carrier testing, and genetic counseling directed toward prospective prevention of a uniformly fatal childhood disease and demonstrate that such an effort can dramatically affect disease incidence (dramatic decreased in the incidence of TSD (Kaback et al. 1993).

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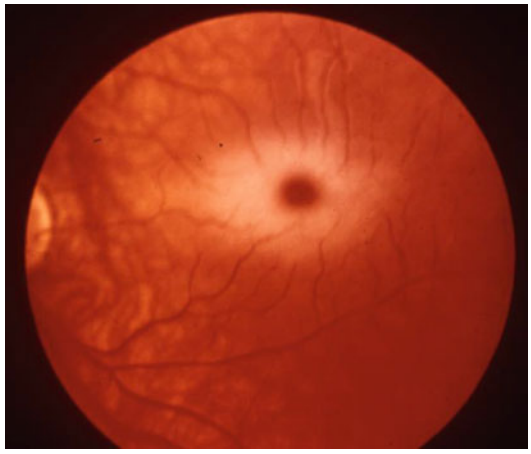

Fig. 1 A cherry-*red* spot on the fovea centralis of the macula from the fundus of an infant with Tay-Sachs disease

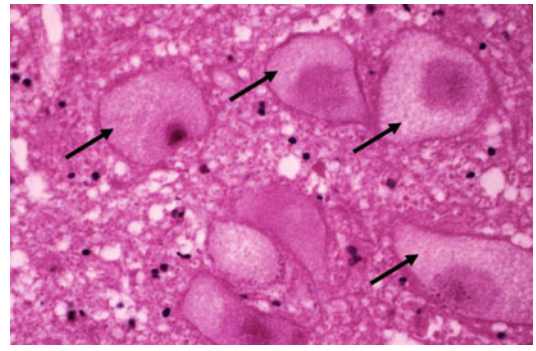

Fig. 3 A section of medulla showing a group of neurons with markedly distended foamy cytoplasm (*arrows*) due to accumulation of GM2-ganglioside (H & E, ×1,000)

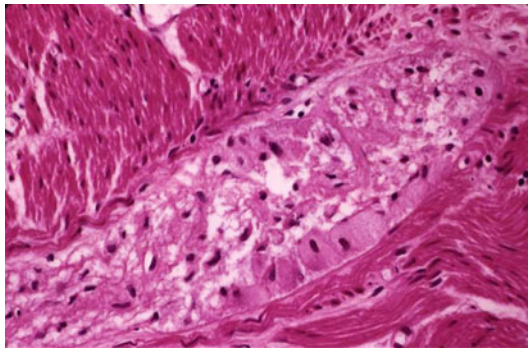

Fig. 2 Myenteric plexus of the rectum (H & E, ×400) showing many enlarged ganglion cells with abundant foamy cytoplasm due to ganglioside storage. Rectal biopsy can be a good source of neurons in confirming neuronal storage disease. In this patient, Tay-Sachs disease was confirmed by electron microscopic examination of ganglion cells

Tetrasomy 9p Syndrome

Contents

Tetrasomy 9p syndrome, a clinically diagnosable condition, is a rare cytogenetic disorder characterized by tetrasomy 9p associated with a distinctive patterns of multiple congenital anomalies. In *1973*, Ghymers et al. (1973) first described the syndrome.

Synonyms and Related Disorders

Supernumerary isochromosome 9p syndrome

Genetics/Basic Defects

1. Caused by de novo supernumerary isodicentric chromosome 9p (presence of four copies of the short arm of the chromosome 9) (9pter to 9q2101) (Abe et al. 1977)
    1. Pure tetrasomy 9p
    2. Tetrasomy involving the varying segment of the short arm of chromosome 9
2. Cytogenetic types of tetrasomy 9p
    1. Presence of an extra dicentric chromosome 9 consisting entirely of 9p
    2. Presence of an extra dicentric chromosome 9 consisting of 9p and the proximal part of 9q
    3. Mosaicism involving tetrasomy 9p: mosaic of i(9p) cells
    4. Nonmosaic partial tetrasomy involving all of the short arms and asymmetrical segments of the long arms (Shapiro et al. 1985)
3. Hypotheses proposed to explain tetrasomy 9p
    1. A meiosis I disturbance with nondisjunction and rearrangement in two of the four chromatids of a bivalent 9, resulting in the formation of an isochromosome 9p
    2. Meiosis II nondisjunction followed by rearrangements (isochromosome formation) with duplication of the short arm and loss of the acentric long arm at the subsequent mitosis
    3. Dicentric versus monocentric (de Azevedo Moreira et al. 2003)
        1. Using conventional cytogenetics and banding techniques revealed an additional dicentric 9p chromosome in most cases.
        2. Using molecular studies using a chromosome 9 classic satellite probe shows an error in the division of centromere 9 by a double-break event, resulting in the formation of a monocentric isochromosome 9p.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_226

Clinical Features

1. Tetrasomy 9p: a unique, clinically recognizable syndrome (Jalal et al. 1991; Fryns 1998)
2. Craniofacial abnormalities (El Khattabi et al. 2015)
    1. Delayed closure of the anterior fontanel
    2. Ocular hypertelorism
    3. Telecanthus
    4. Strabismus
    5. Enophthalmos/microphthalmia
    6. Epicanthal folds
    7. Prominent beaked or bulbous nose
    8. Down-turned corners of the mouth
    9. Microretrognathia
    10. Low-set, malformed ears
    11. Cleft lip/palate
    12. High-arched palate
3. Cardiac anomalies
    1. Ventricular septal defect
    2. Atrial septal defect
    3. Patent ductus arteriosus
    4. Persistent left superior vena cava
    5. Double outlet of the right ventricle
    6. Hypoplastic right ventricle
    7. Hypoplastic left heart ventricle
4. Lung anomalies
    1. Lung hypoplasia
    2. Abnormal lobulation of the lung
5. Renal anomalies
    1. Renal hypoplasia
    2. Multicystic dysplasia
    3. Hydroureter
    4. Hydronephrosis
6. Genital anomalies
    1. Cryptorchidism
    2. Genital hypoplasia
    3. Micropenis
    4. Hypoplastic shawl-like scrotum
    5. Ambiguous genitalia
    6. Duplications 9p may result in impairment of ovarian function (Cuoco et al. 1982)
7. Gastrointestinal anomalies
    1. Intestinal malrotation
    2. Hirschsprung disease (Melaragno et al. 1992)
8. CNS anomalies
    1. Psychomotor retardation
    2. Hypotonia
    3. Microcephaly
    4. Brachycephaly
    5. Hydrocephalus
    6. Cerebral hypoplasia
    7. Dandy-Walker cyst
    8. Absence of olfactory bulbs
    9. Hypoplastic cerebellum
9. Skeletal anomalies
    1. Growth retardation
    2. Short stature
    3. Short neck
    4. Dysplastic fingernails
    5. Limb anomalies
    6. Clinodactyly of the fifth fingers
    7. Club feet
    8. Articular dislocations
    9. Shortened hands and feet
10. Other features
    1. Single umbilical artery
    2. Failure to thrive
    3. Redundant skin
    4. Widely spaced nipples
    5. Single palmar crease
    6. Sacral dimple
    7. Mosaic tetrasomy 9p predisposes to pediatric-onset inflammatory myositis and lupus-like features (Frémond et al. 2015)
11. The severity of the phenotype correlates with size of the tetrasomic region and the degree of tissue mosaicism for the tetrasomy 9p.
12. A case of nonmosaic tetrasomy 9p with long-term survival reported (Tonk 1997)
13. Cases of isochromosome tetrasomy 9p mosaicism associated with a normal phenotype reported (Papoulidis et al. 2012)

Diagnostic Investigations

1. Cytogenetic studies to identify supernumerary marker chromosomes (Tan et al. 2007)
    1. Conventional and high-resolution analyses
    2. A whole-chromosome paint probe for chromosome 9 to identify the supernumerary chromosome, using the fluorescence in situ

hybridization (FISH) technique (Callen et al. 1992; Crolla et al. 1998; Eggermann et al. 1998)
3. Microdissection and reverse FISH (micro-FISH) (Mahjoubi et al. 2005; de Pater et al. 2006)
4. Multiplex-FISH (M-FISH) technique (Uhrig et al. 1999)
5. Centromere-specific multicolor-FISH assays (Nietzel et al. 2001)
6. AcroM-FISH technique (Langer et al. 2001): involves a newly generated probe mix, which consists of painting probes for all acrocentric chromosomes, centromere probes for chromosomes 13/21, 14/22, 15, and a probe specific for rDNA, each labeled with a specific combination of fluorochromes. This probe mix is sufficient to characterize approximately 80% of all SMCs (supernumerary marker chromosomes). For the other 20% of SMCs, chromosomes can be analyzed in a second hybridization by multicolor karyotyping, for example, multiplex FISH (M-FISH), to check for the presence of euchromatin of other chromosomes.
7. Tissue-limited mosaicism (Lloveras et al. 2004): Isochromosome 9p shows a strong propensity to tissue-limited mosaicism. It occurs predominantly in peripheral blood cultures, often at a lower frequency or even absent in skin, amniotic fluid, or chorionic villous cell cultures. Tissue-limited nature of mosaicism may render prenatal detection of this condition very difficult. This cytogenetic interpretation was substantiated by quantitative measurement of erythrocyte galactose-1-P-uridyltransferase (GALT) activity, which is consistent with the expression of four normal GALT genes (Papenhausen et al. 1990)
8. Array CGH is able to detect mosaicism, establish the euchromatic content of supernumerary marker chromosomes, and identify imbalances elsewhere in the genome allowing more accurate counselling and prognosis for patients (Shehab et al. 2011)

2. Echocardiography for cardiovascular malformations
3. Radiography
    1. Microcephaly
    2. Hypertelorism
    3. Hypoplastic first and 12th ribs
    4. Kyphoscoliosis
    5. Clinodactyly and brachymesophalangy of the fifth fingers
    6. Delayed ossification of pubic bones and ischiopubic synchondrosis
    7. Delayed ossification of femoral heads
    8. Spina bifida occulta
    9. Generalized osteoporosis
4. Ultrasonography of renal abnormalities

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased
    2. Patient's offspring: patient not surviving to reproductive age
2. Prenatal diagnosis
    1. Ultrasonography (Dhandha et al. 2002; Tan et al. 2007; Nakamura-Pereira et al. 2009)
        1. Increased nuchal translucency in the first trimester
        2. Intrauterine growth retardation
        3. Genitourinary/renal anomalies
        4. Cleft lip/palate
        5. CNS anomalies
            1. Dandy-Walker malformation
            2. Ventriculomegaly
            3. Hypoplastic/absent vermis
            4. Agenesis of corpus callosum
        6. Limb malformations: bilateral club feet
        7. Vertebral anomalies
        8. Cardiac anomalies
        9. Genitourinary anomalies
        10. Polyhydramnios/oligohydramnios
        11. Absent nasal bone as a marker of tetrasomy 9p (Podolsky et al. 2011)
    2. 3D ultrasonography at 16 weeks' gestation (Lazebnik and Cohen 2015)
        1. Widely open metopic suture and anterior fontanel

2. Abnormal profile due to micrognathia and low-set posteriorly rotated ears
3. Abnormal connection between the posterior fossa and the fourth ventricle, suggesting Dandy-Walker malformation of the cerebellum
4. Echogenic focus in the fetal heart
5. Single umbilical artery
6. Cervical spine abnormality as well as 11 bilateral ribs
7. Bilateral rocker bottom clubfoot

3. Chromosome analysis to demonstrate tetrasomy of the short arm of chromosome 9 (+i(9)(p10)) of amniocytes (Tang et al. 2004), CVS, or fetal blood from cordocentesis (Schaefer et al. 1991): Microdissection and pre-G-banded FISH is important in determining the origin of supernumerary marker chromosome in prenatal diagnosis
4. Prenatal diagnosis of mosaic tetrasomy 9p (Wang et al. 2015)
   1. Karyotype: 47,XX,+idic(9)(q12)/47,XX,+idic(9)(q12)
   2. Partial G-banded and C-banded karyotype showed two normal chromosomes 9 and the i psu dic(9)(pter → q12::q12 → pter)
   3. FISH with subtelomere probe: A chromosome 9p specific subtelomeric probe (TelVysion 9p, green signal) (Vysis, Downers Grove, IL, USA) demonstrates green signals on both ends of the supernumerary idic(9)
5. Mosaic tetrasomy 9p at amniocentesis (Chen et al. 2014)
   1. Array comparative genomic hybridization analysis of uncultured amniocytes detected a genomic gain at 9p24.3-9q21.11.
   2. Interphase fluorescence in situ hybridization analysis of uncultured amniocytes using a 9p24.3-specific probe RP11-31 F19 (spectrum red) showed four red signals in 47.1% (49/104 cells) in uncultured amniocytes.
   3. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47, XX, +idic(9)(pter → q21.11::q21.11 → pter)[4]/46,XX[20] and 16.7% (4/24 colonies) mosaicism for tetrasomy 9p.
   4. Quantitative fluorescent polymerase chain reaction confirmed a maternal origin of tetrasomy 9p.
   6. Tissue specific mosaicism in tetrasomy 9p which rendered the anomaly undetectable by CVS. It also demonstrates the mild end of the clinical spectrum associated with tetrasomy 9p (Grass et al. 1993)
3. Management
   1. Early intervention programs for mild developmental delay with minor anomalies
   2. Supporting care for severe cases with early death

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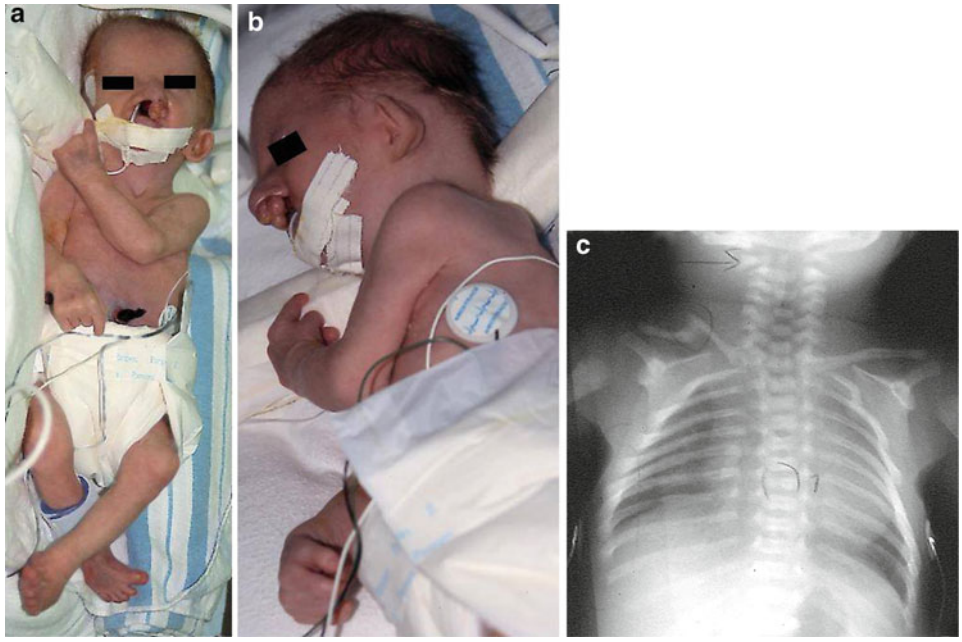

Fig. 1 (**a**–**c**) An infant (**a**, **b**) with tetrasomy 9p syndrome presenting with widened anterior fontanel, microbrachycephaly, a broad nasal root, telecanthus, bilateral cleft lip and palate, retromicrognathia, small eyes, low-set lop ears, and a skin tag on the antihelix of the right ears. In addition, the infant had short neck with excess nuchal fold, bilateral webbing of the anterior axillary folds, pectus excavatum, congenital heart defects, right hydronephrosis, diastasis recti with an umbilical hernia, a right inguinal hernia, sacral dimple with a tag, micropenis, bilateral metatarsus adductus, bilateral transverse palmar creases, clinodactyly of the fifth fingers, short thumbs, and hypoplastic nails. Chest X-ray (**c**) showed hemivertebrae in the thoracic spine and fractured right clavicle with callus formation. A rectal biopsy confirmed the diagnosis of Hirschsprung disease

Thalassemia

Contents

The term thalassemia was first applied to the anemias encountered frequently in people of the Italian and Greek coasts and nearby islands. The term now refers to a group of inherited disorders of globin chain synthesis. Thalassemia comprises of a group of hemoglobinopathies, which are classified according to the specific globin chain (α or β) whose synthesis is impaired. Thus, α-thalassemia and β-thalassemia are depression of synthesis of the respective chain.

Synonyms and Related Disorders

Alpha-thalassemia (Hb H disease or alpha-thalassemia intermedia, Hb Bart's hydrops fetalis, or alpha-thalassemia major); Beta-thalassemia (beta-thalassemia major or Cooley anemia or homozygous beta-thalassemia, beta-thalassemia intermedia or compound heterozygote, beta-thalassemia minor or beta-thalassemia trait

Genetics/Basic Defects

1. Inheritance
   1. Autosomal recessive.
   2. Most β-thalassemias are inherited in a Mendelian recessive fashion, but there is a subgroup of β-thalassemia alleles that behave as dominant negatives (Thein 2013).
2. α-Thalassemia syndromes (Kelly 2012)
   1. α-Thalassemia occurs when there is a defect or deletion in one or more of the four genes responsible for α-globin production, leading to insufficient or absent α-globin synthesis.
   2. A defect or deletion of one α-globin gene leads to a condition called silent trait that is completely asymptomatic.
   3. The presence of two defective α-globin genes causes α-thalassemia trait, manifesting as a mild microcytic, hypochromic anemia. Hemoglobin electrophoresis can aid in diagnosis, but only during the neonatal period, when hemoglobin Bart is detected at 3–10%. Because hemoglobin F predominates at birth, impaired production of α-globin chains results in excess unpaired γ-globin chains that form tetramers, making hemoglobin Bart. After birth, as the infant's dominant hemoglobin transitions from F to A, γ-globin chain production subsides, and hemoglobin Bart is

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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no longer detected. No treatment is necessary for α-thalassemia trait.

4. The presence of three defective α-globin genes causes hemoglobin H disease. Hemoglobin Bart is detected (15–30%) on electrophoresis during the neonatal period. Later in life, when hemoglobin A should predominate, excess unpaired β-globin chains accumulate and form tetramers, making hemoglobin H. Unstable hemoglobin H precipitates in circulating red blood cells, leading to hemolysis. Patients have microcytic, hypochromic anemia and hepatosplenomegaly and also may have bony abnormalities resulting from marrow expansion, as well as cholelithiasis and icterus. Transfusion usually is not required, but occasionally patients require splenectomy.
5. Hydrops fetalis occurs when all four α-globin genes are defective or absent. In the affected fetus, no α-globin chains are synthesized, and hemoglobin Bart is the predominant hemoglobin. Oxygen delivery to tissues is severely impaired, and the affected fetus has profound anemia, hepatosplenomegaly, and anasarca and usually is stillborn or dies shortly after birth. Lifelong transfusion therapy is required for those infants who survive.

3. α-Thalassemia (Vichinsky 2010)
    1. Normal fetal hemoglobin synthesis
        1. Early in gestation, embryonic hemoglobins (Gower1, Gower2, and Portland), which do not contain α-globin chains, are the predominant hemoglobins.
        2. They are rapidly replaced by fetal and then adult hemoglobin, which contain α-globin chains.
        3. Therefore, α-thalassemia mutations become phenotypically evident by 12 weeks of gestation.
    2. Synthesis of α-chains is directed by four α-genes, two on each chromosome 16.
    3. α-Thalassemia represents a group of conditions with reduced or absent synthesis of one to all four of α-globin genes.
        1. α-Thalassemia-2 (α-/αα): resulting from deletion of one of the two α-globin genes.
        2. α-Thalassemia-1 (−−/αα): resulting from deletion of both α-globin genes.
        3. Hb H disease (−−/-α): resulting from deletion of three α-globin genes.
        4. Hb Bart's hydrops fetalis (−−/−−): resulting from deletion of all four α-globin genes. Physiologically nonfunctional homotetramers γ_4 and β_4 make up most of the hemoglobin in the erythrocytes in infants with the Bart's hydrops fetalis syndrome.
    4. When both α-genes on a single chromosome are inactive, the designation α^o-thalassemia is used. When there is some production of α-globin chains, α^+-thalassemia is designated.
4. β-Thalassemia
    1. Synthesis of β-chains: directed by a single β-gene on each chromosome 11
    2. Caused by the reduced (β^+) or absent (β^o) synthesis of the β-globin chains of the hemoglobin tetramer which is made up of two α-globin and two β-globin chains ($\alpha_2\beta_2$)
    3. Mutations in β-thalassemia
        1. In contrast to the α-thalassemias, most of the common β-thalassemia mutants are caused by point mutations rather than by gene deletion.
        2. Single base-pair mutations in the DNA alter processing of messenger RNA: most common.
        3. Chain terminator defects.
        4. Frameshift mutations.
        5. Polyadenylation mutations.
        6. Promoter mutations.
    4. β^o-Thalassemia
        1. The mutations prevent β-globin chain synthesis entirely.
        2. Absent β-globin synthesis in β^o-thalassemia homozygotes.
        3. Accounts for about one-third of thalassemia patients.

5. β^{+}-Thalassemia
    1. The mutations prevent β-chain synthesis partially.
    2. β-Globin synthesis reduces to 5–30% of normal levels in β^{+}-thalassemia homozygotes.
6. β^{+}/β^{o}-Thalassemia compound heterozygotes

5. Pathogenesis (Yaish 2010)
    1. Basic defect in all types of thalassemia: imbalanced globin chain synthesis.
    2. A decrease in the rate of production of a certain globin chain (α, β, γ, δ) impedes hemoglobin (Hb) synthesis and creates an imbalance with the other globin chain that normally produce globin chains.
    3. Consequences of impaired production of globin chains.
        1. Result in less Hb deposit in each RBC, leading to hypochromasia.
        2. Deficiency in Hb causes RBCs to be smaller, leading to the classic hypochromic microcytic features of thalassemia.
6. Phenotype-genotype correlation (Origa 2015)
    1. Homozygosity or compound heterozygosity for β-thalassemia most commonly results in the clinical phenotype of transfusion-dependent thalassemia major.
    2. However, a consistent proportion of homozygotes develop milder forms, called thalassemia intermedia, which range in severity from thalassemia major to the β-thalassemia carrier state.
    3. Ascertained molecular mechanisms leading to thalassemia intermedia.
        1. β-Thalassemia mutations
            1. Mild mutation
            2. Silent mutation
            3. Mild/silent mutation
        2. Coinherited α-thalassemia
            1. Single α-globin gene deletion (-α/αα)
            2. Deletion of two α-globin gene (-α/-α or – /αα)
            3. Point mutations of the major α-2-globin gene
        3. Genetic determinant of high Hb F production
            1. Due to the β-thalassemia mutation per se (δβ-thalassemia, β-promoter deletion)
            2. Coinherited Agamma or Ggamma promoter mutation (−158 Ggamma (A → T); −196 Agamma (C → T))
            3. Heterocellular HPFH, BCL11A on chromosome 2, and HBS1L-MYB region on chromosome 6

Clinical Features

1. α-Thalassemia (Harteveld and Higgs 2010; Origa et al. 2013)
    1. The most common genetic disorder of hemoglobin synthesis, affects up to 5% of the world's population (Vichinsky 2010)
    2. Found in people of African descent, Indochina, Malaysia, and China
    3. Clinical classification of α-thalassemia (Galanello and Cao 2011)
        1. Silent carrier: clinically and hematologically normal
        2. Thalassemia trait
            1. Microcytosis
            2. Hypochromia
            3. Mild anemia
        3. Hb H disease
            1. Moderate to severe microcytic, hypochromic, hemolytic anemia
            2. Mild jaundice
            3. Moderate hepatosplenomegaly
        4. Hb Bart's hydrops fetalis syndrome
            1. Severe anemia
            2. Generalized edema
            3. Ascites
            4. Marked hepatosplenomegaly
            5. Skeletal and cardiovascular malformations, usually death in utero
    4. Severity of resulting anemia quite variable ranging from asymptomatic carriers to a fatal in utero disease: depends on the number of functioning α-genes
        1. α-Thalassemia-2 or silent carrier α-thalassemia (α-/αα) (deficiency of only one globin gene)

1. Twenty-five percent of African Americans
2. 3.4% of Greek Americans
3. Slight microcytic red blood cells
4. Borderline or minimal anemia

2. α-Thalassemia-1 or α-thalassemia trait (– /αα)(deficiency of two globin genes)
   1. Fifteen to twenty percent of Thai.
   2. Mildly anemic.
   3. Microcytic red blood cells.
   4. Slight variation in red blood cell size.
   5. Mild splenomegaly.
   6. Work capacity not impaired.
   7. Same phenotypic effect in the individual homozygous for α-thalassemia-2 (α-/α-): This form is much more common in black populations.
3. Hb H disease or α-thalassemia intermedia (−−/-α) (deficiency of three globin genes)
   1. One percent of Thai.
   2. Significant hypochromic anemia in the neonatal period.
   3. Microcytic anemia.
   4. Reticulocytosis.
   5. Jaundice.
   6. Splenomegaly (may be severe and occasionally complicated by hypersplenism).
   7. Growth retardation may be seen in children.
   8. Hemolysis precipitated by infections or oxidant drugs (e.g., iron, sulfonamides).
   9. Leg ulcers.
   10. Gallstones.
   11. Folic acid deficiency.
   12. Needs occasional transfusions, splenectomy, or avoidance of precipitating drugs.
   13. Severity of clinical features: related to the molecular basis of the disease. Patients with nondeletional types of Hb H disease are more severely affected than those with the common deletional types of Hb H disease.
4. Hb Bart's hydrops fetalis or α-thalassemia major (−−/−−) (deficiency of all four globin genes)
   1. Most severe form of α-thalassemia
   2. Incompatible with life unless intrauterine blood transfusion is given because not enough functional hemoglobin is produced to sustain tissue oxygenation
   3. Profound oxygen deprivation in utero with resulting heart failure (hydrops fetalis)
   4. Stillborn or die soon after birth
   5. Pale edematous infant with signs of cardiac failure (edema and ascites) and prolonged intrauterine anemia
   6. Massive hepatosplenomegaly
   7. Severe erythroblastic anemia
   8. Retardation in brain growth
   9. Skeletal and cardiovascular anomalies
   10. Enlargement of the placenta

2. β-Thalassemia (Cao and Galantello 2010; Kelly 2012; Origa 2015)
   1. Found largely in people of African and Mediterranean descent, Far East, Middle East, and the Asian subcontinent
      1. Highest incidence
         1. Cyprus (14%)
         2. Sardinia (12%)
         3. Southeast Asia
      2. The high gene frequency of beta-thalassemia in these regions
         1. Most likely related to the selective pressure from *Plasmodium falciparum* malaria, as it is indicated by its distribution quite similar to that of present or past malaria endemics. Carriers of beta-thalassemia are indeed relatively protected against the invasion of *Plasmodium falciparum*.
         2. However, because of population migration and, to a limited extent, slave trade, beta-thalassemia is, at present, also common in Northern Europe, North and South America, Caribbean, and Australia.

2. Classification of beta-thalassemia (Galanello and Origa 2010)
    1. Beta-thalassemia
        1. Thalassemia major
        2. Thalassemia intermedia
        3. Thalassemia minor
    2. Beta-thalassemia with associated Hb anomalies
        1. HbC/beta-thalassemia
        2. HbE/beta-thalassemia
        3. HbS/beta-thalassemia (clinical condition more similar to sickle cell disease than to thalassemia major or intermedia)
    3. Hereditary persistence of fetal Hb and beta-thalassemia
    4. Beta-thalassemia associated with other manifestations
    5. Beta-thalassemia-trichothiodystrophy
    6. X-linked thrombocytopenia with thalassemia
3. Clinical features dependent on reduced (β^+) or absent (β^o) synthesis of β-globin
    1. β-Thalassemia major (also known as Cooley's anemia or homozygous β-thalassemia)
        1. Due to inheritance of two β-thalassemia alleles, one on each copy of chromosome 11.
        2. Generally recognized to be a homozygous state for whichever thalassemia gene is involved.
        3. Clinically a severe disorder.
        4. Infants born free of significant anemia, protected by prenatal Hb F production.
        5. Onset: 6–12 months.
        6. Diagnosis: evident by 2 years of age.
        7. Manifestations in early childhood: anemia, pallor, growth retardation, tiredness, abdominal swelling due to hepatosplenomegaly, infection, and jaundice.
        8. Manifestations in childhood and adult: severe anemia, infection, tiredness, growth retardation, distinctive facies, hepatosplenomegaly, cardiomegaly, abdominal pain, leg ulcers, osteoporosis, and iron overload.
        9. At significant risk for developing overwhelming, often fatal infection after splenectomy (postsplenectomy syndrome).
        10. Severe anemia usually necessitating chronic blood transfusions.
        11. Craniofacial manifestation of β-thalassemia major (Javid and Said-Al-Naief 2015): The most characteristic oral and maxillofacial/head and neck skeletal changes are the upslanted eyes and the so-called chipmunk faces, with prominent frontal bossing, prominent cheekbones, and nasal bridge depression, accompanied by hypertrophied maxilla (often with exposure of the maxillary teeth) and mandible caused by excessive active bone marrow hyperplasia. In the maxilla, in particular, the large, widened medullary spaces and trabeculae radiographically mimic a "chicken wire" radiographic pattern.
        12. Prognosis: average survival of children with untreated thalassemia major (<4 years)
    2. β-Thalassemia intermedia (compound heterozygotes)
        1. Due to inheritance of two β-thalassemia mutations (one mild and one severe or two mild mutations) or occasionally due to inheritance of complex combinations such as α-β-thalassemia.
        2. Affected individuals: either compound heterozygotes for two different thalassemia genes or heterozygotes for a structural variant plus a thalassemia gene. Homozygotes for the milder β^+-thalassemia also have thalassemia intermedia.
        3. Less severe clinical phenotype: cardiomegaly, osteoporosis, fractures, arthritis, and splenomegaly in some patients.

4. Neurological complications of beta-thalassemia: Cognitive impairment, abnormal findings on evoked potentials, complications due to extramedullary hematopoiesis, cerebrovascular disease, and peripheral neuropathy comprise the broad spectrum of neurological involvement (Nemtsas et al. 2015).
5. Significant anemia but usually do not require chronic blood transfusions.

3. β-Thalassemia minor (also known as β-thalassemia trait or heterozygous β-thalassemia)
   1. Due to presence of a single β-thalassemia mutation and a normal β-globin gene on the other chromosome
   2. Clinically asymptomatic but may have mild or minimal anemia
4. Silent carrier β-thalassemia
   1. No symptoms except for possible low RBC indices.
   2. Mutation causing thalassemia is very mild and represents β + -thalassemia.

3. Practical guide to the diagnosis of thalassemia (Dumars et al. 1996)
   1. The first involves any patient with a low mean corpuscular volume (MCV) with or without anemia.
   2. The second is a neonatal screening result indicating possible presence of thalassemia.
   3. Finally, evaluation for thalassemia should be considered in the context of family planning or pregnancy in patients whose ethnicity indicates origin from high-risk geographic areas.

Diagnostic Investigations

1. Screening tests for thalassemias.
   1. Low MCV (mean corpuscular volume)
      1. Increased Hb A_2 and/or Hb F: indicate β-thalassemia syndrome
      2. Normal Hb A_2 and Hb F, and ferritin >20 ng/mL: suggest possible α-thalassemia syndrome
   2. Normal MCV, normal electrophoresis: thalassemia syndrome unlikely
2. α-Thalassemia (Chen 1992; Origa et al. 2013): More difficult to diagnose because characteristic elevations in Hb A_2 ($\alpha_2\delta_2$) or Hb F ($\alpha_2\gamma_2$), seen in β-thalassemia, do not occur.
   1. α-Thalassemia-2
      1. Laboratory notation: FA + Bart's
      2. Small amount of Hb Bart's (1–2%) in affected infants at birth
      3. Remainder of the hemoglobin: Hb F and Hb A ($\alpha_2\beta_2$)
      4. Hb F and Hb Bart's: disappear after a few months of age
      5. Minimal microcytosis: remains
   2. α-Thalassemia-1
      1. Laboratory notation: FA + Bart's (impossible to differentiate the two forms of α-thalassemia from the electrophoretic pattern).
      2. Slightly larger amount of Hb Bart's in cord blood (3–5%).
      3. Hb F and Hb Bart's: disappear after birth.
      4. Unequivocal microcytosis: Mean red cell volume of 65–70 fl/cell remains.
      5. Abnormally low Hb A_2 proportion.
   3. Hb H disease
      1. Reduction in α-chain does not affect the production of β-chain which is produced in excess and tends to form tetramers (β^4 or Hb H).
      2. Hb A + Hb H (β^4) + Hb Bart's (γ^4).
      3. Presence of Heinz bodies: inclusions representing β-chain tetramers (Hb H), which are unstable and precipitate in the RBC, giving the appearance of a golf ball
   4. Hb Bart's hydrops fetalis
      1. Hypochromic macrocytes with nucleated red blood cells
      2. γ^4 (Bart's hemoglobin): nonfunctional as an oxygen transporter
   5. Targeted mutation analysis
      1. Deletion of a single α-globin gene (α^+-thalassemia mutations)

2. Deletion of both α-globin genes on one chromosome (α°-thalassemia mutations)
3. Sequence variant $Hb^{Constant\ Spring}$
6. Sequence analysis: used to identify point mutations (including rare termination codon mutations and hyperunstable α-globin variants) in the coding regions of HBA1 and HBA2 when an α-globin deletion is not identified and suspicion for α-thalassemia is high
7. Deletion/duplication analysis can be used to detect common, rare, and/or novel deletions and duplications involving HBA1 and HBA2.

3. β-Thalassemia (Chen 1992)
   1. β-Thalassemia major
      1. Small, thin, and distorted red blood cells containing markedly reduced amounts of hemoglobin
      2. Peripheral blood smear
         1. Severe microcytic hypochromic anemia (no anemia at birth)
         2. Anisocytosis
         3. Poikilocytosis (speculated teardrop and elongated cells)
         4. Abundant nucleated red cells (i.e., erythroblasts)
         5. Occasional immature leukocytes
      3. Hemolytic anemia
      4. Hemoglobin profile: predominant Hb F
      5. In patient with homozygous β^{o}-thalassemia: absent Hb A with normal amounts of Hb A_2
      6. In newborn with β^{+}-thalassemia: Hb F (about 90%) decreases with advancing age but always considerably higher than normal (10–90%)
   2. β-Thalassemia intermedia (Haddad et al. 2014)
      1. Intermediate Hb concentration (7–10 g/dL)
      2. Microcytic hypochromic anemia
      3. HPLC electrophoresis
         1. Hb A2 (>4%)
         2. Hb F (5–99%)
      4. Molecular characteristics
         1. Mild/silent mutation.
         2. Coinheritance of α-thalassemia may be present.
         3. Hereditary persistence of Hb F, δ-β-thalassemia, Gγ XMN1 polymorphism.
   3. β-Thalassemia minor
      1. Mild hypochromic microcytosis (Rucknagel 1992)
      2. Target cells
      3. Mild to minimal anemia (hemoglobin concentration average 1–2 g/dL below normal)
      4. Elevation of Hb A_2 and Hb F (70–99%) during early years of life
      5. Anemia worsen during pregnancy
4. Imaging studies
   1. Chest X-ray to evaluate cardiac size and shape
   2. Skeletal survey
      1. Skeletal response to marrow proliferation
         1. Expanding marrow space
         2. Thinning of cortical bone
         3. Resorption of cancellous bone
         4. Resulting in generalized loss of bone density
         5. Frequent small lucencies resulting from focal proliferation of marrow
         6. "Periosteal response" caused by perforation of the cortex by hypertrophic and hyperplastic marrow subperiosteally
      2. Classic facies observed in thalassemia major
         1. Classic "hair-on-end" appearance of the skull
         2. Maxilla overgrowth resulting in maxillary overbite
         3. Prominent upper incisors
         4. Separation of the orbits
      3. Various bone deformities seen in ribs, long bones, and flat bones
      4. Premature fusion of the epiphyses
   3. MRI/CT scans to evaluate the amount of iron in the liver in patients on chelation therapy
5. Carrier screening
   1. α-Thalassemia (Vichinsky 2010)
      1. Commonly, microcytosis using an MCV <82 fL and/or hypochromia (MCH

<27 pg) is often used as a population screening technique.
1. Anemia is unreliable and is often not present in adults with two α-globin gene deletions.
2. Once iron deficiency is ruled out or corrected, microcytosis should be further evaluated in the individual and his or her partner in order to determine their risk for hydrops.

2. Molecular diagnosis for α-globin mutations: essential for at-risk couples.

2. β-Thalassemia
1. Ongoing in several at-risk populations in the Mediterranean (Cao et al. 2002).
2. Carrier testing relies on hematological analysis: When the hematological analysis indicates a beta-thalassemia carrier state, molecular genetic testing of *HBB* can be performed to identify a disease-causing mutation.

6. Molecular genetic testing for α- and β-thalassemias
1. α-Thalassemia (Origa et al. 2013)
1. *HBA1*, the gene encoding α_1-globin, and *HBA2*, the gene encoding α_2-globin, are the two genes most commonly associated with α-thalassemia.
2. Molecular genetic testing of *HBA1* and *HBA2* detects deletions in about 90% and point mutations in about 10% of affected individuals.

2. β-Thalassemia (Origa 2015)
1. Molecular genetic testing of the gene encoding the hemoglobin subunit beta (HBB): available clinically
1. Targeted mutation analysis
2. Sequence analysis

Genetic Counseling

1. Recurrence risk (Chen 1992)
1. α-Thalassemia
1. Patterns of inheritance of the α-thalassemia when both parents are α-thalassemia-1 (−−/αα).
1. 25% normal
2. Fifty percent α-thalassemia-1
3. Twenty-five percent Hb Bart's (hydrops fetalis)

2. Patterns of inheritance of the α-thalassemia syndrome when one parent is α-thalassemia-1 (−−/αα) and the other parent is α-thalassemia-2 (α-/αα).
1. Twenty-five percent normal
2. Twenty-five percent α-thalassemia-1
3. Twenty-five percent α-thalassemia-2
4. Twenty-five percent Hb H disease

3. If the carrier of α^+-thalassemia is a homozygote, clearly, the risk of Hb H disease is 1:2 (50%) (Harteveld and Higgs 2010).
4. Patient's offspring: not increased unless the spouse is a carrier.
5. Twenty-five percent of African Americans have heterozygous α-thalassemia-2 (α-/αα). Thus, 1.5% are homozygotes for α-thalassemia-2 (α-/α-). But since the more severe α-thalassemia-1 is not present, subsequent children are not at risk of having Hb H or Bart's hydrops fetalis.

2. β-Thalassemia (Galanello and Origa 2010)
1. Patient's sib: 25%
2. Patient's offspring: not increased unless the spouse is a carrier

2. Prenatal diagnosis: available to all families at risk of either severe α-thalassemia or β-thalassemia
1. α-Thalassemia
1. Ultrasonography (Tongsong et al. 1996).
1. Hepatosplenomegaly (>90%)
2. Cardiomegaly (>90%)
3. Edematous placenta (>90%)
4. Ascites (>90%)
5. Oligohydramnios (82%)
6. Subcutaneous edema (75%)
7. Decreased fetal movement (74%)
8. Cord edema (63%)
9. Enlarged umbilical vessel (62%)
10. Pericardial or pleural effusion (15%)

2. Sonographic markers of fetal α-thalassemia major (Li et al. 2015).
1. Classic sonographic characteristics of hydrops fetalis syndrome do not

appear until the late second trimester (Tongsong et al. 1996), but it has been reported that some cases of hydrops fetalis can be identified by sonography in the early second trimester (Lam et al. 1997).
2. Moreover, cardiovascular responses secondary to α-thalassemia major can take effect in the first trimester, bringing more blood flow to vital organs such as the heart and brain (Ghosh et al. 1994; Lam et al. 1999; Picklesimer et al. 2007).
3. Therefore, many sonographic markers may be observed before the onset of fetal hydrops (Ghosh et al. 1987) and could be used to detect fetuses with α-thalassemia major.
4. Among all markers, the cardiothoracic ratio, placental thickness, and middle cerebral artery PSV (peak systolic velocity) are the most studied ones.

3. Molecular hybridization technique to detect complete absence of α-genes in fetal amniocytes in a pregnancy at risk for homozygous α-thalassemia-1 and the hydrops fetalis syndrome (Dozy et al. 1979).
   1. The DNA obtained from cultured amniotic fluid cells was studied by hybridization with globin cDNA in solution and on filters (Southern technique).
   2. Both analyses demonstrated no alpha-globin structural genes.
   3. Following termination of the pregnancy, the diagnosis was established by the presence of only hemoglobins Bart's (gamma 4) and Portland (zeta 2 gamma 2) in the fetal blood.
4. Quantitative polymerase chain reaction for the rapid prenatal diagnosis of homozygous α-thalassemia (Hb Bart's hydrops fetalis).
5. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the pathogenic variants have been identified (Origa et al. 2013).

2. β-Thalassemia
   1. Available to couples who are carriers of β-thalassemia and their hemoglobin gene mutations have been identified by DNA analysis.
   2. Direct DNA analysis by molecular hybridization methods for the presence of the thalassemia mutation from fetal cells obtained by amniocentesis and chorionic villus biopsy.
   3. Detection of point mutations in single gene disorders by enriching fetal cells from maternal blood by magnetic cell sorting followed by isolation of pure fetal cells by microdissection. In two pregnancies at risk for sickle cell anemia and beta-thalassaemia, we successfully identified the fetal genotypes (Cheung et al. 1996). Thus, prenatal diagnosis of single gene disorders by recovering fetal cells from maternal circulation appears to be a feasible approach.
   4. Approach to prenatal diagnosis complicated by presence of the heterogeneity of thalassemia mutations.
   5. Preimplantation genetic diagnosis available for at-risk pregnancies requires prior identification of the disease-causing mutations in the family (Galanello and Origa 2010).
3. Preimplantation genetic diagnosis (Cao and Kan 2013)
   1. Performed either by biopsy of one to two blastomeres in eight-cell embryos after in vitro fertilization (by intracytoplasmic sperm injection)
   2. By biopsy of trophectoderm cells from blastocyst (Kuliev et al. 1998; Kokkali et al. 2007).
4. Preconceptional diagnosis (Cao and Kan 2013)
   1. Based on the analysis of the first polar body of unfertilized eggs followed by analysis of the second polar bodies after fertilization, which is performed to avoid

misdiagnosis resulting from recombination during the first meiosis (Verlinsky et al. 1990).
2. Diagnosis was obtained by multiple nested PCR analysis to detect the mutations as well as polymorphic alleles at the β-globin cluster (Kuliev et al. 2011; Zachaki et al. 2011).
3. HLA typing of the embryo to select a nonaffected fetus HLA compatible with a previous affected sibling was recently proposed (Kuliev et al. 2011).

3. Management
   1. α-Thalassemia (Segel et al. 2002)
      1. No therapy necessary for patients with α-thalassemia trait
      2. Avoid exposure to oxidant medications (e.g., iron, sulfonamides) which accelerate precipitation of Hb H and exacerbate hemolysis
      3. Prompt treatment of infection especially in postsplenectomy
      4. Hb H disease
         1. Folate supplementation
         2. Chronic transfusion therapy (consider iron chelation therapy to avoid iron overloading)
         3. Splenectomy in rare instances of hypersplenism
         4. Allogeneic bone marrow transplantation limited to the most severely affected patients
      5. Bart's hemoglobinopathy
         1. Usually results in neonatal death.
         2. Patients rarely salvaged by intrauterine transfusions and subsequent stem cell transplantation.
         3. The diagnosis, management, and prognosis of homozygous α-thalassemia/hydrops fetalis is changing; advances in antenatal diagnosis, intrauterine intervention (Carr et al. 1995), and postnatal therapy have resulted in long-term survival of children previously felt to have an invariably fatal disease (Singer et al. 2000; Weisz et al. 2009; Vichinsky 2010).
      6. Homozygous α-thalassemia and hydrops fetalis (Vichinsky 2009)
         1. A complex, usually fatal disease that is devastating to the entire family.
         2. There is a diversity in the genotype and phenotype expression of this syndrome that presents challenges in at-risk couple counseling and population screening.
         3. Presently, counseling and testing of at-risk populations is inadequate.
         4. More cases are being diagnosed unexpectedly.
         5. Intrauterine transfusion therapy appears promising in minimizing the morbidity and mortality of homozygous α-thalassemia. However, most of these patients require lifetime transfusion therapy and chelation.
         6. Recent advances in stem cell transplantation have resulted in some patients being cured.
         7. Successful cases of related, unrelated, and mismatched stem cell transplantation for α-thalassemia major have been reported.
      7. α-Thalassemia syndromes are common and have a wide range of clinical phenotypes (Vichinsky 2013). Hemoglobin H disease morbidity is often underappreciated. These patients require early diagnosis and ongoing monitoring. Hemoglobin Bart's hydrops is a tragic, usually fatal complication that can be prevented by adequate screening and counseling. Improved outcome with intrauterine transfusions creates ethical issues for the family and health care providers.
   2. β-Thalassemia (Galanello and Origa 2010; Origa 2015)
      1. No specific therapy required for β-thalassemia trait.
      2. Regular blood transfusions in thalassemia major.
         1. Correct the anemia.
         2. Suppress erythropoiesis.

3. Inhibit increased gastrointestinal absorption of iron.

3. Treatment of individuals with thalassemia intermedia (Taher et al. 2012).
   1. Symptomatic treatment
   2. Blood transfusion
   3. Splenectomy
   4. Folic acid supplementation
   5. Iron chelation
   6. Treatment of extramedullary erythropoietic masses (radiotherapy, transfusions, or hydroxyurea in selected cases)
4. Iron chelation with desferrioxamine to eliminate the iron overload secondary to multiple blood cell transfusions and to increase iron absorption.
5. Role of natural agents (Kukreja et al. 2013).
   1. Various natural agents like angelicin, rapamycin, FT, bergamot, romidepsin, wheatgrass, *Curcuma comosa*, *Astragalus*, apicidin, curcuminoid, piceatannol, and resveratrol have been reported to induce HbF level in beta-thalassemic patients.
   2. Various natural compounds like wheatgrass, desferrioxamine, and *Tetracarpidium conophorum* have also been known for their iron chelation property for the treatment of beta-thalassemia.
   3. More data are needed on the bioavailability of these natural compounds and their effects on human.
6. Bone marrow transplantation (Lucarelli et al. 1995; Giardini and Lucarelli 1999) remains to be the only definitive cure currently available for patients with thalassemia.
   1. From an HLA-identical sib
   2. Outcome dependent on pretransplantation clinical conditions, specifically the presence of hepatomegaly, extent of liver fibrosis, and magnitude of iron accumulation
   3. Risk of chronic graft-versus-host disease (GVHD) of variable severity: 5–8%
7. Cord blood transplantation (Kelly et al. 1997; Locatelli et al. 2003).
   1. From a related donor offers a good probability of a successful cure and is associated with a low risk of GVHD.
   2. Possibility of using cord blood obtained from unrelated donors with a decrease in the incidence of graft-versus-host disease.
   3. Human umbilical cord blood contains hematopoietic stem cells capable of reconstituting bone marrow.
8. Recent trends in the gene therapy of β-thalassemia (Finotti et al. 2015).
   1. A strong emphasis on the most recent findings, for β-thalassemia model systems
   2. For β-, γ-, and anti-sickling β-globin gene addition and combinatorial approaches including the latest results of clinical trials
   3. For novel approaches, such as transgene-mediated activation of γ-globin and genome editing using designer nucleases

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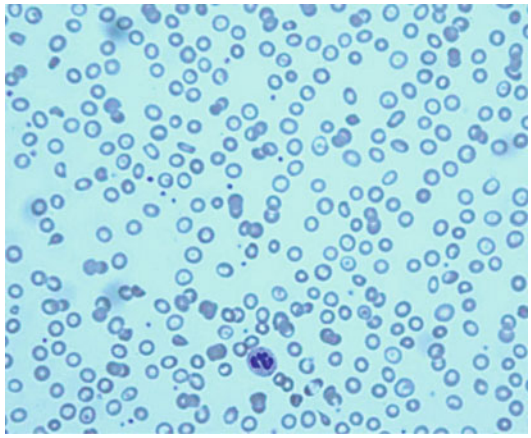

Fig. 1 Peripheral blood smear from a 58-year-old woman with microcytic anemia and frequent target cells (codocytes). Hemoglobin electrophoresis showed an AA pattern with an increased hemoglobin A_2 (5.8% by HPLC) consistent with beta$^+$- thalassemia trait

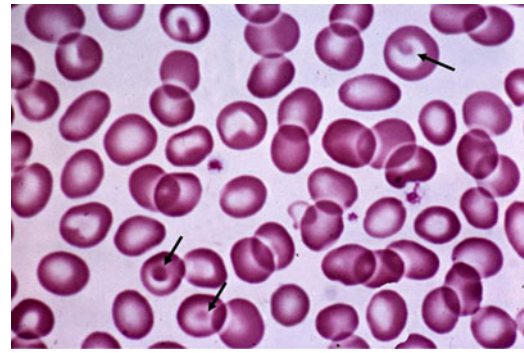

Fig. 2 Peripheral blood smear from a patient with alpha-thalassemia minor shows hypochromia, target cells (*arrows*), and anisopoikilocytosis (Wright-Giemsa stain, ×1,000)

Thanatophoric Dysplasia

Contents

Thanatophoric dysplasia was originally described by (Maroteaux et al. 1967). The term "thanatophoric" was coined to mean "death bearing" in Greek. Thanatophoric dysplasia is probably the most common lethal neonatal dwarfism with an estimated incidence of 0.2–0.5 per 10,000 births.

Synonyms and Related Disorders

Thanatophoric dysplasia type I (thanatophoric dwarfism; lethal short-limbed platyspondylic dwarfism, San Diego type; platyspondylic lethal skeletal dysplasia, San Diego type); Thanatophoric dysplasia type II (cloverleaf skull with thanatophoric dwarfism, thanatophoric dysplasia with kleeblattschadel, thanatophoric dysplasia with straight femur and cloverleaf skull)

Genetics/Basic Defects

1. Genetic heterogeneity:
   1. Sporadic in most cases
   2. A new autosomal dominant mutation (Martinez-Frias et al. 1988)
   3. Caused by mutations in the transmembrane domains of the fibroblast growth factor receptor 3 (*FGFR3*)
2. Having the most extreme micromelia and the most extensive craniofacial involvement compared to two other short-limb skeletal dysplasias (achondroplasia and hypochondroplasia) which are also caused by mutations of *FGFR3*.
3. Pathogenesis for the phenotypic features of thanatophoric dysplasia:
   1. Normal function of *FGFR3*: to regulate endochondral ossification by "putting the brakes on growth"
   2. "Gain-of-function" type of known mutations on *FGFR3*:
      1. Primarily affects the cranial base and nasal capsule (endochondral bones)
      2. With secondary effect on membrane bones which articulates with endochondral bones
4. Two major forms (TD1, TD2) of thanatophoric dysplasia, postulated based on subtle differences in skeletal radiographs and the underlying genetic mutation (Tavormina et al. 1995; Defendi 2014):

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1. TD1:
   1. Curved femora
   2. Very flat vertebral bodies
   3. Very few TD1 patients with cloverleaf skull
   4. Molecular defect consisting of a stop codon mutation or missense mutation in the extracellular domain of the FGFR3 protein, resulting in a newly created cysteine residue (Arg248Cys, most common) (Rousseau et al. 1995, 1996)
2. TD2 (Partington et al. 1971; Norman et al. 1992):
   1. Straight femora
   2. Taller vertebral bodies
   3. Most TD2 patients with cloverleaf skull (severe craniosynostosis)
   4. Molecular defect consisting of a single-nucleotide substitution resulting in replacement of lysine with glutamine at position 650 (Lys650Glu) in the tyrosine kinase 2 domain of the receptor

5. Activating mutations in the *FGFR3* gene can cause the following conditions (Bonaventure et al. 1996a, b; Cohen 1998; Vajo et al. 2000; Karczeski and Cutting 2013):
   1. Achondroplasia
   2. Thanatophoric dysplasia type I and type II
   3. Hypochondroplasia
   4. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)
   5. Crouzon syndrome with acanthosis nigricans
   6. Familial acanthosis nigricans
   7. Nonsyndromic coronal synostosis
   8. Platyspondylic lethal skeletal dysplasia, San Diego type (PLSD-SD)
   9. LADD syndrome (lacrimo-auriculo-dento-digital syndrome) (Levy-Hollister syndrome)

Clinical Features

1. Unique and homogeneous clinical features observed in patients with TD1
2. General features:
   1. Virtually lethal neonatally
   2. A few reports with survival up to 4–5 years of age with aggressive neonatal intervention:
      1. Markedly limited growth potential
      2. Markedly delayed cognitive development
      3. Respiratory insufficiency
      4. Neurologic abnormalities
      5. Long-term medical care and chronic ventilator dependence
3. Craniofacial features:
   1. Head:
      1. Disproportionally large (macrocephaly)
      2. Frontal bossing
      3. With or without cloverleaf (kleeblattschädel) anomaly of the skull resulting from premature closure of cranial sutures (Isaacson et al. 1983)
   2. Facial features:
      1. Bulging eyes
      2. Hypertelorism
      3. Severely depressed or indented nasal bridge
4. Short neck
5. Chest:
   1. Extremely narrow
   2. Constricted thoracic cage
   3. Reduced size of the thoracic cavity
   4. Short ribs
   5. Hypoplastic lungs
6. Protuberant abdomen
7. Limbs:
   1. Extremely short
   2. Thickened skin
   3. Excessive skinfolds
   4. Usually outstretched arms
   5. Externally rotated legs with abducted thighs
   6. Syndactyly
8. Early death in most children secondary to:
   1. Chest constriction and consequent respiratory insufficiency
   2. Foramen magnum stenosis resulting in failure of respiratory control
9. A few children with longer survival (up to 9–10 years) (Stensvold et al. 1986; Tonoki 1987; MacDonald et al. 1989):
   1. Respiratory insufficiency:
      1. Reduced chest circumference

2. Upper cervical cord compression resulting from a diminutive foramen magnum
2. Markedly limited growth potential
3. Markedly delayed cognitive development
4. Seizures
5. Hearing loss
6. Additional CNS anomalies (Wongmongkolrit et al. 1983; Coulter et al. 1991; Baker et al. 1997):
    1. Hydrocephalus
    2. Polymicrogyria
    3. Neuronal heterotopia
    4. Megalencephaly
    5. Cerebral gyral disorganization
    6. Hippocampal malformation
    7. Temporal lobe malformations
    8. Nuclear dysplasia
    9. Abnormal axonal bundles
    10. Cerebellar hypoplasia in the small posterior fossa
    11. Partial agenesis of the corpus callosum
    12. Spinal stenosis
    13. Hyperreflexia
    14. Clonus
7. Acanthosis nigricans, an associated rare skin disorder

10. Differential diagnosis (Schild et al. 1996):
    1. Achondroplasia:
        1. Autosomal dominant disorder
        2. Rhizomelic shortening of the bones, less prominent than thanatophoric dysplasia
        3. Macrocrania
        4. Heterozygous achondroplasia:
            1. Compatible with normal life span
            2. Normal intelligence
        5. Homozygous achondroplasia with two affected parents
    2. Campomelic dysplasia:
        1. Autosomal recessive disorder
        2. Typical anterior bowing of the lower limbs
        3. Hypoplastic fibula
        4. Hypoplastic scapulae
        5. A sex reversal phenomenon (phenotypical female with male karyotype)
    3. Osteogenesis imperfecta type II and type III:
        1. Varying degree of bone demineralization
        2. Shortened long bones with multiple fractures
        3. Blue sclerae
        4. Polyhydramnios frequently associated with type II
    4. Hypophosphatasia:
        1. Demineralization of bone tissue
        2. Lack of calcification of the fetal skull
        3. Mild-to-moderate shortening of limb bones
        4. Difficult to differentiate from osteogenesis imperfecta if fractures are present
    5. Achondrogenesis:
        1. Severe micromelia
        2. Poor ossification of the vertebral bodies, cranium, pelvis, and sacrum
        3. Narrow and shortened thorax
        4. Frequent complications with fetal hydrops and hydramnios
    6. Short rib-polydactyly and other rare skeletal dysplasia syndromes

Diagnostic Investigations

1. Radiographic features (Langer et al. 1987; Wilcox et al. 1998):
    1. Skull:
        1. Relatively large calvarium
        2. A small foramen magnum
        3. Trilobed skull with a towering calvarium and bitemporal bulging in the cloverleaf skull type (type II)
    2. Ribs:
        1. Very short ribs with cupped anterior ends
        2. Short ribs (type II)
    3. Vertebrae:
        1. Flat vertebral bodies (platyspondyly)
        2. Increasing intervertebral disk space
        3. "Inverted U-shaped or H-shaped" vertebral bodies (Weber et al. 1998)
        4. Narrow interpediculate distance at the lumbar level
        5. Taller vertebral bodies (type II)

4. Pelvis:
    1. Short
    2. Small sacrosciatic notches
5. Tubular bones:
    1. Extremely shortened long bones of the limbs
    2. Rhizomelic shortening of the limbs
    3. Flared metaphyses
    4. "Telephone receiver"-like curved femora in the noncloverleaf type
    5. Relatively straight femora (type II)

2. Histologic features:
    1. Generalized disruption of endochondral ossification (Yang et al. 1976; Horton et al. 1988; Lemyre et al. 1999):
        1. Hallmark of the histologic findings.
        2. Physeal growth zone shows minimal proliferation and hypertrophy of chondrocytes with the absence of column formation.
        3. Lateral overgrowth of metaphyseal bone around the physis.
        4. Mesenchymal cells extending inward from the perichondrium as a narrow band at the periphery of the physeal zone (the so-called fibrous bands, fibrovascular bands, and fibrovascular bundles). (Weber et al. (1998)
        5. Increased vascularity of the resting cartilage.
    2. Brain:
        1. Neuronal migration abnormalities of the temporal lobe
        2. Hydrocephalus
        3. Partial agenesis of the corpus callosum
        4. Upper cord compression
        5. Spinal stenosis

3. DNA mutation analysis of *FGFR3*:
    1. TD1:
        1. 742C → T (Arg248Cys): most common
        2. Tyr373Cys
        3. Ser249Cys
        4. Other missense mutations
        5. Stop codon mutations
    2. TD2: missense mutation of 1948A → G (Lys650Glu) in TD2
    3. Clinical testing:
        1. Targeted mutation analysis
        2. Sequence analysis of select regions of FGFR3 or of the entire *FGFR3* coding region

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: because TD generally occurs as the result of a de novo mutation, the risk to the sibs of a proband is small (Karczeski and Cutting 2008) (about 2%).
    2. Patient's offspring: not surviving to reproduction age.

2. Prenatal diagnosis:
    1. 2D, 3D, 4D ultrasonography (De Biasio et al. 2000; Machado and Bonilla-Musoles 2001; Chitty et al. 2013):
        1. Hydramnios in most cases.
        2. Increased nuchal translucency.
        3. Megacephaly with or without cloverleaf-shaped skull.
        4. The findings of dysmorphic choroid plexus, early-onset hydrocephalus, and cloverleaf skull at first-trimester scan may be early, useful ultrasound markers of TD type II (Tonni et al. 2014).
        5. Frontal bossing.
        6. Progressive hydrocephaly.
        7. Hypoplastic thorax disproportionately small in relation to the abdomen.
        8. Small chest and lung measurement to predict severe pulmonary hypoplasia.
        9. Short ribs.
        10. Short limbs with curved "telephone handle-shaped" or straight femurs.
        11. Excessive skin giving fetus a "boxer's face" appearance.
        12. Flattened vertebrae with increased intervertebral spaces, giving the vertebral bodies the form of an "H."
        13. The use of 4D real-time ultrasound gives the physician the possibility to discuss and counsel the patients with images

that are more understandable to the general public (Vasilj and Mišković 2012):
2. Prenatal radiography for documenting characteristic skeletal anomalies.
3. DNA mutation analysis of *FGFR3* in fetal cells from amniocentesis or CVS (Chen et al. 2001, 2002).
4. Noninvasive prenatal diagnosis: next-generation sequencing (NGS) for the analysis of cell-free fetal DNA in maternal blood (Chitty et al. 2013, 2015).
5. Prenatal and preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified.

3. Management (Karczeski and Cutting 2013):
   1. Limited intervention:
      1. Appropriate because of the inevitable lethal outcome
      2. Aggressive neonatal management, at times, not even resulting in short-term survival
   2. Debatable issues about the level of intensity of medical care for unanticipated long-term survival:
      1. Long-term medical care.
      2. Development of seizures, progression of craniocervical stenosis, ventilator dependence and limitations in motor and cognitive abilities (Nikkel et al. 2013).
      3. Requiring extensive health maintenance measures.
      4. Anticipate frequent medical exacerbations requiring recurrent hospitalizations.
      5. Possibility of lethal complication, an ever present concern.
      6. Special education programs for the longer survivals.

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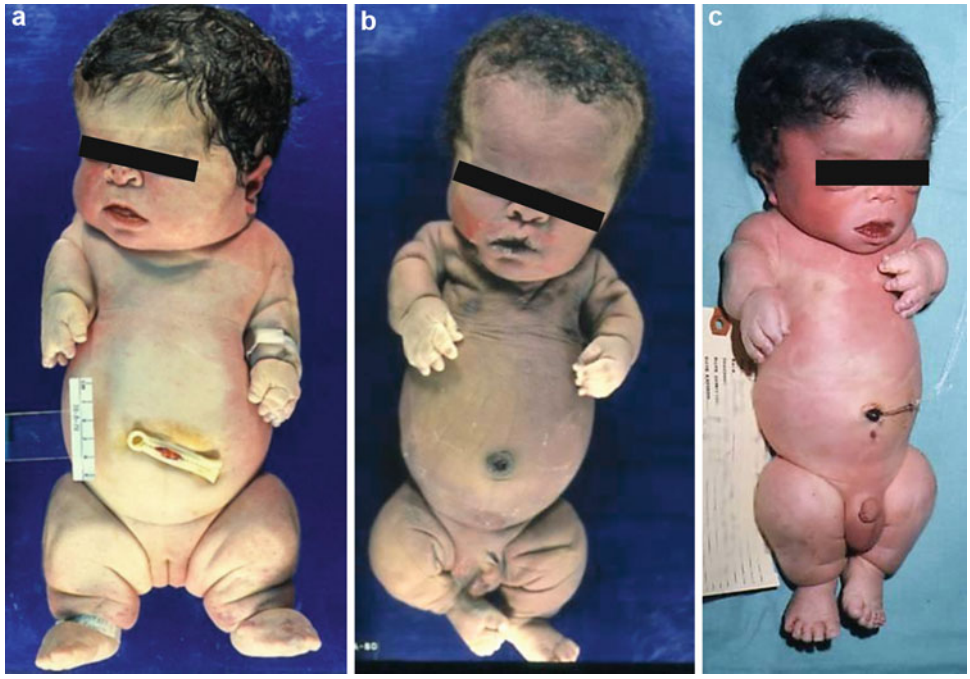

Fig. 1 (**a**–**c**) Front views of three infants showing frontal bossing, flat facies, short neck, micromelia, and small chest

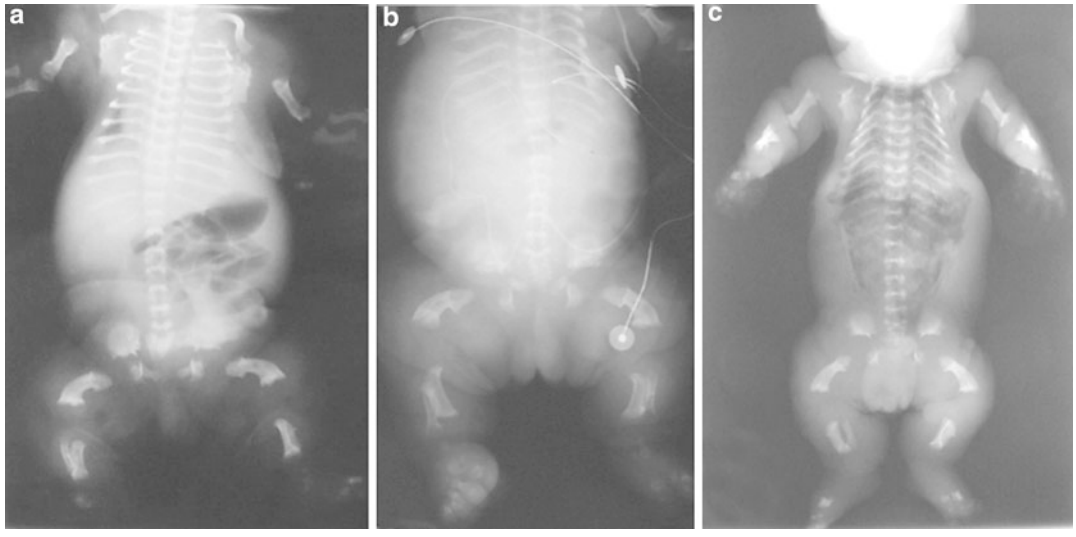

Fig. 2 (**a**–**c**) AP radiographic views of three infants with typical findings of TD1 showing profound platyspondyly, decreased thoracic volume, characteristic pelvic configuration, micromelia, and the so-called "telephone receiver" femoral bowing

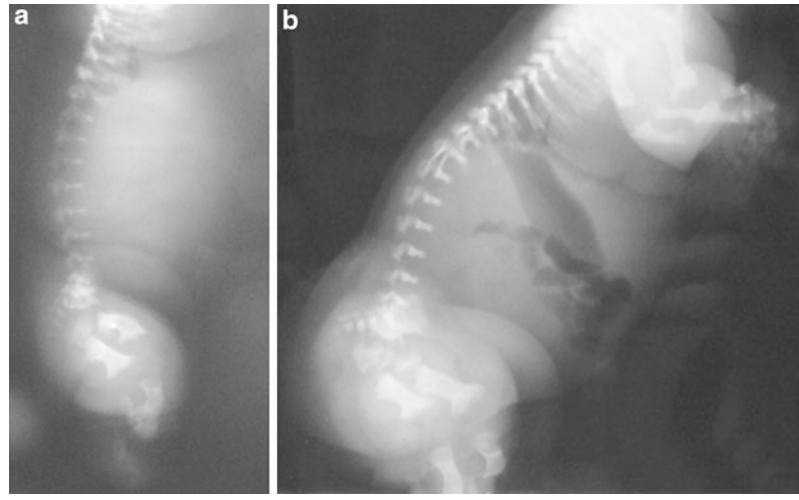

Fig. 3 (**a**, **b**) Lateral radiographic views of the spines of two infants with typical TD1 showing extreme platyspondyly and short ribs

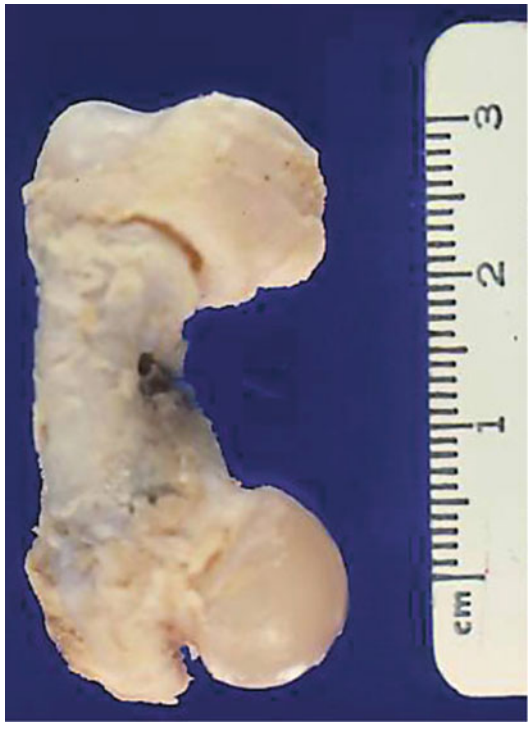

Fig. 4 Gross appearance of a femur resembling a "telephone receiver"

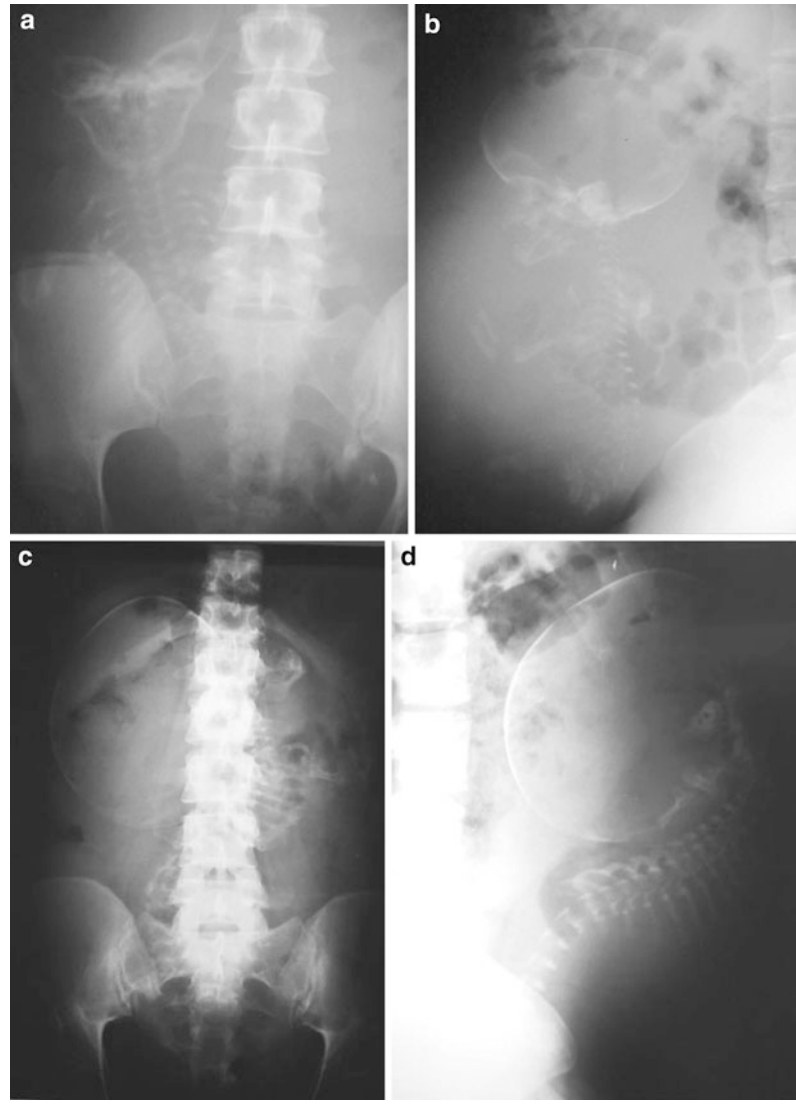

Fig. 5 (**a**–**d**) Prenatal radiographs of two fetuses affected with thanatophoric dysplasia showing platyspondyly, short ribs, and micromelia

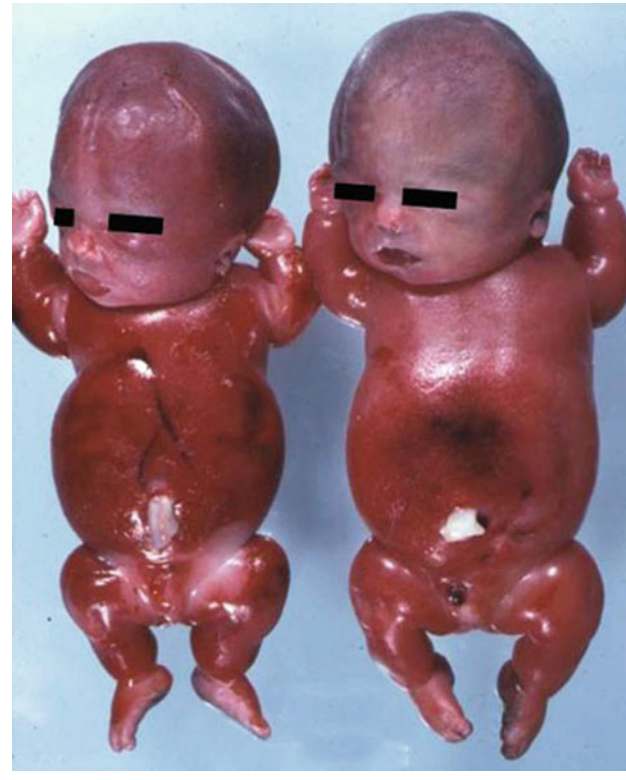

Fig. 6 Thanatophoric dysplasia in identical twin fetuses. The pregnancy was terminated following ultrasonographic diagnosis at 22 weeks' gestation. The placenta was diamniotic monochorionic, consistent with monozygotic pregnancy

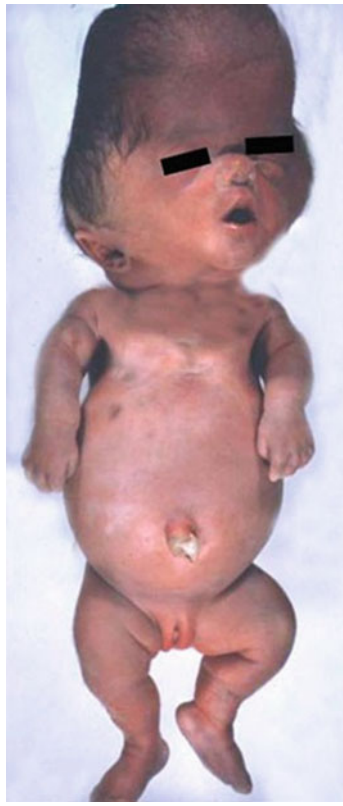

Fig. 7 Thanatophoric dysplasia with cloverleaf skull in a neonate. The head is large and trilobed. The narrow chest and rhizomelic shortening of limbs are similar to those of classic thanatophoric dysplasia. Radiograph revealed platyspondyly and small ilium that are similar to those of classic thanatophoric dysplasia (not shown). However, the femur is straight and not as curved as seen in the classic type (Courtesy of Dr. Samuel Yang)

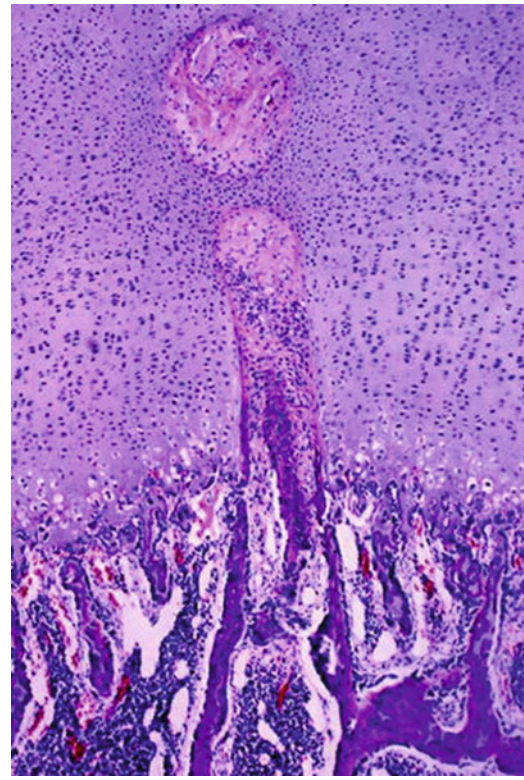

Fig. 8 Photomicrograph of the cartilage-bone junction, cloverleaf skull type of thanatophoric dysplasia. The physeal growth zone is markedly retarded and disorganized. Similar changes are seen in the classic-type thanatophoric dysplasia. A partially ossified cartilage canal is present at the center of physis. It is more prominent in size and number in the cloverleaf type than in the classic type

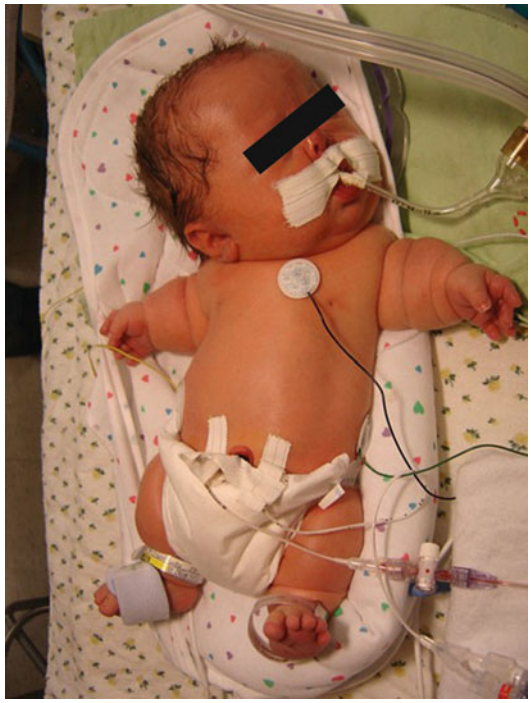

Fig. 9 A neonate with short-limb dwarfism, characterized by flat face, short neck, short chest, and micromelia. A single-sequence mutation (Nt742C > T) was identified in the *FGFR3* gene. This causes the substitution of arginine for cysteine at codon 248 (C248R). This mutation has been previously reported in thanatophoric dysplasia type I

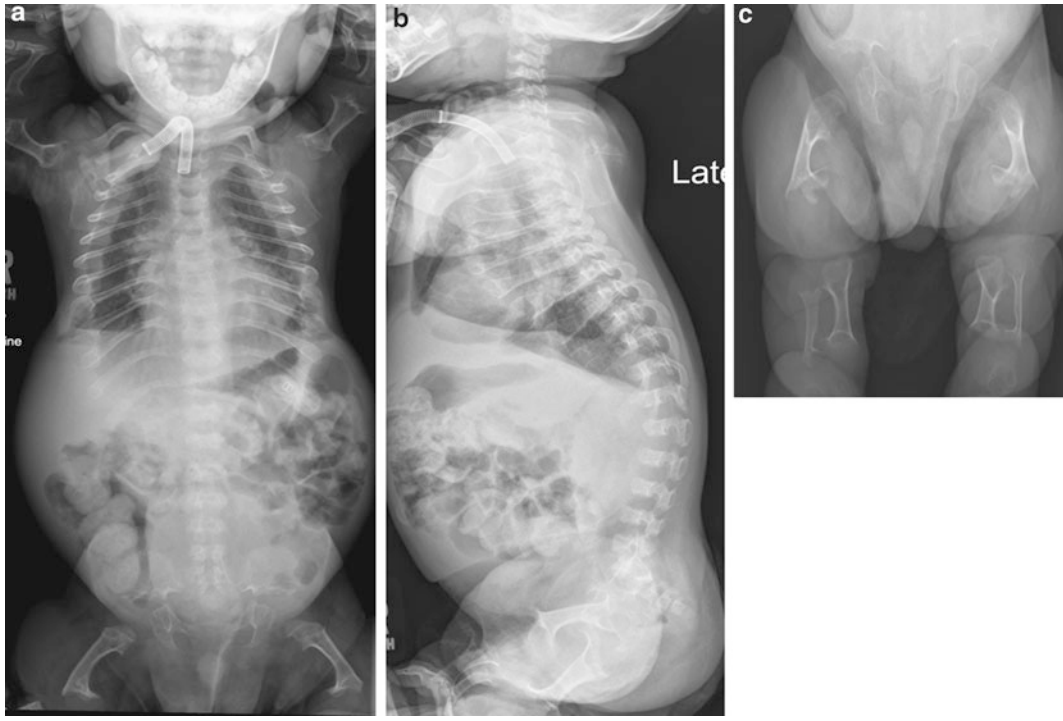

Fig. 10 (**a**–**c**) A 2-year-old boy was seen with diagnosis of type 1 thanatophoric dysplasia. Prenatal ultrasonographs noted features consistent with thanatophoric dysplasia. Amniocentesis at 21 weeks of gestation showed a 46,XY karyotype with DNA mutation study of amniocytes showing c.742C > T (Arg248Cys) in *FGFR3* gene, which confirmed the diagnosis of type 1 thanatophoric dysplasia. He has extremely short limbs with developmentally delay, especially in motor milestones. The radiographs showed bullet-shaped vertebral bodies with posterior scalloping. There was progressive narrowing of the interpediculate distances in the lumbar spine. The rib cage was small with short ribs and prominent anterior ends. The long bones of the lower extremities were markedly shortened with flaring and irregularity of the metaphyses. There was also bowing of bilateral femurs which appears as a typical "telephone receiver" femur. The iliac wings were short and squared with irregular acetabular roofs (Courtesy of Dr. Grace Guo)

Thrombocytopenia-Absent Radius Syndrome

Contents

Thrombocytopenia-absent radius (TAR) syndrome is a congenital malformation syndrome characterized by congenital hypomegakaryocytic thrombocytopenia and bilateral absence of the radii with presence of both thumbs.

Synonyms and Related Disorders

TAR syndrome

Genetics/Basic Defects

1. Genetic inheritance: autosomal recessive inheritance suspected based on the following observations
   1. Families with at least two affected children born to unaffected parents
   2. Rare instances of association with consanguinity
2. A microdeletion of chromosome 1q21.1: observed in all investigated patients with TAR syndrome (Klopocki et al. 2007; Tassano et al. 2015)
   1. Associated with an interstitial microdeletion of 200 kb on chromosome 1q21.1 in all 30 investigated patients with TAR syndrome, detected by microarray-based comparative genomic hybridization.
   2. Analysis of the parents revealed that this deletion occurred de novo in 25% of affected individuals.
   3. The recessive inheritance pattern of TAR syndrome requires an additional causative allele that until recently was unknown. A low-frequency single-nucleotide polymorphism (SNP) in the *RBM8A* gene is detected as the second causative allele in the origination of TAR syndrome (Albers et al. 2012).
3. Etiology of thrombocytopenia: unknown but is considered to be the result of a decreased production of platelets from the bone marrow

Clinical Features

1. Thrombocytopenia (100%)
   1. May be transient.
   2. Symptomatic in over 90% of cases within the first 4 months of life.
      1. Purpura
      2. Petechiae

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DOI 10.1007/978-1-4939-2401-1_229

3. Epistaxis
4. Gastrointestinal bleeding
    1. Hematemesis
    2. Melena
5. Hemoptysis
6. Hematuria
7. Intracerebral bleeding

3. More severe thrombocytopenia can be precipitated by stress, infection, gastrointestinal disturbances, or surgery (Fayen and Harris 1980).
4. Platelet count tends to rise as the child gets older and may approach normal levels in adulthood (spontaneous improvement of platelet counts after 1 year).

2. Upper extremity anomalies (100%) (Hall 1987)
    1. Bilateral absence of the radius (100%): the most striking skeletal manifestation
    2. Hand anomalies
        1. Presence of the thumbs (100%)
            1. An important clinical feature distinguishing TAR syndrome from other disorders featuring radial aplasia, which are usually associated with absent thumbs
            2. Relatively functional thumbs
            3. Thumbs often adducted
            4. Thumbs often hypoplastic
        2. Radially deviated
        3. Limited extension of the fingers
        4. Hypoplasia of the carpal and phalangeal bones
        5. Severe phenotype with phocomelia (Hall et al. 1969, 1987; Klopocki et al. 2007)
        6. Phocomelia and lower limb anomalies (28%) in TAR syndrome associated with 1q21.1 deletion (Houeijeh et al. 2011)
    3. Associated ulnar anomalies
        1. Usually short
        2. Usually malformed
        3. Absent ulna
            1. Absent bilaterally in about 20% of cases
            2. Absent unilaterally in about 10% of cases
    4. Associated humeral anomalies
        1. Often abnormal in about 50% of cases
        2. Absent humeri in about 5–10% of cases (rare phocomelia)
    5. Associated shoulder and arm anomalies
        1. One arm shorter than the other in about 15% of cases
        2. Hypoplasia of muscles and soft tissue in the arm and shoulder
        3. Abnormal shoulder joint secondary to abnormal humeral head
3. Lower limb anomalies (47%) (Ray et al. 1980; Christensen and Ferguson 2000; Greenhalgh et al. 2002)
    1. Correlation exists between the severity of skeletal changes in the lower limbs and the severity of abnormalities of the upper limbs.
    2. Variable involvement but usually milder than the upper limbs.
        1. Dislocation of the patella and/or of the hips
        2. Knee involvement
            1. Dysplasia: rare severe knee dysplasia due to agenesis of cruciate ligaments and menisci
            2. Ankylosis
            3. Subluxation
        3. Hip dislocation
        4. Coxa valga
        5. Absent tibiofibular joint
        6. Femoral or tibial torsion
        7. Lower limb phocomelia
        8. Valgus and varus foot deformities
        9. Abnormal toe placement
        10. Severe cases with lower limb phocomelia
4. Cow's milk intolerance (Whitfield and Barr 1976) (62%)
    1. Presentation symptoms
        1. Persistent diarrhea
        2. Failure to thrive
    2. Thrombocytopenia episodes
        1. Precipitated by introduction of cow's milk
        2. Relieved by its exclusion from the diet
5. Urogenital anomalies (23%)
    1. Horseshoe kidney
    2. Absent uterus
6. Cardiac anomalies (22–33%)
    1. Tetralogy of Fallot

2. Atrial septal defect
3. Ventricular septal defect

7. Other associated congenital anomalies
   1. Facial capillary hemangiomata in the glabella region
   2. Micrognathia
   3. Cleft palate
   4. Intracranial vascular malformation
   5. Sensorineural hearing loss
   6. Epilepsy
   7. Other skeletal anomalies
      1. Scoliosis
      2. Cervical rib
      3. Fused cervical spine
      4. Short stature
   8. Neural tube defect
8. Prognosis
   1. Variable clinical course among patients.
   2. Survival related to the severity and duration of thrombocytopenia.
   3. Good prognosis after surviving the first year of life.
   4. Early diagnosis and treatment with platelet therapy minimize mortality risks.
   5. Mental retardation secondary to intracranial bleed (7%).
   6. Good hand and upper extremity functions, especially if bilateral radial aplasia is the only skeletal abnormality.
9. Variable phenotypes of TAR syndrome associated with 1q21.1 deletion (Houeijeh et al. 2011)
   1. Ranging from syndactyly to severe TAR syndrome.
      1. A boy and a maternal uncle with TAR syndrome and a maternal aunt harboring isolated mild radial hypoplasia (Schnur et al. 1987)
      2. A stillbirth male fetus with TAR syndrome who had two paternal uncles presenting with isolated webbed toes (Donnenfeld 1994)
   2. Presence of one or more frequent event (s) (mTAR) that could modulate the expression of the deletion (Klopocki et al. 2007).
   3. Female predominance could suggest the presence of X-linked modifying factors (mTAR) (Schnur et al. 1987).
10. Differential diagnosis (Hall 1987; Hedberg and Lipton 1988; Greenhalgh et al. 2002; Toriello 2014)
    1. Holt-Oram syndrome (please see the chapter)
       1. An autosomal dominant condition caused by mutations in the *TBX5* gene
       2. Often with a family history of heart and limb defects
       3. Absence of the thumb associated with radial aplasia
       4. Absence of thrombocytopenia
       5. Conventional cytogenetic analysis: usually normal
    2. Roberts syndrome (please see the chapter)
       1. An autosomal recessive trait
       2. Pre- and postnatal growth retardation
       3. Facial clefting
       4. Genitourinary abnormalities
       5. Limb defects involving upper or lower limbs or both
       6. Conventional cytogenetic analysis: characteristic chromosome abnormality in the majority (79%) of cases
          1. Premature centromere separation (PCS)
          2. "Puffing" of the chromosomes caused by repulsion of the heterochromatic regions near the centromeres of chromosomes 1, 9, and 16 with splaying of the short arms of the acrocentric chromosomes and of distal Yp.33
          3. Evidence of abnormal mitosis
       7. Postulated that TAR syndrome and Roberts syndrome might be part of the same condition, with TAR syndrome being the milder and Roberts the severer variant
    3. Fanconi anemia (please see the chapter)
       1. An autosomal recessive disorder.
       2. Bone marrow failure.
       3. Skeletal defects.
       4. Cutaneous pigmentation.
       5. Microcephaly.
       6. Short stature.
       7. May present with thrombocytopenia.
       8. Upper limb abnormalities also involve the radial ray.

9. Hypoplastic thumbs may be accompanied by radial hypoplasia, but absence of the radius is associated with absence of the thumbs.
10. Spontaneous chromosome breakage, a consistent feature of Fanconi anemia and is a reliable diagnostic test.

4. Aase syndrome
   1. Radial hypoplasia
   2. Triphalangeal thumbs
   3. Hypoplastic anemia, similar to Blackfan-Diamond syndrome
   4. Thrombocytopenia, not a feature
5. Thalidomide embryopathy
   1. May present with radial anomalies of the upper limb
   2. Malformations of the lower limbs showing a less consistent pattern
   3. Diagnosed based on:
      1. Phenotype
      2. History of exposure to thalidomide during pregnancy
      3. Increasing use of thalidomide as a therapeutic agent for the treatment of conditions such as Beçhet disease, graft versus host disease, multiple myeloma, and Kaposi sarcoma
6. Rapadilino syndrome (acronym for *ra*dial defects, absent/hypoplastic *pa*tella (and high/cleft *pa*late), *di*arrhea (and joint *di*slocations), and little size, long/slender *no*se (and *no*rmal intelligence))
   1. Absent thumbs and radial aplasia/hypoplasia
   2. Patellar aplasia/hypoplasia
   3. Cleft palate
7. Other syndromes with limb reduction abnormalities predominantly involving the upper extremities (Donnenfeld et al. 1990)
   1. Duane anomaly-radial aplasia
      1. Duane anomaly (inability to abduct the eye)
      2. Radial anomalies of varying severity, ranging from thenar hypoplasia to radial aplasia
      3. Renal and skeletal anomalies
      4. Hearing loss or ear anomalies
   2. Adams-Oliver syndrome (please see the chapter)
      1. Transverse limb defects
      2. Aplasia cutis congenita
      3. Growth deficiency
   3. Aglossia-adactylia
      1. Absence/hypoplasia of digits
      2. Absence/hypoplasia of the tongue
   4. Amniotic band sequence (please see the chapter on "Amniotic Deformity, Adhesions, Mutilations (ADAM) Complex)"
      1. Limb constriction or amputation
      2. Asymmetric facial clefts
      3. Cranial defects
      4. Compression deformities
   5. CHILD syndrome
      1. Unilateral hypomelia
      2. Ichthyosiform erythroderma
      3. Cardiac septal defect
   6. Cornelia de Lange syndrome
      1. Micromelia
      2. Growth deficiency
      3. Facial dysmorphism
   7. Femur-fibula-ulnar syndrome
      1. Femoral/fibular defects associated with malformations of the arms
      2. Amelia
      3. Peromelia at the lower end of the humerus
      4. Humeroradial synostosis
      5. Defects of the ulna and ulnar rays
   8. Poland anomaly (please see the chapter on "► Möbius Syndrome")
      1. Unilateral defect of pectoralis major muscle
      2. Ipsilateral limb abnormalities
   9. VATER association (vertebral, anal, tracheoesophageal, renal, and radial anomalies) (please see the chapter "► VATER (VACTERL) Association)"
   10. Townes-Brocks syndrome

1. Imperforate anus (82%)
2. Dysplastic ears: overfolded superior helices and preauricular tags (88%) frequently associated with sensorineural or conductive hearing impairment (65%)
3. Thumb malformations (triphalangeal thumbs, duplication of the thumb (preaxial polydactyly), rarely hypoplasia of the thumbs)

11. Weyers ulnar ray/oligodactyly syndrome
    1. Deficient ulnar and fibular rays
    2. Oligodactyly
    3. Hydronephrosis

8. Megakaryocytic aplasia
    1. Amegakaryocytic thrombocytopenia
    2. Congenital hypoplastic thrombocytopenia with microcephaly
    3. Thrombocytopenia associated with trisomy 13 and trisomy 18

Diagnostic Investigations

1. Hematological studies
    1. Blood platelet counts: thrombocytopenia
    2. Anemia secondary to bleeding
    3. Eosinophilia
    4. Leukemoid reaction (Hall 1987)
        1. Reported in about 60–70% of patients during the first year of life
        2. White blood counts >35,000 per mm^3 with a shift to the left, particularly with the stress and infections
        3. Usually associated with worse thrombocytopenia and often with hepatosplenomegaly
    5. Bone marrow aspirates
        1. Normal or hypercellular bone marrow
        2. Hypomegakaryocytic thrombocytopenia (<100,000 platelets per mm^3) (Dell and Sheppard 1982; Hall 1987)
            1. Absence of megakaryocytes in two thirds of cases
            2. Decreased in number of megakaryocytes, which are small, immature, basophilic, and vacuolated, in the rest of cases
2. Chromosome analysis (normal): to differentiate from chromosome abnormality syndrome
3. Molecular genetic analysis
    1. Common microdeletion in patients with TAR syndrome that encompasses 200 kb and 11 genes on chromosome 1q21.1 (Klopocki et al. 2007)
        1. De novo deletion: 25%
        2. Deletion inherited from either the unaffected mother or the unaffected father: 75%
    2. Array comparative genomic hybridization (aCGH): individuals with TAR syndrome have a minimally deleted 200-kb region at chromosome band 1q21.1, which is distinct from the region involved in the 1q21.1 deletion/duplication syndrome. Deletion of this segment is necessary but not sufficient to cause the phenotype. Identification of the 200-kb minimally deleted region is sufficient to verify the diagnosis of TAR syndrome in individuals with bilateral absence of the radius and presence of thumbs (Toriello 2014).
    3. SNP array CGH analysis: thrombocytopenia-absent radius syndrome in a child showing a larger 1q21.1 deletion than the one in his healthy mother and a significant downregulation of the commonly deleted genes (Guastadisegni et al. 2012).
    4. Deletion/duplication analysis to identify a 200-kb minimally deleted region in chromosome band 1q21.1: sufficient to verify the diagnosis of TAR syndrome (Al Kaissi et al. 2015).
    5. Summary of molecular genetic testing used in TAR syndrome (Toriello 2014).
        1. Deletion/duplication analysis
        2. Sequence analysis
        3. Targeted mutation analysis
4. Radiography
    1. Upper extremities
        1. Bilateral radial aplasia
        2. Radial club hand

3. Hypoplastic carpals and phalanges
4. Thumb and fingers always present
5. Hypoplastic ulnae, humeri, and shoulder girdles
6. Syndactyly and clinodactyly of fingers and toes

2. Lower extremities
   1. Hip dislocation
   2. Femoral torsion
   3. Tibial torsion
   4. Knee dysplasia
   5. Absent patella
   6. Valgus and varus foot deformities
   7. Abnormal toe placement
   8. Overriding toes

Genetic Counseling

1. Recurrence risk (Toriello 2014)
   1. TAR syndrome: inherited in an autosomal recessive manner and results from compound heterozygosity of *RBM8A* pathogenic variants.
   2. Affected individuals: typically with one *R8BM8A* hypomorphic mutation along with a null mutation, usually a minimally deleted 200-kb region at chromosome band 1q21.1.
   3. Approximately 50–75% of probands have inherited the 200-kb minimally deleted region from an unaffected parents; the deletion occurs de novo in about 25–50% of probands.
   4. Sibs of a proband:
      1. If both parents carry one allele: at conception each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
      2. If only one parent is a carrier of a pathogenic variant (and the other mutation/deletion is de novo): each sib of an affected individual has a 50% chance of being an asymptomatic carrier and a 50% chance of being unaffected and not a carrier.
      3. When both parents are carriers: once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is two thirds.
      4. Heterozygotes (carriers) are asymptomatic.
   5. Patient's offspring:
      1. The offspring of an individual with TAR syndrome: obligate heterozygotes (carriers) for a pathogenic variant in *RBM8A*.
      2. If an individual with TAR syndrome has children with a carrier of a pathogenic variant in *RBM8A*: their offspring have a 50% chance of being affected and a 50% chance of being carriers. This may account for the reports of parent-to-child transmission (Ward et al 1986).
2. Prenatal diagnosis: reported mostly in pregnancies with a prior affected sibling (Donnenfeld et al. 1990; Uhrig et al. 2007; Toriello 2014)
   1. Prenatal ultrasonography:
      1. Bilateral radial aplasia, club hands with normal thumbs, and metacarpals (Luthy et al. 1979).
      2. Phocomelia: most important differential diagnoses include TAR, Holt-Oral, and Roberts syndromes.
      3. First-trimester detection of TAR syndrome is feasible using 2D/3D US scanning combined with virtual reality (Baken et al. 2014).
   2. Cordocentesis:
      1. Often considered to evaluate fetal platelet count (thrombocytopenia) and establish the diagnosis of TAR syndrome and to differentiate from other syndromes with malformations of the upper limbs (Boute et al. 1996; Shelton et al. 1999; Tongsong et al. 2000; Bellver et al. 2005)
      2. Platelet counts: often <50 platelets/nl (normal range 150–400 platelets/nl) (Ballmaier et al. 1997)
      3. Carries 1–2% risk of fetal loss (22)
   3. X-ray (Omenn et al. 1973).
   4. Fetoscopy (Filkins et al. 1984).
   5. The sonographic finding of upper limb malformations in the fetus together with the

detection of the 1q21.1 microdeletion. Physical examination of the terminated fetus revealed malformed upper extremities and absence of both radii, with opposable thumbs in an adducted position (Uhrig et al. 2007).

6. Prenatal detection of TAR syndrome in a fetus with compound inheritance of an RBM8A SNP and a 334-kb deletion in the 1q21.1 region, detected by array-comparative genomic hybridization (Papoulidis et al. 2014).
7. Prenatal diagnosis and postmortem examination in a fetus with thrombocytopenia-absent radius (TAR) syndrome due to compound heterozygosity for a 1q21.1 microdeletion and a RBM8A hypomorphic allele.
8. Prenatal diagnosis for pregnancies at increased risk for TAR syndrome is possible using molecular genetic testing to detect the 200-kb minimally deleted region and ultrasound examination to evaluate the limbs (Bottillo et al. 2013).
9. Preimplantation genetic diagnosis: may be available for families in which the pathogenic variants have been identified.

3. Management (McLaurin et al. 1999; Wu et al. 2014; Toriello 2014)
   1. Platelet infusions
      1. Remains the only real option for treatment of thrombocytopenia
      2. To prevent the intracerebral hemorrhage, which was previously the main cause of mortality
      3. Potential risks of platelet transfusion
         1. Avoid platelet transfusion in older individuals whose platelet counts exceed a particular threshold (10/nL): alloimmunization and infection (hepatitis viruses, HIV).
         2. Anaphylaxis.
         3. Hemolytic reaction.
      4. Surveillance: platelet count whenever evidence of increased bleeding tendency (bruising, petechiae) occurs
   2. Avoidance of cow's milk to reduce the severity of gastroenteritis and to avoid exacerbations of thrombocytopenia
   3. Injury prevention strategies
      1. Avoid contact sports.
      2. Use appropriate protective gear (helmet, padding).
   4. Splenectomy usually effective for the treatment of thrombocytopenia in adults
   5. Bone marrow transplantation as an option for patients who continue to remain thrombocytopenic with bleeding despite platelet transfusions
   6. Physical and occupational therapies to improve function and quality of life
   7. Management of the upper extremity
      1. Postpone surgery till later as thrombocytopenic-related bleeding problems are less frequent in older individuals.
      2. Reconstructive surgery (Al Kaissi et al. 2015).
      3. Prosthetic fitting: generally rejected by patients as most patients are able to perform tasks by approximating themselves closely enough to an object to use their own hands.
      4. Adaptive devices for feeding, dressing, and toileting: generally well tolerated.
   8. Management of the lower extremity
      1. Rejection of any lower extremity intervention by most patients
      2. Use of power wheelchair or motorized cart for ambulation

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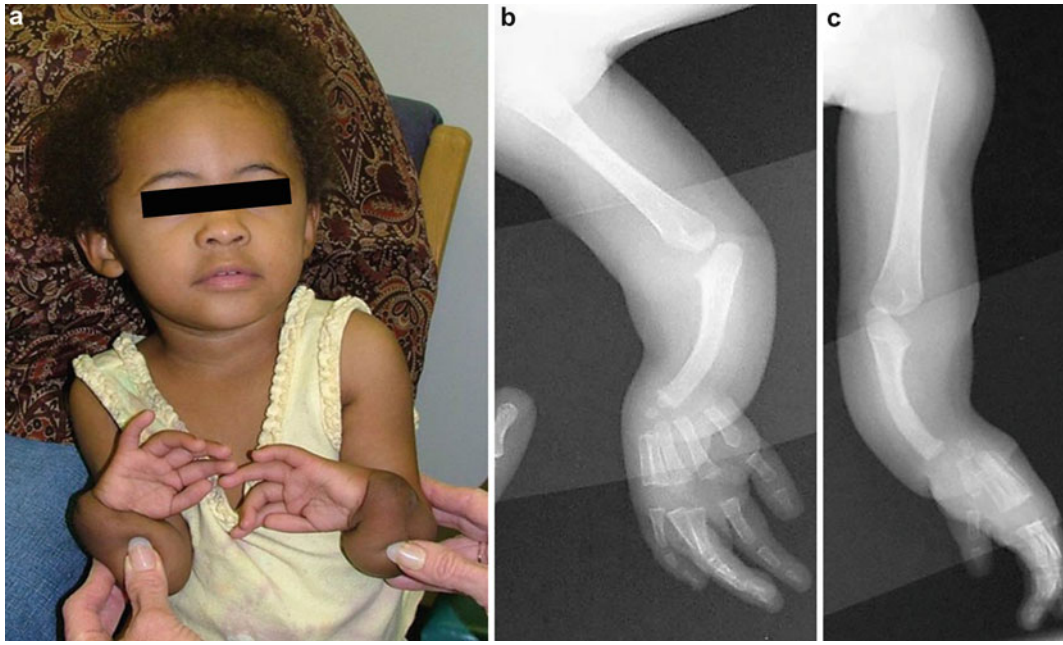

Fig. 1 (**a**–**c**) A 2 1/2-year-old girl with TAR syndrome (**a**) showing club hands with fingerlike thumbs and radial aplasia, illustrated by radiographs (**b**, **c**). The patient had thrombocytopenia early in life

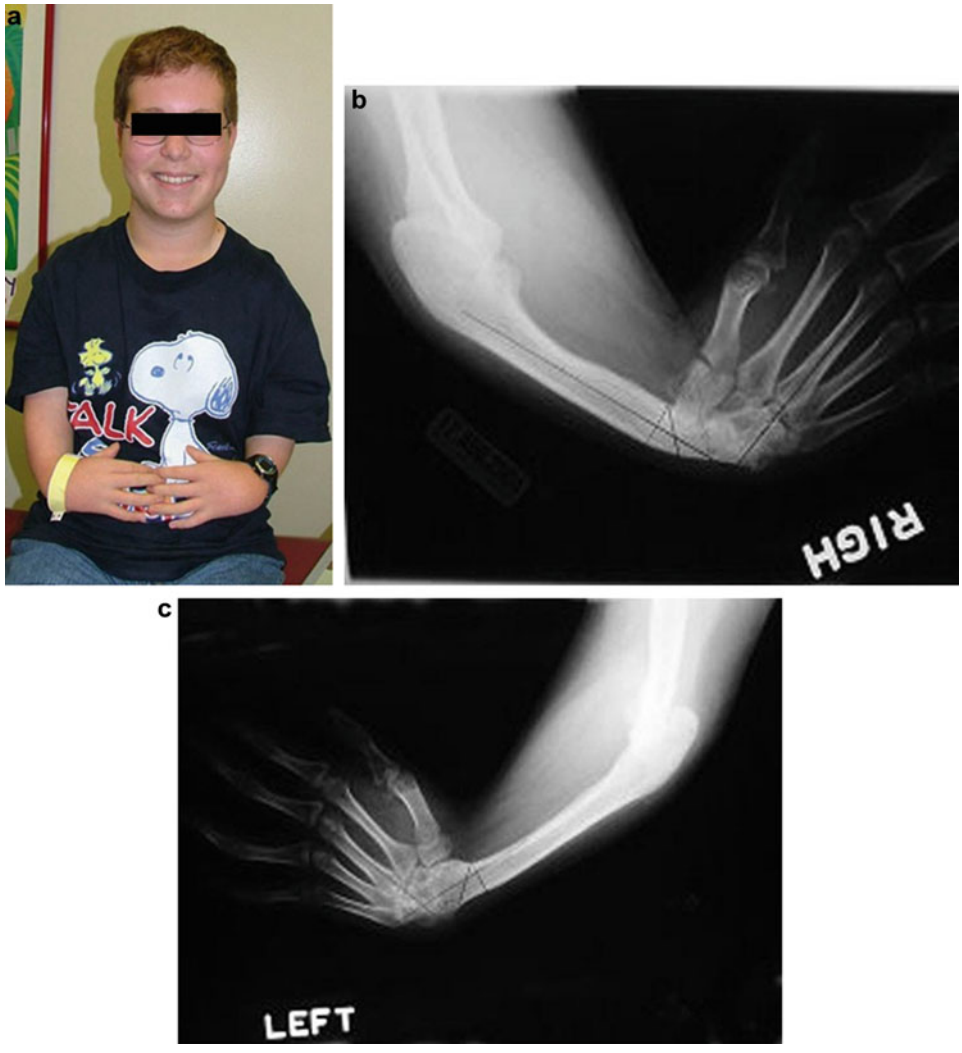

Fig. 2 (**a**–**c**) A 14-year-old boy with TAR syndrome showing similar clinical (**a**) and radiographic (**b**, **c**) features

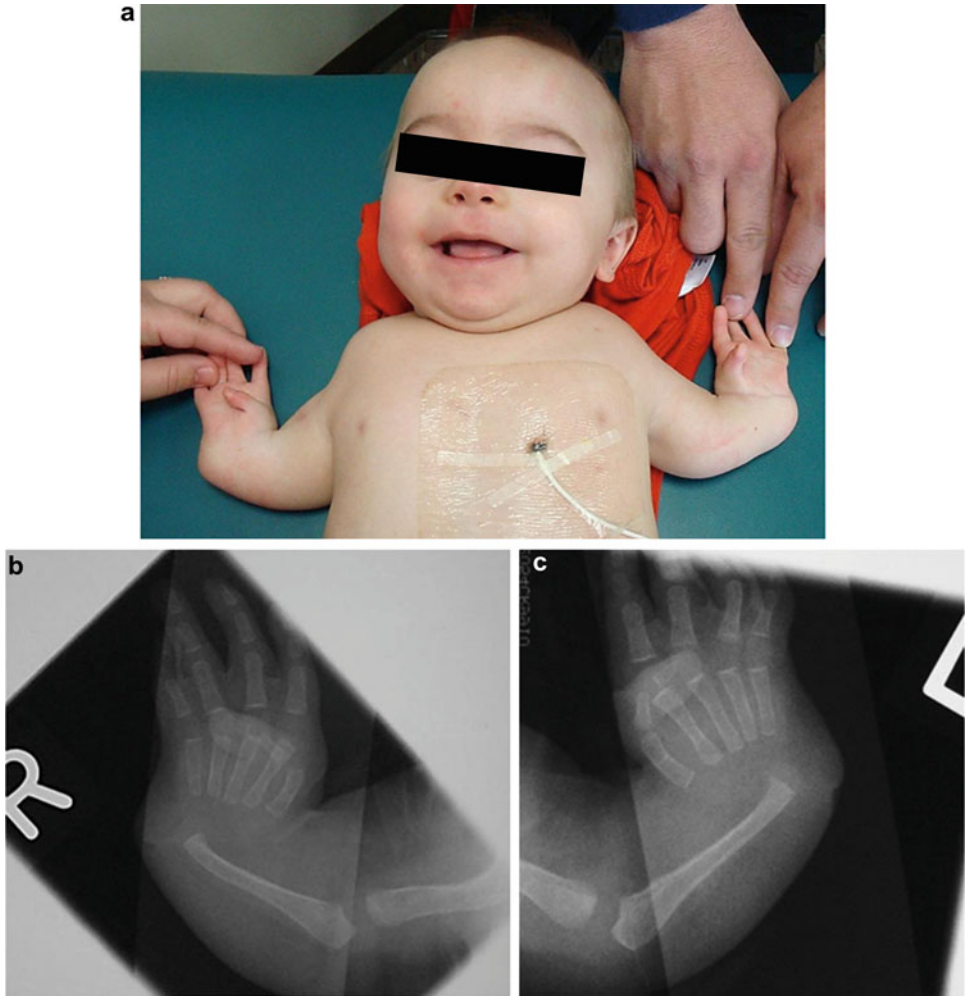

Fig. 3 (**a**–**c**) An 8-month-old boy (**a**) was noted to have club hands with radial aplasia (**b**, **c**). Platelet count was 28,000 at birth. He was diagnosed to have thrombocytopenia, necessitating repeat platelet infusions

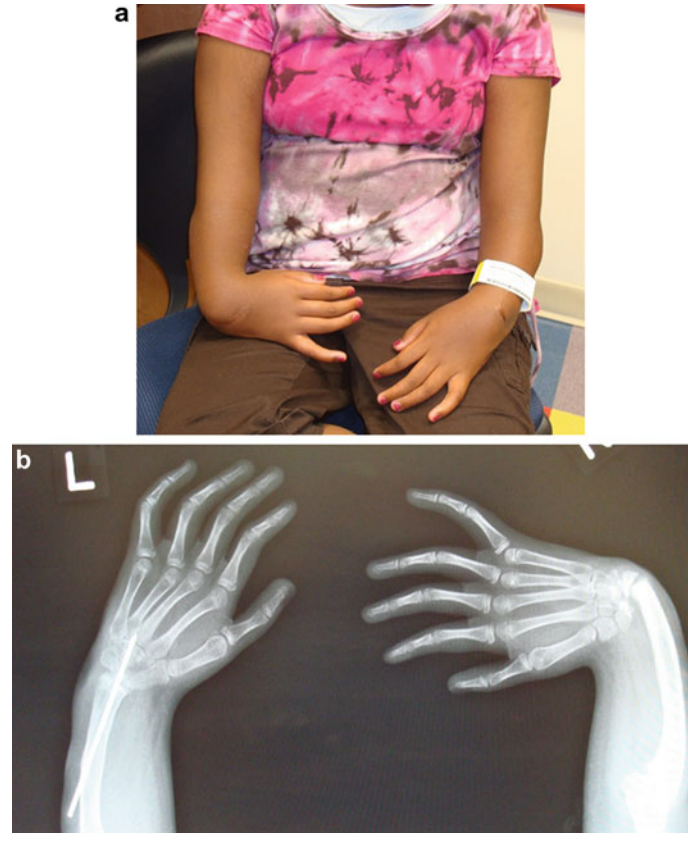

Fig. 4 (**a**, **b**) An 8-year-old girl with TAR syndrome showing similar clinical (**a**) and radiographic (**b**) features

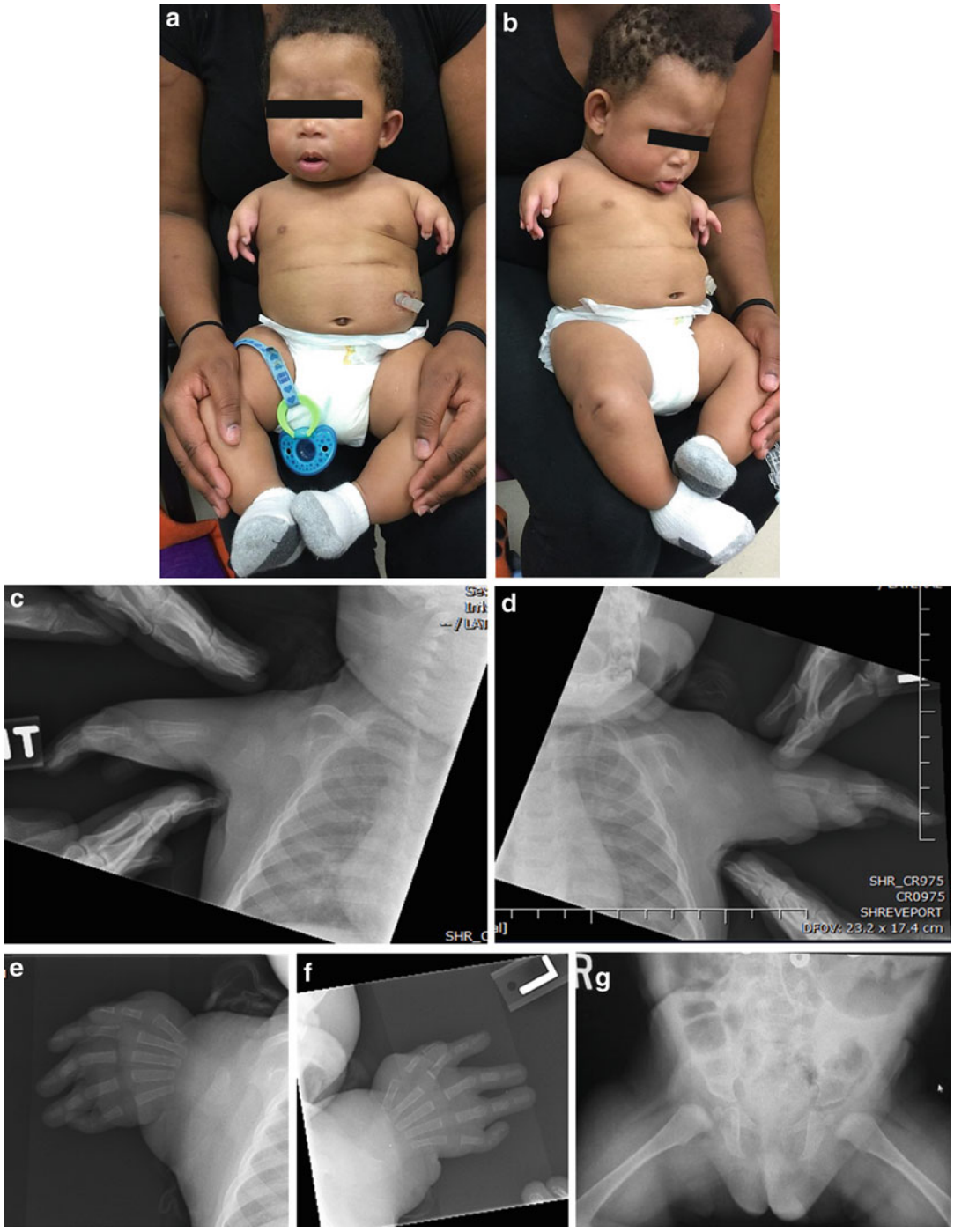

Fig. 5 (**a**–**g**) This 9-month-old boy was evaluated for thrombocytopenia-absent radius syndrome, showing phocomelia of both upper extremities (**a**, **b**). After delivery, she was noted to have phocomelia, abnormal legs and knees, and was in the hospital requiring repeat platelet transfusions due to thrombocytopenia (Platelet count of 20,000). Radiographs showed prominent hypoplasia and dysplasia of both humeri and shoulder girdles, radial and

Fig. 5 (continued) ulnar aplasia (**c**, **d**), presence of thumbs, hypoplasia of the middle and distal phalanges of the little fingers, and proximal soft tissue syndactyly between all digits (**e**–**f**). Hip radiograph showed bilateral hip dysplasia (**g**) with prominent genu varum deformity and bilateral flexion deformity at the knees (not shown). Microarray CGH identified a deletion of approximately 1,754 Mb at 1q21.1q21.2. This alteration span over the region 1q21.1 susceptibility locus for TAR syndrome, sufficient to verify the diagnosis of TAR syndrome (Al Kaissi et al. 2015)

Tibial Hemimelia

Contents

Tibial hemimelia, known as congenital longitudinal deficiency of the tibia, is a very rare anomaly with an incidence of approximately 1 in 1,000,000 births (Fernandez-Palazzi et al. 1998). It is characterized by deficiency of tibia with relatively intact fibula and marked shortening of the involved extremity with a severe equinovarus deformity (Weber 2007). Although the majority of cases of tibial hemimelia are sporadic, familial incidence of tibial aplasia has been observed (Fernandez-Palazzi et al. 1998; Javid et al. 2000; Leite et al. 2010).

Synonyms and Related Disorders

Tibial aplasia; Tibial hemimelia–polydactyly–triphalangeal thumb syndrome; Tibial hypoplasia

Genetics/Basic Defects

1. Etiology:
   1. Sporadic
   2. Autosomal dominant inheritance
   3. Possible autosomal recessive inheritance: report of isolated tibial hemimelia in two sibs born to phenotypically normal parents (McKay et al. 1984)
2. Molecular defect in tibial hemimelia–polydactyly–triphalangeal thumb syndrome (autosomal dominant trait):
   1. Identification of 404 G > C mutation in ZRS (zone of polarizing activity in developing embryonic limbs regulatory sequence) in a family with absent tibiae–polydactyly–triphalangeal thumbs with fibular dimelia, previously described by Vargas et al. (1995) and another family with tibial hemimelia–polydactyly–triphalangeal thumb syndrome (Wieczorek et al. 2010)
   2. Identification of 404 G > A mutation in ZRS in a sporadic case presenting with bilateral complete tibial hemimelia, preaxial polydactyly of the toes, and five-fingered hands (Cho et al. 2013)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_281

Clinical Features

1. The defect can range from moderate hypoplasia to the complete absence of the tibia (aplasia).
2. Can occur either as a solitary disorder or as a part of more complex malformation syndrome (Fernandez-Palazzi et al. 1998; Matsuyama et al. 2003).
3. Generally bilateral.
4. Shortened and medially bowed varus leg.
5. Fibular dimelia.
6. Frequently associated with preaxial mirror polydactyly of the feet or aplasia of the hallux (Verghese et al. 2007; Wilcox et al. 2015).
7. Associated foot anomalies include tibial ray(s) deficiencies or tarsal coalitions and hand malformations (Richieri-Costa et al. 1987; Schoenecker et al. 1989; Tokmakova et al. 2003; Lezirovitz et al. 2008).
8. Jones classification of congenital tibial aplasia and dysplasia (Jones et al. 1978):
    1. Type Ia, tibia not visible with hypoplastic distal femoral epiphysis
    2. Type Ib, absent tibia with normal distal femoral epiphysis
    3. Type II, absent distal tibia
    4. Type III, absent proximal tibia
    5. Type IV, hypoplastic distal tibia with ankle diastasis
9. Weber classification of tibial hemimelia (Weber 2008):
    1. I (tibial hypoplasia)
    2. II (tibial diastasis)
    3. III (distal tibial aplasia with (IIIa) or without (IIIb) cartilaginous anlage)
    4. IV (proximal tibial aplasia with (IVa) or without (IVb) cartilaginous anlage)
    5. V (bifocal tibial aplasia with (Va) or without (Vb) cartilaginous anlage)
    6. VI (tibial agenesis with double fibula with (Via) or without (VIb) cartilaginous anlage)
    7. VII (tibial agenesis with a single fibula with (VIIa) or without (VIIb) cartilaginous anlage)
10. Main syndromes associated with tibial hemimelia (Bergère et al. 2015):
    1. Tibial hemimelia–polysyndactyly–triphalangeal thumb syndrome (THPTTS):
        1. Tibial aplasia/hypoplasia
        2. Polysyndactyly
        3. Triphalangeal thumb
    2. Gollop–Wolfgang complex:
        1. Tibial aplasia/hypoplasia
        2. Femoral duplication
        3. Ectrodactyly
    3. Short rib polydactyly syndrome type 2 (Majewski type) (see the chapter):
        1. Micromelia
        2. Short ribs
        3. Polydactyly
    4. Trichorhinophalangeal syndrome type 2 (Langer–Giedion syndrome):
        1. Sparse scalp hair
        2. Bulbous nasal tip
        3. Short stature
        4. Multiple exostoses
    5. Split-hand/split-foot malformation:
        1. Tibial aplasia/hypoplasia
        2. Ectrodactyly of fingers and toes

Diagnostic Investigations

1. Radiographic features (Clément's classification) (Clement et al. 2000; Bergère et al. 2015):
    1. Type I (59%): total absence of the tibia
    2. Type IIa (10%):
        1. Presence of a proximal tibia (cartilaginous epiphysis).
        2. Although not detectable in young infants, the bone gradually develops via secondary ossification.
        3. Hypoplasia of the adjacent distal epiphysis of the femoris often observed.
    3. Type IIb (24%): presence of a proximal tibia comprising a portion of metaphysis and diaphysis, as well as a normal epiphysis and normal growth plate
    4. Type III (1.5%): presence of a distal tibia only

5. Type IV (5%):
    1. The entire tibia is present but shows either extensive hypoplasia or just hypoplasia of its distal end.
    2. The distal end is also tapered and sometimes deviates from the distal end of the fibula to articulate with the medial side of the ankle.
6. Other features:
    1. In most cases, the fibula is normal in both size and appearance, although shortened and/or deformed fibulas can be observed.
    2. The position of its proximal end depends on the presence and size of the tibia.
    3. Rarely, the fibula is also found to be absent.
    4. Unlike in fibular hemimelia, the femur is often normal.
    5. In other cases, tibial hemimelia can be associated with moderate femoral hypoplasia, femoral duplication, or hypoplasia of the distal femoral ossification center.
    6. The foot may be normal (but in varus equinus) or hypoplastic and deformed.
2. Molecular study of ZRS gene

Genetic Counseling

1. Recurrence risk depending on the etiology and the mode of inheritance:
    1. Patient's sib:
        1. Isolated: not increased
        2. Autosomal dominant inheritance: not increased unless a parent is affected
        3. Autosomal recessive inheritance: 25%
    2. Patient's offspring:
        1. Isolated: unknown
        2. Autosomal dominant inheritance: 50%
        3. Autosomal recessive inheritance: not increased unless the spouse is also a carrier
2. Prenatal diagnosis by ultrasonography: prenatal diagnosis of Gollop–Wolfgang complex was made by ultrasound at 17 weeks of gestation, showing tibial agenesis and femoral bifurcation (Mendilcioglu et al. 2009).
3. Management:
    1. Limb reconstruction (Al Kaissi et al. 2014):
        1. Transferring the upper end of the fibula to the intercondylar notch of the femur and correcting the equinovarus deformity of the ankle by centralizing the fibula into the talus.
        2. May be necessary to ablate the foot and hence the child becomes a below-knee amputee whose knee joint needs external support (Kalamchi and Dawe 1985; Loder and Herring 1987; Pattinson and Fixsen 1992).
    2. Limb-preservation (salvage) surgeries (Wada et al. 2006; Shahcheraghi and Javid 2015):
        1. Foot centralization
        2. Tibiofibular fusion for partial deficiency of the tibia
        3. Fibular transfer for complete deficiency of the tibia
        4. Leg lengthening of either femur or fibula

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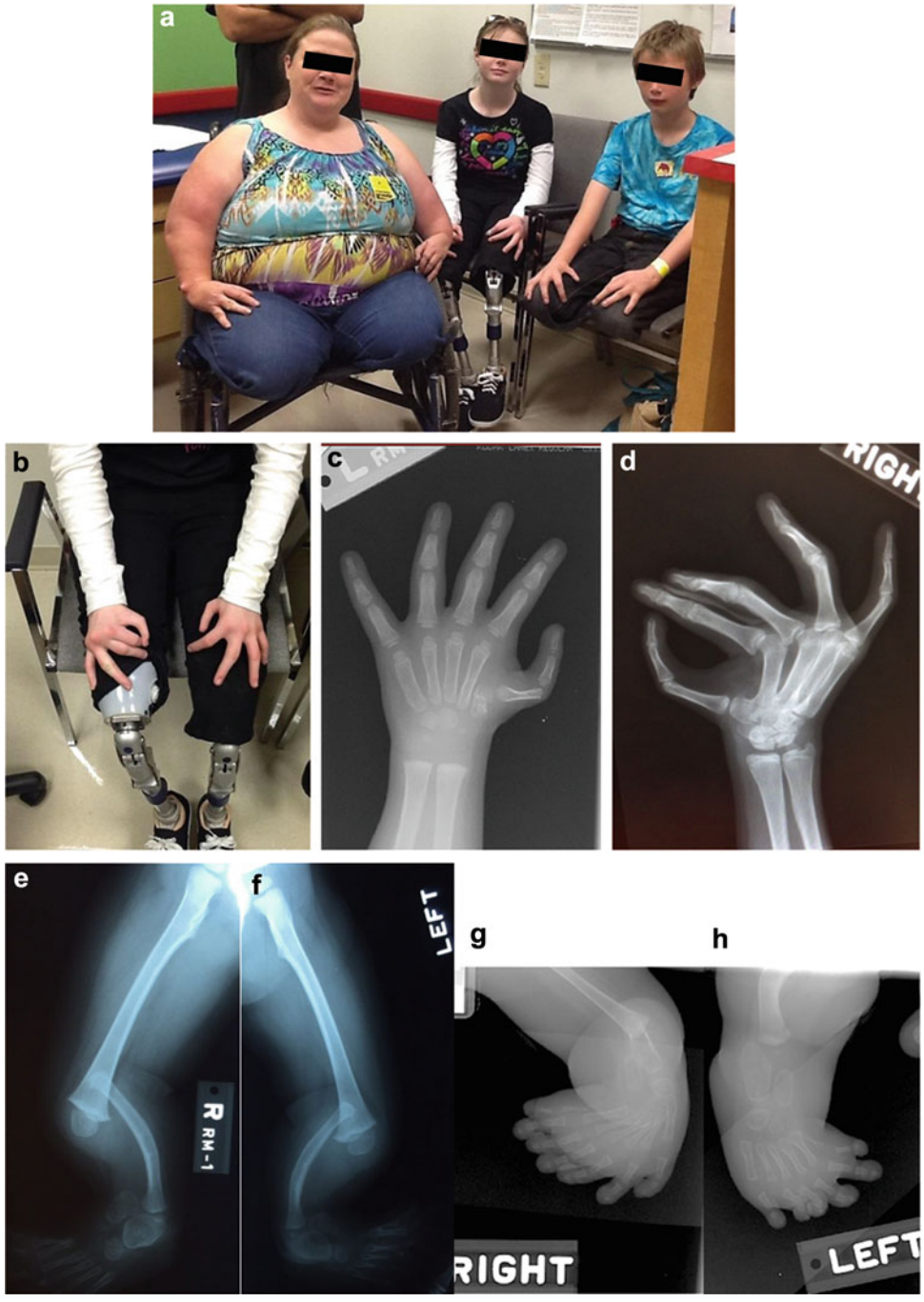

Fig. 1 A 15-year-old female, her 14-year-old brother, and their mother (**a**) were evaluated for multiple abnormalities of the limbs, including bilateral tibial aplasia. She was born with five fingers (**b**) on the right with fingerlike thumb, five digits on the left hand (**c),** and radial deviation of the right 2nd–3rd fingers (**d**) (radiograph of the left hand at 3 years and 8 months and the right hand at 15 years of age). She was also born with bilateral tibial aplasia (**e, f**) with dislocation at the knee joint, right foot with seven digits (**g**), left foot with six digits (**h**), clubfoot, and very short and curved fibulae. Both legs were amputated at the knees (**b)**

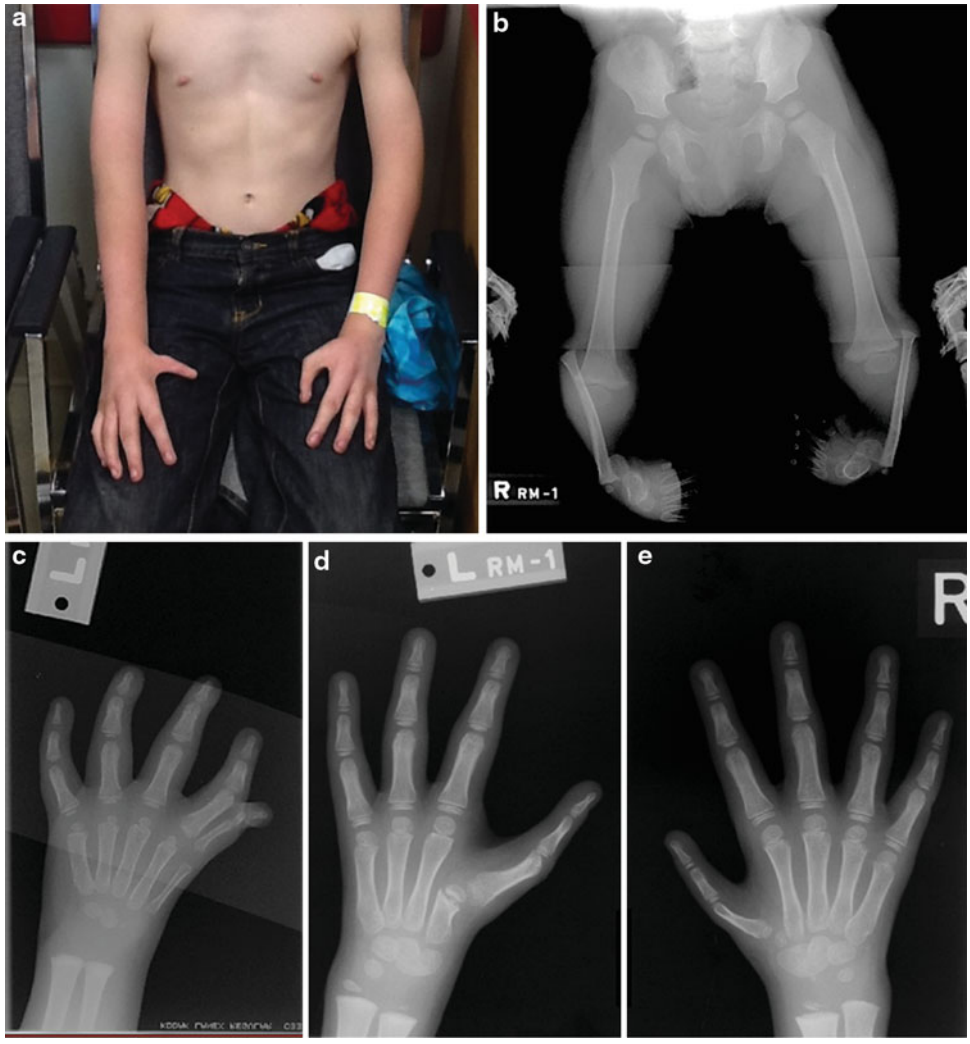

Fig. 2 Her brother (**a**) was born with absent tibias, dislocation and superior displacement of the fibula, and prominent clubfoot deformity with 14 toes (duplication of the 1st ray of both feet) (**b**). Left hand with hypoplastic thumb (**c**) which was removed (**d**), five digits on the right hand (**e**), and short forearms. Both legs were amputated at the knees

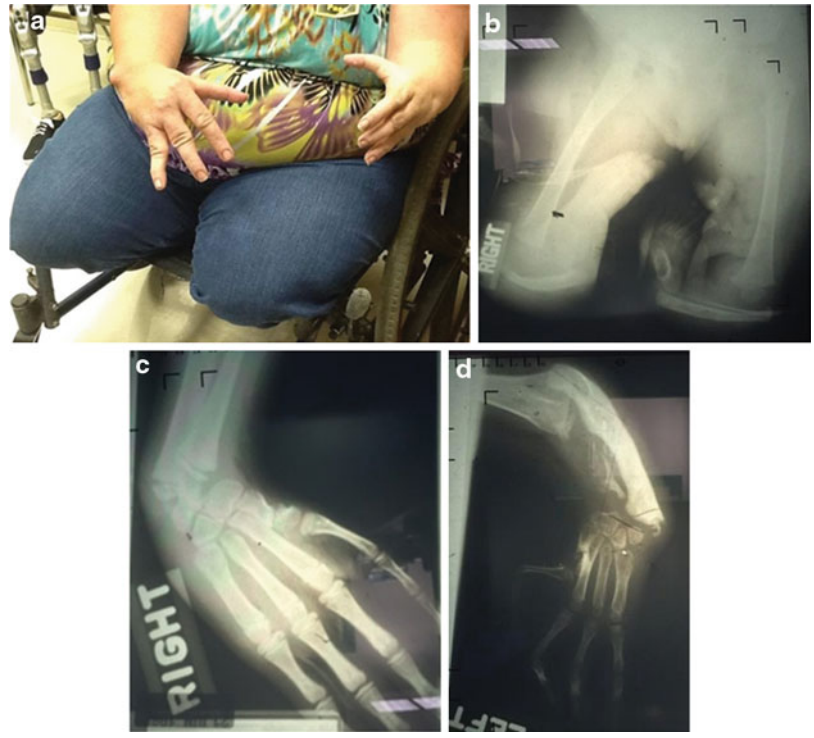

Fig. 3 The mother (**a**) had foreshortened forearms, clubhands with missing thumbs, and both hands with four fingers. The radiographs (**b–d**) showed the absence of bilateral tibias, bilateral clubfeet, left foot with five metatarsals and seven phalanges, and right foot with five metatarsals; short right radius, absent left radius, clubhands, four metacarpals, and absent bilateral thumbs. She was amputated at the knees (**a**)

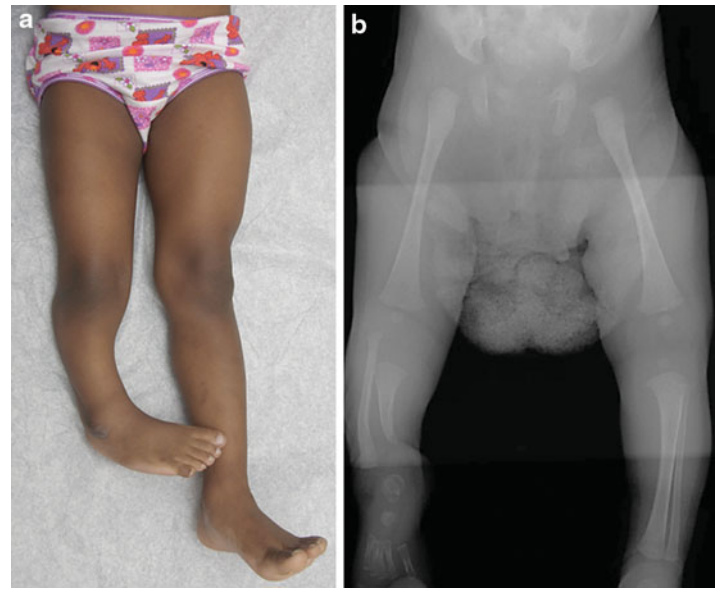

Fig. 4 A 3-year-old girl (**a**) was evaluated for right tibial hemimelia. The radiograph (**b**) at a month of age showed a shortened and deformed tibia with a deformed fibula of the right lower leg. The bilateral femurs, left tibia, and left fibula appear normal. Her family history shows an aunt and a cousin with clubfoot (Courtesy of Dr. Grace Guo)

Treacher-Collins Syndrome

Contents

Treacher-Collins syndrome (TCS), also called Treacher Collins-Franceschetti syndrome or mandibulofacial dysostosis, is an autosomal dominant disorder affecting the development of structures derived from the first and second branchial arches during early embryonic development (Poswillo 1975). The incidence is estimated to be 1 in 50,000 live births.

Synonyms and Related Disorders

Berry-Treacher Collins syndrome; Franceschetti-Zwahlen-Klein syndrome (Rogers 1964); Mandibulofacial dysostosis (Franceschetti and Klein 1949); Mandibulofacial dysostosis with microcephaly (mandibulofacial dysostosis, Guion-Almeida type); Treacher Collins-Franceschetti syndrome

Genetics/Basic Defects

1. Inheritance
    1. An autosomal dominant disorder (Murty et al. 1988)
        1. Rare incomplete penetrance
        2. Wide variability
    2. Forty percentage of cases have a previous family history.
    3. Sixty percentage of cases possibly arise from de novo mutations of *TCOF1*.
2. The *Treacher Collins-Franceschetti syndrome 1* (*TCOF1*) gene
    1. The only gene currently known to be associated with TCS
    2. Mapped to chromosome 5q32-q33.1
    3. Positional cloning of a gene (Treacle) involved in the pathogenesis of Treacher-Collins syndrome (The Treacher Collins Syndrome Collaborative Group 1996)
    4. Encoding a serine/alanine-rich protein, called "treacle" (Jones et al. 1999; Isaac et al. 2000)
    5. A complete coding sequence of the Treacher Collins-Franceschetti syndrome 1 gene (*TCOF1*) (Wise et al. 1997) has been identified (Dixon et al. 1997).
    6. Mutations in the *TCOF1* gene (Marszalek et al. 2002)
        1. Type of mutations

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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1. Deletions
2. Insertions
3. Missense mutations

2. Two mutations affecting splicing of the primary transcript are located in:
   1. Introns 3 (304 + 5 G → C)
   2. Introns 22 (3550 + 1G → A)
3. Most mutations result in a premature termination codon (Dixon 1996), producing a truncated protein devoid of the nuclear localization signals (NLSs).

3. TCS occurs as a result of a mutation in 1 of 3 genes: *TCOF1*, *POLR1C*, or *POLR1D* (Fisher 2011; Katsanis and Cutting 2012; Chung et al. 2014).
   1. Mutation of the *TCOF1* gene: most commonly found, accounting for 78%–93% of TCS cases.
   2. Mutations of *POLR1C* and *POLR1D* account for approximately 8%.
   3. TCS caused by heterozygous mutation in *TCOF1*, or less commonly *POLR1D*, is inherited in an autosomal dominant manner, whereas compound heterozygous mutations in *POLR1C* are inherited in an autosomal recessive manner.
   4. Autosomal dominant inheritance accounts for the majority of TCS cases.
   5. It is estimated that 60% of autosomal dominant cases of TCS arise as the result of de novo mutations, and 40% are familial.
4. Mandibulofacial dysostosis with microcephaly (Guion-Almeida type) (Huang et al. 2016)
   1. Mandibulofacial dysostosis with microcephaly (MFDM; MIM# 610536) is a multiple malformation syndrome comprising microcephaly, first and second branchial arch anomalies (Pierre-Robin sequence, malar hypoplasia, zygomatic clefting, microtia, middle ear malformations, choanal atresia, and/or auditory atresia), hearing loss, dysmorphic features, and variable systemic malformations (esophageal atresia, short stature, cardiac and/or genitourinary anomalies, and proximally placed thumbs) (Guion-Almeida et al. 2006; Wieczorek et al. 2007, 2009).
   2. Haploinsufficiency of *EFTUD2* (MIM# 603892), encoding U5–116 kDa, a spliceosomal GTPase, is responsible (Lines et al. 2012).
   3. The majority of described mutations are de novo, with a variety of documented mutation types (missense, nonsense, frameshift, splice site, and complete or partial gene deletions, including cytogenetically visible deletions); however, autosomal dominant inheritance and, less commonly, germline mosaicism have been reported (Lines et al. 2014).
   4. Mutations in several other genes involved in spliceosomal function or linked aspects of mRNA processing have also recently been identified in human disorders with specific craniofacial malformations (Lehalle et al. 2015).
      1. *SF3B4* in Nager syndrome, an acrofacial dysostosis (AFD)
      2. *SNRPB* in cerebrocostomandibular syndrome, characterized by Robin sequence and rib defects
      3. *EIF4A3* in the AFD Richieri-Costa–Pereira syndrome, characterized by Robin sequence, median mandibular cleft, and limb defects
      4. *TXNL4A* in Burn-McKeown syndrome, involving specific craniofacial dysmorphisms
5. Pathogenesis (Trainor et al. 2009)
   1. Prenatal mandibulofacial dysostosis: The pathogenesis of the events leading to the deformities of the first and second branchial arches is extrapolated to 7 weeks in utero (Behrents et al. 1977).
   2. Detection of an appropriate kinase activity in branchial arches I and II that coincides with peak expression of the Treacher-Collins syndrome gene product, treacle (Jones et al. 1999)
   3. General cranioskeletal hypoplasia occurs due to generation of insufficient neural crest cells.

4. Insufficient neural crest cell number is a consequence of neuroepithelial progenitor cell death.
5. Tcof1/Treacle is an important spatiotemporal regulator of ribosome biogenesis.
6. Haploinsufficiency of Tcof1/Treacle results in deficient ribosome biogenesis, which is incapable of meeting the proliferative needs of the neuroepithelium.
7. Deficient ribosome biogenesis leads to nucleolar stress activation and stabilization of p53, which causes the high degree of neuroepithelial apoptosis and consequent loss of neural crest cells.
8. In an experimental animal-based strategy, genetic and/or chemical inhibition of p53-dependent apoptosis can restore the normal complement of neural crest cells and prevent the development of TCS craniofacial anomalies.

Clinical Features

1. Interfamilial and intrafamilial variability (van Gijn et al. 2013)
2. Facial characteristics (Cobb et al. 2014)
    1. Usually present bilaterally and symmetrically
    2. Parotid gland hypoplasia/aplasia
    3. Pseudo macrorhinia: apparent large beak-like nose because of lack of malar development and hypoplastic supraorbital ridges
    4. Sideburn hair on cheek (25%)
3. Eyes/eyelids
    1. Short and downslanting palpebral fissures
    2. Colobomata and hypoplasia of the lower lids and lateral canthi
    3. Lower lid eyelashes aplasia
    4. Partial absence of eyelid cilia
    5. Hypertelorism
    6. Euryblepharon (a congenital anomaly characterized by sagging of the lateral aspect of the lower eyelid away from the eye)
4. Ears (Posnick and Ruiz 2000)
    1. External ear anomalies
        1. Small/absent, rotated, and low-set pinnas
        2. External auditory canals bilateral stenosis/atresia
        3. Extra ear tags and/or fistulas
    2. External auditory canal abnormalities
        1. Symmetric (88%)
        2. Atretic (54%)
        3. Stenotic (31%)
        4. Normal (15%)
    3. Middle ear cavity ossicular deformities
        1. Symmetric (96%)
        2. Hypoplastic (85%)
        3. Hypoplasia/agenesis of malleus and incus
        4. Monopodal stapes
        5. Ankylosis of stapes
    4. Conductive hearing loss results from variable degrees of hypoplasia of the external auditory canals and ossicles of the middle ears (Marres 2002).
5. Nose/mouth
    1. Respiratory compromise in severely affected patients as a result of the following two factors (Posnick and Ruiz 2000):
        1. Presence of maxillary hypoplasia, which tends to constrict the nasal passages and results in a degree of choanal stenosis or atresia
        2. Presence of mandibular micrognathia and a retropositioned tongue obstructing the oropharyngeal and hypopharyngeal spaces
    2. Nasal deformity
    3. Macrostomia (15%)
    4. Cleft palate with or without cleft lip (33%)
    5. Velopharyngeal incompetence
    6. Difficulties with swallowing and feeding secondary to musculoskeletal underdevelopment and cleft palate
    7. High-arched palate
    8. Dental anomalies (60%)
        1. Tooth agenesis (33%)
        2. Enamel deformities (20%)

3. Malposition of maxillary first molars (13%)
4. Malocclusion

9. Hypoplastic and retropositioned tongue
10. Open bite

6. Facial bone malformations: the most characteristic findings
   1. Hypoplasia of the malar bones
      1. Often with clefting through the arches
      2. Limited formation of the residual zygomatic complex
   2. Orbits
      1. Hypoplastic lateral aspects of the orbits
      2. Dysplastic inferior-lateral orbits
   3. Maxilla and mandible
      1. Characteristically hypoplastic (malar hypoplasia)
      2. Variable effects on the temporomandibular joints and the muscles of mastication
      3. Anterior open bite malocclusion
      4. A steep (clockwise-rotated) occlusal plane
7. Airways
   1. Airway problems secondary to mandibular hypoplasia
   2. Pharyngeal hypoplasia
   3. Choanal atresia
   4. Tracheo-esophageal fistula
   5. Small or obstructed nasal passages
8. Neurological
   1. Normal intelligence
   2. Conductive hearing loss
   3. Vision loss associated with strabismus, refractive errors, and Anisometropia
   4. Impaired vision (underdeveloped lateral orbit and extraocular muscles)
9. Sleep apnea and sudden infant death syndrome
10. Fetal phenotype: Affected fetuses identified prenatally or at autopsy tend to have a more severe phenotype than living patients, with an increased frequency of Pierre Robin sequence (Konstantinidou et al. 2013).
11. Differential diagnosis (Dixon 1995)
    1. Nager acrofacial dysostosis (please see the chapter on ▶ "Nager Acrofacial Dysostosis")
       1. Features similar to those of TCS
          1. Zygomatic hypoplasia
          2. Downward slanting of the palpebral fissures
          3. Micrognathia
          4. Anomalies of the external ears
          5. Cleft palate
       2. Limb defects (not observed in TCS)
          1. Often asymmetrical
          2. Preaxial limb defects
          3. Hypoplastic or absent thumbs
          4. Radial hypoplasia or aplasia
          5. Radioulnar synostosis
    2. Miller acrofacial dysostosis
       1. Facial features similar to TCS and Nager syndrome
       2. Limb defects
          1. Postaxial limb defects
          2. Most commonly with absence or incomplete development of the fifth digital ray of all four limbs
    3. Oculoauriculovertebral (OAV) spectrum
       1. OAV spectrum
          1. Sporadic occurrence in vast majority of cases
          2. One to two percentage of cases with a previous family history
          3. Includes hemifacial microsomia and Goldenhar syndrome
       2. Hemifacial microsomia
          1. Primarily affecting development of the ear, mouth, and mandible
          2. Wide variable expression
          3. Affecting primarily only one side of the face
       3. Goldenhar syndrome (please see the chapter on ▶ "Goldenhar Syndrome")
          1. Facial involvement
          2. Vertebral anomalies
          3. Epibulbar dermoids

Diagnostic Investigations

1. Radiography and CT for evaluation of craniofacial abnormalities (Megalhães et al. 2007)
   1. Mandibular hypoplasia

2. Bilateral condylar hypoplasia
3. Coronoid process absence/hypoplasia
4. Maxillary bone hypoplasia
5. Malar bone hypoplasia
6. Narrowed frontal bone
7. Maxillary sinus walls hypertrophy
8. Auricular canals atresia
9. C1-C2 fusion
10. Temporal muscle hypotrophy
11. Masseter muscle hypotrophy
12. Lateral pterygoid hypotrophy
13. Decreased oropharyngeal space
14. Conchae hypertrophy

2. Audiological evaluation for hearing impairment
3. DNA diagnosis: Direct sequencing of the coding and flanking intronic regions of *TCOF1* detects mutations in about 90–95% of patients (Katsanis and Cutting 2012).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: low unless a parent is affected in which case the risk to the sibs is 50% or has germline mosaicism
   2. Patient's offspring: 50%
2. Prenatal diagnosis available for pregnancies at increased risk for TCS
   1. Two-dimensional and preferably three-dimensional sonography (Meizner et al. 1991; Ochi et al. 1998; Hsu et al. 2002; Pereira et al. 2013)
      1. Polyhydramnios
      2. Demonstration of characteristic facies of TCS (Crane and Beaver 1986; Cohen et al. 1995)
         1. Slanting forehead
         2. Downward slanting palpebral fissures
         3. Microphthalmos
         4. Micrognathia
         5. Abnormal appearance of the nose with narrow nostrils
         6. Cleft lip/palate
         7. Low-set dysplastic ears (microtia)
         8. Abnormal fetal swallowing
   2. Prenatal diagnosis of Treacher-Collins syndrome in the first trimester using combined linkage analysis and ultrasound imaging (Edwards et al. 1996).
   3. Amniocentesis or CVS
      1. To detect *TCOF1* mutation (Ellis et al. 2002)
      2. The disease-causing allele of an affected individual must be identified before prenatal testing can be performed.
      3. The presence of a *TCOF1* mutation detected by prenatal diagnosis does not predict the specific malformations or severity of the disease.
   4. Prenatal diagnosis by fetoscopy in the second trimester of pregnancy (Nicolaides et al. 1984)
      1. Mandibular hypoplasia
      2. Abnormalities of the palpebra and auricles
      3. An associated cleft palate
   5. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member.
3. Management
   1. Multidisciplinary team (Thompson et al. 2009)
      1. Geneticist
      2. Neonatologist
      3. Pulmonologist
      4. Ophthalmologist
      5. Otolaryngologist
      6. Audiologist
      7. Speech pathologist
      8. Dentist/orthodontist
      9. Radiologist
      10. Psychologist/social worker
      11. Craniofacial surgeons
   2. Severe case
      1. Secure airway by tracheostomy if necessary
      2. A gastrostomy for feeding
   3. To promote normal language development
      1. Cleft palate repair
      2. Evaluation by an otolaryngologist, audiologist, and speech pathologist
   4. Orthodontic alignment of the teeth

5. Craniofacial reconstruction (Posnick 1997)
    1. Zygomatic and orbital reconstruction
    2. Maxillomandibular reconstruction
    3. Nasal reconstruction
    4. Soft tissue reconstruction
    5. External ear reconstruction
    6. External auditory canal and middle ear reconstruction
    7. The improvement in the patients' facial appearance seems to have a direct, positive influence, creating psychosocial and social benefits for them (Arndt et al. 1987)
6. Bimaxillary orthognathic surgery in the Treacher-Collins patients may be performed safely with long-term dental and skeletal stability (Nguyen et al. 2016)

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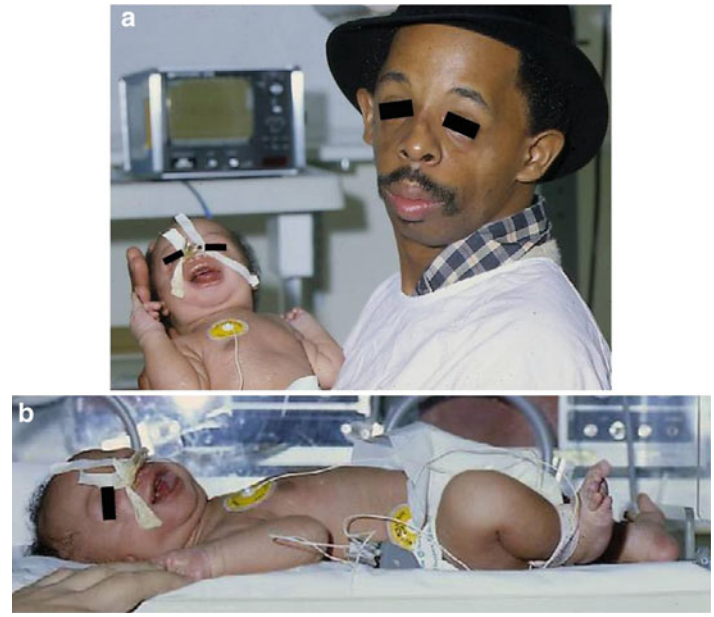

Fig. 1 (**a**, **b**) A child and the father with Treacher-Collins syndrome. The faces are characterized by an antimongoloid slant of the palpebral fissure, colobomata and hypoplasia of the lower lids, and small and receding chins

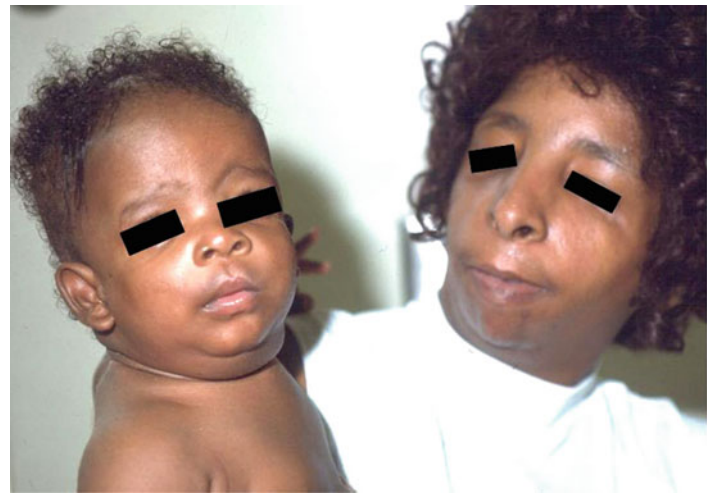

Fig. 2 An infant and his mother with Treacher-Collins syndrome showing similar features. The infant is mildly affected

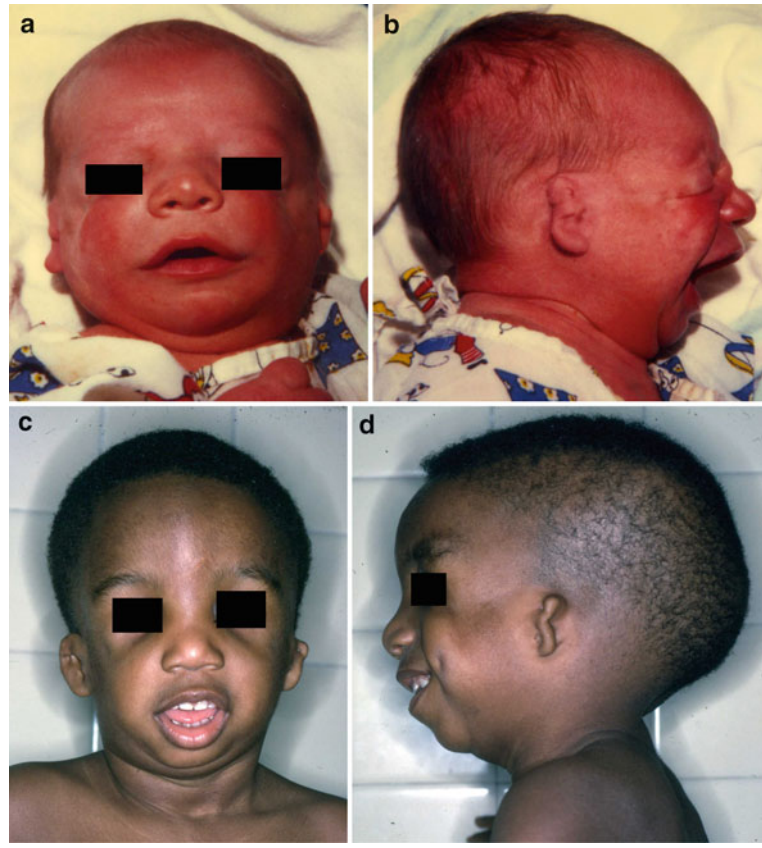

Fig. 3 (**a**–**d**) A newborn (**a**, **b**) and a child (**c**, **d**) with Treacher-Collins syndrome showing antimongoloid slant of the palpebral fissures, coloboma and hypoplasia of the lower lids, and microtia

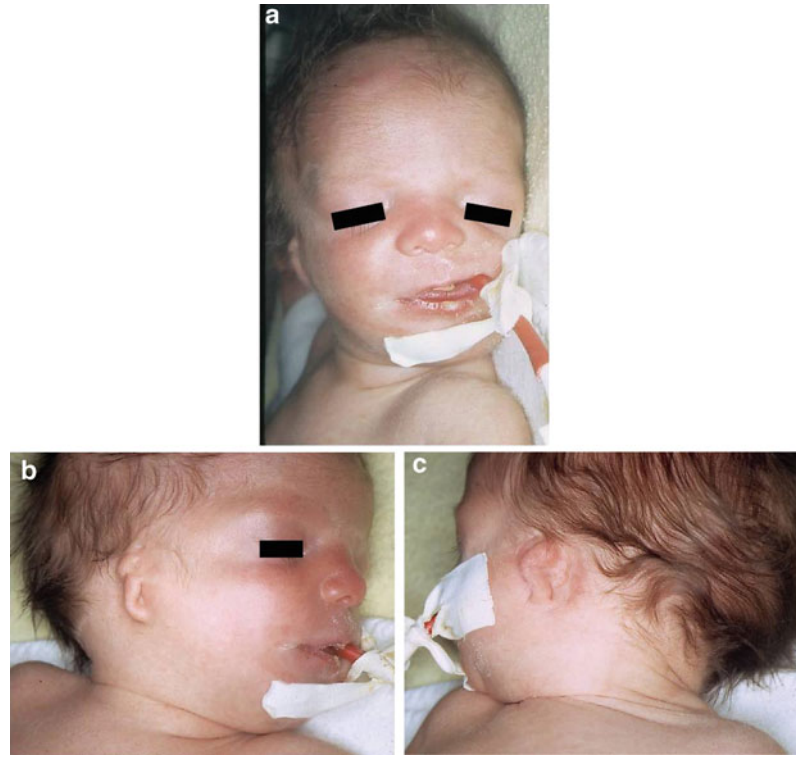

Fig. 4 (**a**–**c**) Another infant with typical Treacher-Collins syndrome

Trimethylaminuria

Contents

Trimethylaminuria, also called fish odor syndrome, is a metabolic disorder characterized by a distinctive decaying fish odor of sweat, urine, breath, and other body secretions due to the presence of abnormal amounts of the dietary-derived tertiary amine, trimethylamine (TMA).

Synonyms and Related Disorders

Fish-odor syndrome

Genetics/Basic Defects

1. Inheritance (Rehman 1999)
   1. Autosomal recessive (Ayesh et al. 1993)
   2. The incidence of heterozygous carriers of the allele for impaired *N*-oxidation is estimated to be of the order of 1%.
2. Basic defect
   1. Caused by deficiency of the flavin-containing mono-oxygenase isoform 3 (FMO3) (Akerman et al. 1999a, b). A defect in hepatic *N*-oxidation of dietary-derived TMA (trimethylamine) causes excess excretion of TMA, leading to affected individuals to have a body odor resembling rotten fish (Basarab 1999).
   2. Caused by loss-of-function mutations in the *FMO3* gene (mapped on 1q24.3) encoding an isoform of flavin-containing mono-oxygenase have been shown to underlie trimethylaminuria/fish odor syndrome (Lambert et al. 2001; Lunden et al. 2002).
   3. Defects in *FMO3* underlie fish-odor syndrome and that the Pro 153 → Leu 153 missense mutation described is a cause of this distressing condition (Dolphin et al. 1997).
   4. Common variants in the *FMO3* gene lead to greatly reduced enzyme activity in vivo, shown to cause mild to transient trimethylaminuria (Zschocke 1999).
   5. A report of a novel homozygous deletion of exons 1 and 2 in an Australian of Greek ancestry with trimethylaminuria, the first report of a deletion causative of trimethylaminuria (Forrest et al. 2001).
   6. Also can be caused by liver, kidney, and/or gastrointestinal dysfunction, including dietary carnitine overloading secondary to the gut-generated substrate overwhelming the hepatic enzymes' oxidizing capacity.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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7. Trimethylaminuria reflects how genetic constitution can adversely influence interactions with one's diet (Mitchell 2001).

3. TMA (Lunden et al. 2002)
   1. Trimethylaminuria (fish-odor syndrome) (Al-Waiz et al. 1987a, 1988)
      1. An inborn error of oxidative metabolism.
      2. Trimethylaminuria is an inborn error in the ability to *N*-oxidize TMA which is inherited as an autosomal recessive trait.
      3. Furthermore, an oral challenge dose with 600 mg of TMA may be used to identify carriers of the condition (Al-Waiz et al. 1989).
   2. Derived from the intestinal bacterial degradation of foods rich in choline and carnitine, such as egg yolk, liver, kidney, soybeans, peas, and saltwater fish
   3. Readily absorbed from the gut and is normally oxidized by the liver FMO3 to odorless trimethylamine *N*-oxide which is then excreted in the urine
   4. Impaired oxidation of TMA, thought to be the cause of the fish odor syndrome, is responsible for the smell of rotting fish.
4. FMO3
   1. One of the major enzyme systems protecting humans from the potentially toxic properties of drugs and chemicals.
   2. Converts nucleophilic heteroatom-containing chemicals and endogenous materials to polar metabolites, which facilitate their elimination.
   3. *N*-oxygenates trimethylamine to trimethylamine *N*-oxide which is excreted in a detoxication (Cashman 2000) and deoderation process.
   4. The *N*-oxidation of TMA in humans is polymorphic and under single gene diallelic control in which individuals who are homozygous for the variant allele exhibit marked *N*-oxidation deficiency and trimethylaminuria (Al-Waiz et al. 1987b).
   5. Prevalent polymorphisms of the human FMO3 may contribute to low penetrance and predispositions to diseases associated with adverse environmental exposures to heteroatom-containing chemicals, drugs (e.g., tricyclic antidepressants, ranitidine, amphetamine, methamphetamine, clozapine, chlorpromazine, methimazole), and endogenous amines.
5. Biological basis of primary trimethylaminuria (Christodoulou 2011)
   1. Dietary sources of choline, lecithin, and trimethylamine-*N*-oxide (TMAO) are converted to trimethylamine by anaerobic bacteria in the large intestine.
   2. Normally, any trimethylamine absorbed from the gut into the bloodstream is converted back to odorless TMAO by FMO3 in the liver.
   3. However, when this enzyme is defective, trimethylamine, which has the distinctive odor of "rotting fish," accumulates and is eliminated in sweat, urine, and breath.
6. Classification of the disorder (Mitchell 2001; Mitchell and Smith 2001; Cashman et al. 2003; Mackay et al. 2011)
   1. Primary genetic form (primary trimethylaminuria)
      1. The best understood of the various forms of the disorder
      2. Accounts for a large proportion of the known cases
      3. Human FMO3
         1. Highly polymorphic.
         2. Some mutations, either alone or in combination, are associated with dysfunctional enzyme activity and the metabolic disorder.
         3. Two relatively common polymorphisms (P153L and E305X) appear to account for the majority of severe cases of trimethylaminuria.
         4. Some other mutations are associated with inactivation of FMO3.
         5. Combinations of intragenic polymorphisms within FMO3 appear to determine a modified and less severe form of the condition.
         6. Some mutations appear to be benign.

2. Acquired form (secondary trimethylaminuria)
    1. Several cases of clinically and biochemically diagnosed trimethylaminuria have been reported to emerge in adult life.
    2. No previous history in childhood
    3. No familial background
    4. Possible mechanism: Viral hepatitis may have been responsible for precipitation of the condition possibly by insertion of viral DNA into the genome thereby affecting normal expression of the human *FMO3* gene.
    5. Transient childhood forms
        1. A transient or mild form of trimethylaminuria may occur during early childhood.
        2. Compound heterozygosity for several mutations has been detected by molecular analysis in some cases.
        3. As with her parents and one of her two brothers, the proband carried three polymorphisms: c.472 G > A p. E158K in exon 4, c.627 + 10 C > G (IVS5 + 10G > C) and c.485-21 G > A (IVS4-22G > A) in intronic regions. Despite the same genotypic condition only the girl had symptoms attributable to the trimethylaminuria (transient childhood form) (D'Angelo et al. 2014).
    6. Transient form associated with menstruation
        1. Fish odor intensifies with onset of menstruation.
        2. Trimethylaminuric condition deepens just prior to the onset of menstruation.
    7. Precursor overload
        1. Overload of precursors, such as choline, lecithin, and carnitine, saturates the existing levels of flavin monooxygenase.
        2. Exposure to unusually high levels of such precursors may hasten a fish odor syndrome, especially if the individual is a haplotype for certain mutations.
    8. Disease states that impair trimethylamine metabolism
        1. Advanced liver disease
        2. Advanced renal disease
        3. Association with temporal lobe epilepsy (Pellicciari et al. 2010) and behavioral disturbances
        4. Bacterial vaginosis with fish odor in vaginal secretions
    9. Exacerbating factors
        1. Pyrexic states
        2. Stress
        3. Puberty
        4. Sweating
        5. Exercise
        6. Emotional upsets
        7. Menstruation
        8. Oral contraceptives
        9. Foods rich in choline

Clinical Features

1. Present from birth but manifests itself with the introduction of a diet, including foods that contain high amounts of choline or trimethylamine *N*-oxide (Chalmers et al. 2006)
2. Unmistakable, strong fishy body odor from excess unmetabolized trimethylamine in the urine, sweat, and other body secretions (breath, saliva, vaginal secretions)
3. An early report of trimethylaminuria or fish odor syndrome in a child (Marks et al. 1976)
4. Seven percent of a group of subjects complaining of unpleasant body odor had the fish odor syndrome (Ayesh et al. 1993).
5. Skin sores induced by choline-rich foods
6. A case reported of trimethylaminuria that first developed in adulthood (Ruocco et al. 1989): a characteristic fish odor of his sweat, urine, and to his breath after the consumption of choline-rich foods. Elevated levels of trimethylamine were present in the urine after dietary tests and identified by means of gas chromatography.
7. Serious social/behavioral problems resulting from strong body odor (Mitchell 2001; Cashman et al. 2003)
    1. Subject to ridicule, loss of confidence, and school disruption

2. Destructive to personal, working, and career lives of the affected individuals
3. Clinical depression
4. Attempted suicide

8. Highly variable severity of the syndrome

Diagnostic Investigations

1. Use of choline loading as an aid to diagnosis of trimethylaminuria (Marks et al. 1977)
2. Demonstration of elevated TMA after a choline-rich diet by gas chromatography–mass spectrometry measurement. TMA challenge test (with a 600 mg TMA oral challenge dose and analysis of 0–8 h urine samples) is useful in confirming unequivocally the trimethylaminuric patients as well as indicating the status of the parents as carriers.
3. Quantitative determination of trimethylamine in urine by solid-phase microextraction and gas chromatography–mass spectrometry (Mills 1999)
4. Mass spectroscopy and proton nuclear magnetic resonance (NMR) spectroscopy (Murphy 2000)
    1. Have the advantage of being able to detect TMA and TMA *N*-oxide simultaneously with great sensitivity
    2. NMR has further advantage of requiring no prior extraction or separation of metabolites and thus measurement can be done directly on urine samples.
    3. Urinary TMA concentrations were reduced to virtually nil as measured by mass spectrometry after the elimination of the major choline sources (fish and eggs) from the diet (Hollinger and Sheikholislam 1991).
5. Increase in urinary excretion of trimethylamine with decreased trimethylamine oxide
6. Molecular genetic testing used in primary trimethylaminuria (Phillips and Shephard 2015)
    1. Sequence analysis of *FMO3* gene to detect mutations (~99%)
    2. Gene-targeted deletion/duplication analysis
7. Combination of the proton nuclear magnetic resonance (NMR) spectroscopy to assess activity of the mutant enzyme with gene sequence and expression technology provides a powerful means of determining genotype-phenotype relationships in trimethylaminuria (Murphy 2000).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25%
    2. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis: possible by demonstrating the previously characterized mutation in the fetal DNA obtained by amniocentesis or CVS
3. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified. (Phillips and Shephard 2015).
4. Management (Rehman 1999; Mitchell 2001; Chalmers et al. 2006)
    1. Restriction of dietary sources of trimethylamine: the main therapeutic approach (Chen and Aiello 1993; Phillips and Shephard 2015)
        1. Restriction of trimethylamine (milk obtained from wheat-fed cows)
        2. Restriction of its precursors including choline-rich food
            1. Egg yolk
            2. Liver
            3. Kidney
            4. Peas
            5. Beans
            6. Peanuts
            7. Soya products
            8. Brassicas (include cabbage, broccoli, and turnip)
            9. Legumes
            10. Fish
        3. Trimethylamine *N*-oxide (TMAO) source
            1. Some saltwater fish (cod, skate)
            2. Cephalopods (include cuttlefish, squid, and octopus)

3. Crustaceans (include crabs, lobsters, and shrimps)
4. Dietary restriction appears to be successful in the management of the majority of patients.
5. Appears to be most effective in mild to moderate forms of fish odor syndrome arising from particular mutations or haplotypes

2. Suitable diet include:
   1. Dark green leafy vegetables
   2. Fortified bread and cereals
   3. Orange juice
3. Freshwater fish may be eaten freely.
4. Avoid exacerbation factors such as pyrexia, stress, exercise, or any other cause of increased perspiration (Messenger et al. 2013)
5. Vitamin supplementation with riboflavin, a precursor of the FAD cofactor for flavin monooxygenase function, in an attempt to maximize any residual activity
6. Drug treatment: Occasionally a short course of metronidazole, neomycin, and lactulose may suppress production of TMA by reducing the activity of gut microflora in some patients (Fraser-Andrews et al. 2003).
7. Copper-chlorophyllin tablets to moderate gut flora activity and complex TMA
8. Use of "malodor suppressants" in hygiene products and soaps and body lotions with a low pH (3.5–6.5) to disguise the offensive smell of trimethylamine
9. If clinical improvement is not accomplished through diet alone, metronidazole may be used to decrease microbial gut flora and reduce TMA production (Treacy et al. 1995; Ferrari and Nield 2006; Mackay et al. 2011). Neomycin, activated charcoal, and lactulose have been used in the past but frequently cause diarrhea. To prevent treatment failure related to drug resistance, the administration of metronidazole for 1- to 2-week intervals interspersed with drug-free periods is advised (Treacy et al. 1995; Ulman et al. 2014).
10. Counseling of the social/behavioral problems
11. Gene therapy and enzyme induction with drugs provide hope for the future.

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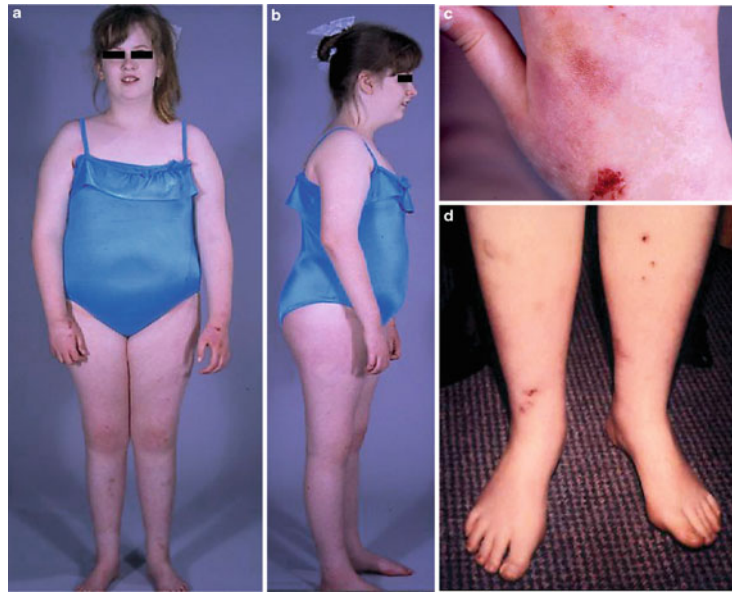

Fig. 1 (**a**–**d**) A 12-year-old girl (**a**, **b**) with trimethylaminuria showing multiple sores on the hands (**c**) and legs (**d**). At age 4, she developed unpleasant fish odor and constant scratching of her skin. Trimethylaminuria was diagnosed based on markedly increased urinary TMA by gas chromatography after loading with choline. The patient started with a baseline level of 0.28 mg TMA/mg creatine that is four times of control. After 8, 16, and 24 h of loading with choline, the values went up to 2.8 mg (41×), 3.99 mg (57×), and 9.93 mg (95×), respectively. In addition, the diagnosis of Prader-Willi syndrome was made at age 9 because of relative obesity, hypotonia, delayed psychomotor development, almond-shaped eyes, small hands and feet, and presence of chromosome abnormality of del(15)(q11q13)

Triploidy

Contents

Triploidy is defined as the presence of three sets of haploid (69) chromosomes. Triploid fetuses occur in about 1% of recognized pregnancies, 1 in 100,000 liveborns, and constitute about 15% of all fetuses with chromosome abnormalities. There is a slight excess of males (M1.5: F1). Most triploid fetuses often result in spontaneous abortions between 7 and 17 weeks of gestation. However, rare instances of a live triploid infant have been reported (Allen and Pritchard 2000).

Synonyms and Related Disorders

Diandric triploidy; Digynic triploidy; Diploidy/triploidy mosaicism; Partial hydatidiform mole of the placenta; Triploid fetus (69,XXY, 69, XXX, diploid/triploid mosaicism)

Genetics/Basic Defects

1. Origin of triploidy (Allen and Pritchard 2000; Baumer et al. 2000; Benn et al. 2001; Daniel et al. 2001)
    1. Diandric origin of the triploid fetuses (type I)
        1. Mechanisms of paternal origin of the supernumerary haploid set (Egozcue et al. 2002)
            1. Dispermy: fertilization of a haploid egg by two haploid sperms (dispermy) accounting for 66% (most common mechanism leading to triploidy)
            2. Faulty meiotic division in the male: fertilization of a normal ovum by a diploid sperm (diandry) (about 24%)
        2. Characteristics of diandric fetuses
            1. Relatively normal fetal growth
            2. Slight macrocephaly
            3. Marked syncytiotrophoblastic hyperplasia
            4. Hydatidiform changes of the placental villi (partial mole) (large cystic placenta)
    2. Digynic origin of triploid fetuses (type II)
        1. Mechanisms of maternal origin of the supernumerary haploid set

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1. Mitotic errors in female germ cell precursors: fertilization of a diploid ovum by a normal sperm (digyny) (about 10%)
2. Errors in maternal meiosis: an error at meiosis I or II or incorporation of the second polar body postulated

2. Characteristics of digynic fetuses
   1. Generally marked fetal (asymmetric) growth retardation
   2. Relative macrocephaly
   3. Small, noncystic placenta
   4. Maternally derived triploidy was often found in those fetuses that survived until late pregnancy.
   5. The extra set was maternal in origin in all cases, supporting previous research indicating longer in utero survival of maternally derived triploid fetuses. These findings provide evidence for an instance of genomic imprinting in humans (Dietzsch et al. 1995).

2. Diploidy/triploidy mosaicism
   1. Mechanisms (Phelan et al. 2001)
      1. Postzygotic maldivision of a triploid or diploid zygote
      2. Incorporation of the second polar body into a daughter nucleus of the developing embryo: Second polar body incorporation into a blastomere results in 46, XX/69, XXX mixoploidy (Muller et al. 1993).
      3. Fertilization of a diploid ovum with incorporation of the second diploid polar body
      4. Fertilization of the first polar body and ovum by individual spermatozoa with suppression of one second polar body
      5. Dispermy or diploid sperm fertilization with incorporation of an independently fertilized second polar body
      6. Chimera formation by union of diploid and triploid embryos
      7. Vanishing twin and chimerism
   2. Characteristics of diploid/triploid fetuses: rarer and less severe phenotype than true triploidy
3. Triploidy and in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) (Dayal et al. 2009)
   1. Diandric triploidy is observed with spontaneous as well as conventional IVF and is assumed to be the most common form of triploidy (Jun et al. 2006).
   2. Intracytoplasmic sperm injection, by its virtue of injecting a single sperm into a single oocyte, negates the potential for dispermic triploidy.
   3. Digynic triploidy occurs secondary to failed meiosis II expulsion of the second polar body and subsequent fertilization of a diploid oocyte. Cytogenetic evidence of three pronuclei post-ICSI zygotes that result from failed extrusion of the second polar body (Tsuchiya et al. 2002).
   4. Mechanistically, this may occur with a damaged metaphase plate or oocyte cytoskeleton (Kimura and Yanagimachi 1995), after abnormal spindle formation or increased female age (Spandorfer et al. 1998; Tsuchiya et al. 2002). The latter etiologies may represent an occult oocyte factor.
4. Two different forms of hydatidiform mole (Lawler et al. 1982a, b; Devriendt 2005)
   1. Complete hydatidiform mole
      1. A complete hydatidiform mole is diploid, i.e., the presence of 46 chromosomes, but all chromosomes are of paternal origin.
      2. The complete moles (Szulman and Surti 1978)
         1. Undergo early and total hydatidiform change from edema to central cistern formation, the embryos proper having perished before the establishment of a functioning circulation.
         2. Trophoblastic hyperplasia is conspicuous and the connection of this group to chorioncarcinoma is well established.
      3. As always in the case of the uniparental origin of one or more

chromosomes, this requires at least two sequential errors.
    1. The most frequent mechanism of origin is the fertilization of an oocyte without nucleus (or with inactivated nucleus) by a single sperm, followed by duplication of the haploid genome (Lawler et al. 1982b).
    2. In the remainder (20–25%), an enucleated oocyte is fertilized by two sperm cells (Kovacs et al. 1991).
    3. A third possible cause, the fertilization of an empty oocyte by a diploid sperm cell, is extremely rare (Zaragoza et al. 2000).
  4. As expected also in the hydatidiform mole, all mitochondria have an exclusively maternal origin (Azuma et al. 1991).
  5. Biparental complete hydatidiform mole: In exceptional cases (~10 families have been reported) of histologically typical complete hydatidiform mole, a biparental origin of the chromosomes has been found (reviewed by Fisher et al. 2004).
2. Partial hydatidiform mole
    1. In the partial moles there is a slow hydatidiform change that affects only some of the villi, but which seems to follow along the same lines as in complete moles (Szulman and Surti 1978).
        1. There is focal moderate trophoblastic hyperplasia, villous "trophoblastic inclusions" (that appear in triploids only), and maze-like central cisterns in the later cases.
        2. The partial mole, 46 XX, partakes of morphologic characteristics of both main syndromes and may represent an unusual syndrome of its own.
    2. The partial mole is caused by a triploidy, the presence of three copies of each chromosome.
    3. Triploidy is one of the most common chromosomal anomalies, with an incidence of 10% in spontaneous abortions (Hassold et al. 1980).
    4. The extra haploid set of chromosomes can have either a maternal origin (and then called digynic triploidy) or paternal (diandric triploidy).
    5. The majority of triploidies are sporadic, but a few cases have been reported with recurrent triploidy in three pregnancies (Pergament et al. 2000; Brancati et al. 2003; Huang et al. 2004). In all three cases, the origin of the triploidy could be investigated at least in one pregnancy and all were of maternal origin (digynic). This observation could be explained by a genetic defect in the maternal meiosis.
    6. In digynic triploidy, no partial mole is observed. All paternally derived triploids (diandric) in which a pathologic diagnosis could be made were partial moles, whereas only three of 15 maternally derived triploids (digynic) on which a diagnosis could be made were molar (Jacobs et al. 1982).
    7. Using polymorphic pericentromeric markers, it was shown that the majority of digynic triploidy is the result of errors in the second meiotic division. Digyny accounted for the majority of triploids, even in the embryonic and fetal periods (McFadden and Langlois 2000).
    8. A predominance of maternal origin of the extra haploid set in triploidies diagnosed prenatally, mainly due to longer survival time for digynic triploidies (Miny et al. 1995).
    9. More than 90% of partial moles are secondary to diandric triploidy, and this condition accounts for most cases of persistent trophoblastic disease after partial mole (Jauniaux 1999).
    10. So far, no proven cases of familial recurrent triploidy have been reported.
    11. The majority of triploid fetuses ascertained through a spontaneous abortion are diandric.

Clinical Features

1. The clinical syndrome associated with triploidy (Wertelecki et al. 1976)
    1. Quite typical but is rarely reported in near-term stillborns and newborns
    2. The occurrence of a large placenta with areas of hydatidiform changes in combination with an edematous fetus with macroglossia, facial clefts, eye defects, dysplastic cranial bones, omphalocele, meningomyelocele, syndactyly, and, in males, genital maldevelopment is suggestive of a triploid chromosomal constitution.
2. Prenatal history
    1. IUGR
        1. Asymmetrical (digynic)
        2. Symmetrical (diandric)
    2. Prematurity
    3. Hydrops
    4. Polyhydramnios
    5. Oligohydramnios
    6. Partial hydatidiform mole (placenta)
3. Craniofacial features
    1. Dysplastic calvarium
    2. Microcephaly
    3. Large posterior fontanelle
    4. Ocular hypertelorism or hypotelorism
    5. Epicanthal folds
    6. Exomphalos
    7. Microphthalmia
    8. Iris and choroid colobomas
    9. Midfacial hypoplasia
    10. Arhinia
    11. Small upturned nose
    12. Choanal atresia
    13. Single nostril (in holoprosencephaly)
    14. Micrognathia
    15. Cleft lip/palate
    16. Low-set ears
    17. Short neck
    18. Thick nuchal fold
    19. Cystic hygroma
4. CNS
    1. Hypotonia
    2. Arnold-Chiari malformation
    3. Posterior fossa cyst (Dandy-Walker malformation)
    4. Holoprosencephaly
    5. Hydranencephaly
    6. Hydrocephalus (20%)
    7. Absent corpus callosum (15%)
    8. Absent gyri of the brain
    9. Hypoplastic cerebellum
    10. Absent first cranial nerve
    11. Encephalocele
    12. Lumbosacral meningomyelocele (20%)
5. Gastrointestinal malformations
    1. Omphalocele
    2. Ventral wall defects
    3. Incomplete rotation of colon
    4. Agenesis of gallbladder
    5. Meckel diverticulum
    6. Duodenal atresia
    7. Malfixation of cecum
    8. Inguinal hernia
6. Endocrine abnormalities
    1. Adrenal hypoplasia (Kalousek 1984)
    2. Thyroid hypoplasia
    3. Lingual thyroid
    4. Thymic hypoplasia
    5. Leydig cell hyperplasia
    6. Gonadal dysgenesis
7. Genitourinary abnormalities
    1. 69,XXY triploid fetus
        1. Varying degree of ambiguous genitalia (40%)
        2. Hypospadias (40%)
        3. Cryptorchidism (85%)
        4. Micropenis (75%)
        5. Scrotal abnormalities (60%) including bifidity, scrotal hypoplasia, or agenesis
        6. Leydig cell hyperplasia (20%)
        7. Sex reversal (an example of true hermaphroditism associated with multiple malformations): bilateral ovotestes but no evidence of Müllerian derivatives (Petit et al. 1992)
    2. 69,XXX triploid fetus
        1. Gonadal dysgenesis
        2. Renal abnormalities
            1. Multicystic kidneys

2. Hydronephrosis
3. Glomerulosclerosis

8. Gastrointestinal abnormalities
   1. Omphalocele
   2. Diaphragmatic hernia
   3. Gastroschisis
   4. Malrotation
   5. Gallbladder hypoplasia
   6. Pancreas hypoplasia
9. Cardiovascular anomalies
   1. VSD
   2. ASD
   3. PDA
   4. PA
   5. Tetralogy of Fallot
   6. Truncus arteriosus
   7. Aberrant right subclavian artery
   8. Cardiomegaly
10. Respiratory tract abnormalities
    1. Small chest
    2. Pulmonary hypoplasia
    3. Absent lung lobation
    4. Congenital cystic adenomatoid malformation of the lung
11. Axial skeleton of triploidy fetuses: The most remarkable findings in the axial skeleton of triploid fetuses are vertebral fusions in six of 15 cases (Kjaer et al. 1997).
12. Triploidy syndrome encompasses features found in trisomies 13, 18, and 21 (Saadi et al. 1976).
13. Phenotype of triploidy embryos (Harris et al. 1981)
    1. Retarded limb development
    2. Facial dysplasia
    3. Subectodermal hemorrhage
    4. Cystic chorionic villi
14. Prognosis (intrauterine and postnatal survival) (Baumer et al. 2000)
    1. Majority die early in gestation.
    2. Very few surviving into the third trimester
    3. The fetuses rarely survive to delivery.
       1. Profoundly malformed
       2. Growth-restricted
       3. Survival measured in hours to days
       4. Unusually long survival (2 months) in a case of full triploidy of maternal origin (Fryns et al. 1977)
       5. A report of digynic triploid infant surviving for 46 days (Hasegawa et al. 1999)
    4. Fetuses with extra maternal haploid set of chromosomes appear to survive longer in utero than those with extra paternal haploid set of chromosomes (Allen and Pritchard 2000).
    5. Some cases of diploid/triploid mixoploidy survive after the neonatal period, which is exceptional: a report of triploid-diploid mosaicism in a deeply mentally retarded adult (Fryns et al. 1980)
15. Diploid/triploid mosaicism (Carakushansky et al. 1994; Van De Laar et al. 2002)
    1. A well-known, clinically recognizable syndrome (Tharapel et al. 1983)
    2. Common features
       1. Mental retardation
       2. Growth retardation
       3. Body and/or facial asymmetry
       4. Hypotonia
       5. Truncal obesity
       6. Prominent forehead
       7. Depressed nasal bridge
       8. Micrognathia
       9. Malformed low-set ears
       10. Syndactyly
       11. Clinodactyly
       12. Transverse palmar creases
       13. A small phallus
       14. Cryptorchidism
       15. Precocious puberty
    3. Additional features
       1. Sandal gap
       2. Short halluces
       3. Seizures
       4. Respiratory distress
       5. Microstomia
       6. Irregular skin
       7. Feeding difficulties
       8. Muscular atrophy of the limbs
    4. Rarer and less severe than true triploidy in which infants can survive beyond neonatal period till over 20 years
    5. Presence of a normal diploid cell line and a second triploid cell line in varying degrees and with varying tissue distribution

Diagnostic Investigations

1. Karyotype of fetus and newborn (Niebuhr 1974; Blackburn et al. 1982)
    1. 69,XXX (one third of cases)
    2. 69,XXY (two thirds of cases)
    3. 68,XX (extremely rare) (Kaffe et al. 1989; Merlob et al. 1991)
    4. 45,X/68,XX mixoploidy: A chromosomal microarray demonstrated monosomy X, but her atypical phenotype prompted further evaluation with a chromosome analysis (Posey et al. 2016).
    5. Evidence of a second gamete fusion after the first cleavage of the zygote in a 47,XX, +18/70,XXX,+18 mosaic. A remarkable diploid-triploid discrepancy after CVS (Tuerlings et al. 1993)
        1. A 70,XXX,+18 karyotype was found by chorionic villus sampling, while the fetal fibroblast culture of the affected fetus revealed a 47,XX,+18 karyotype.
        2. From several possible mechanisms, it was assumed that a second gamete fusion occurred after the first cell division of the zygote. According to this interpretation, the mosaicism arose in very early pregnancy (at the two-cell stage). This discrepancy can therefore be explained by selection pressure, due to the differentiation processes in the embryonic tissues.
    6. Diploid/triploid mosaicism
        1. Less severe phenotype
        2. More compatible with life
        3. Harder to diagnose clinically
        4. Peripheral lymphocyte cultures showing a normal karyotype only
        5. Need fibroblast culture to show the cell line with triploid complement
    7. The finding that certain chromosome regions demonstrate a variable fluorescence pattern which can be used as markers offers a possibility to study the origin of several chromosome abnormalities and especially triploidy (Jonasson et al. 1972)
    8. Specific terminal DNA replication sequence of X chromosomes in different tissues of a live-born triploid infant (Yu et al. 1983)
    9. Molecular determination of the origin of the extra haploid set of chromosomes
        1. Fluorescent polymerase chain reaction (F-PCR) analysis of short tandem repeats (STRs) located on chromosomes such as 21, 18, and 13 (Bán et al. 2002)
        2. Assessment of numerous polymorphic DNA markers
2. Radiographic findings in live-born triploidy (Silverthorn et al. 1989)
    1. Poor ossification of calvarium
    2. Small anterior fontanelle
    3. Craniolacunae
    4. Chondrodysplasia punctata-like calcification
    5. Vertebral fusions
    6. Harlequin orbits
    7. Gracile ribs
    8. Upswept clavicles
    9. Diaphyseal overtubulation of long bones
    10. Vertical ilia
    11. Proximal radioulnar synostosis
    12. Asymmetry of occipitoparietal calvaria (50%)
    13. Less specific findings showing many similarities to those found in trisomy 18
3. CT and MRI of the brain
    1. Cortical hypoplasia
    2. Agenesis of corpus callosum (15%)
    3. Hypoplasia of basal ganglia/occipital lobe
    4. Dandy-Walker anomaly
    5. Arnold-Chiari malformation
4. Histopathology of the placenta
    1. Partial hydatidiform mole change of villi on gross and microscopic examination.
    2. The partial mole is caused by a triploidy (Devriendt 2005).
    3. The villi with molar change show hydropic swelling of the stroma, and trophoblastic proliferation (hyperplasia) is also present in scattered areas.
    4. Irregular cystic cavitation may be seen in larger hydropic villi.

5. Partial hydatidiform mole occurs in a minority of triploid conceptuses (MacFadden and Pantzar 1996).

5. Histology of bone and cartilage in the axial skeleton of human triploidy fetuses (Nolting et al. 2002)
    1. The radiographic characteristics of the vertebral corpora observed in frontal and lateral projection varied from small cleft vertebral corpora to fusions between the individual corpora.
    2. Histological examination of the vertebral corpora confirmed the abnormal pattern of ossification seen radiographically.
    3. As a new finding, abnormal metachromasia of the ground substance was observed in the cartilage.
6. A retrospective pathologic review of nearly 100 spontaneous abortions of cytogenetically verified triploid constitution (Szulman et al. 1981)
    1. A majority (86%) falling within the category of partial hydatidiform mole, the chief criteria being:
        1. Focal syncytiotrophoblastic hyperplasia
        2. Focal villous edema leading to cistern formation
        3. Scalloped outline of villi
        4. Frequent "trophoblastic inclusion" formation
    2. The minority (14%) of the conceptuses were nonmolar with a normal or hypoplastic trophoblast.
    3. The triploid fetuses in both groups tended to die at about 8 weeks' menstrual age. Intrauterine retention was generally prolonged in the partial moles, whereas nonmolar conceptuses tended to abort within the first trimester, often with live or recently dead fetuses.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: The true recurrence risk for cytogenetic abnormalities in subsequent offspring is uncertain but may be slightly increased and higher than expected (Graham et al. 1989).
    2. Patient's offspring: a lethal condition not surviving to reproduce
2. Prenatal diagnosis
    1. First-trimester markers screening (De Graaf et al. 1999)
        1. Low serum marker pregnancy-associated plasma protein A (PAPP-A)
        2. Low serum marker free β-chain of chorionic gonadotrophin (free β-hCG)
    2. Second trimester maternal serum screening (Benn et al. 2001)
        1. High maternal serum hCG associated with triploidy
            1. Nearly always indicating placenta with partial mole (93%)
            2. A high frequency of open neural tube defects or ventral wall defects (29%)
            3. With either XXX or XXY karyotype
        2. Low hCG associated with triploidy
            1. Infrequently associated with a molar placenta (9%)
            2. Not appear to be associated with open neural tube defects or ventral wall defects
            3. An excess of XXX over XXY karyotypes
        3. Highly abnormal maternal inhibin and beta-human chorionic gonadotropin levels along with severe HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome at 17 weeks' gestation with triploidy (Craig et al. 2000)
        4. Large placentas with molar changes (diandry) generally associated with increased maternal serum AFP (MSAFP) and high hCG levels
        5. Elevated MSAFP appeared to be related to the presence of a partial mole (Pircon et al. 1989)
        6. Those with digyny and small monocystic placentas generally associated with normal MSAFP and low hCG

3. Screening for triploidy by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10–14 weeks of gestation (Spencer et al. 2000)
    1. The median multiple of the median (MoM) fetal nuchal translucency (NT) thickness was significantly increased (1.89 MoM).
    2. The maternal serum total and free beta-human chorionic gonadotrophin (hCG) were increased (3.13 MoM and 4.59 MoM, respectively).
    3. The alpha fetoprotein (AFP) was increased (2.14 MoM).
    4. The pregnancy-associated plasma protein A (PAPP-A) was decreased (0.12 MoM).
4. Placental insufficiency as a possible cause of low maternal serum human chorionic gonadotropin and low maternal serum unconjugated estriol levels in triploidy (Fejgin et al. 1992)
5. Pregnancies complicated by triploidy (Rijhsinghani et al. 1997)
    1. The risk of developing preeclampsia or hypertension in the second trimester was 35%.
    2. It appears that elevated serum hCG levels and placentomegaly are associated with a higher risk of preeclampsia but low hCG levels are not.
6. Isolation of nucleated red blood cells from the maternal peripheral circulation at the first trimester (12 weeks gestation): FISH analysis using X and Y and other chromosome-specific probes (De Graaf et al. 1999)
7. Amniocentesis/CVS
    1. Triploidy
    2. Diploidy/triploidy mosaicism
    3. Mixoploidy for trisomy 13 and triploidy detected by amniocentesis at 18 weeks of gestation (Phelan et al. 2001)
        1. Mixoploidy for trisomy 13 and triploidy was confirmed postnatally in blood, skin, and placenta.
        2. Examination of chromosome heteromorphisms and DNA markers suggested the presence of two maternal contributions in the triploid cell line. In addition, the extra chromosome 13 in the trisomic cell line was derived from the mother.
8. Ultrasonography of structural anomalies compatible with triploidy (Mittal et al. 1998; Fernández-Moya et al. 2000; Chen et al. 2013; Zalel et al. 2016)
    1. Severe, early onset asymmetrical growth restriction in the late first and early second trimester (the head size remains almost normal whereas the remainder of the fetal body and skeleton is severely growth-restricted)
    2. Oligohydramnios, asymmetric growth restriction, and a small placenta when the third set of chromosomes is maternal
    3. Large, hydropic-appearing placenta consistent with partial moles (60–80%) when the third set of chromosomes is paternal
    4. Most common sonographic abnormalities (Jauniaux et al. 1996)
        1. Large thickened placenta containing multiple sonolucent areas
        2. Characteristic sharply defined, large and small cystic spaces within the placenta
        3. Hydrops
        4. Ventriculomegaly
        5. Dandy-Walker malformation
        6. Holoprosencephaly
        7. Agenesis of the corpus callosum
        8. Micrognathia
        9. Heart anomalies
        10. Echogenic bowel
        11. Omphalocele
        12. Absent gallbladder
        13. Renal malformations
        14. Thickened nuchal folds
        15. Neural tube defects
        16. Club feet
        17. Syndactyly of the third and fourth fingers
        18. Clenched hands

9. The phenotype described from 54 fetuses by prenatal imaging and autopsy findings (Toufaily et al. 2016)
    1. The presence of major malformations and growth restriction during pregnancy makes triploidy a potential diagnosis.
    2. There are no obligate clinical features in triploidy.
    3. Syndactyly, especially 3–4 syndactyly of the hands, is a distinctive feature.
    4. Cystic changes in the placenta can be seen by ultrasound during pregnancy.
    5. There was no difference in the phenotype between triploid infants associated with partial moles and those with nonmolar placentas.
10. The combination of ultrasonographic examination of the fetoplacental features and measurement of the maternal serum level of human chorionic gonadotropin enables the diagnosis of most cases of triploidy at 10–14 weeks' gestation (Jauniaux et al. 1997).
11. Preimplantation genetic diagnosis in conjunction with in vitro fertilization by a single sperm injection: a viable approach when there are clinical or genetic indications of repeated dispermy, unreduced (diploid) spermatozoa, or unreduced (diploid) oocytes (Pergament et al. 2000)

3. Management
    1. No treatment available for true triploidy, a lethal condition.
    2. Supportive therapy for diploid/triploid mosaicism who may survive beyond neonatal period.

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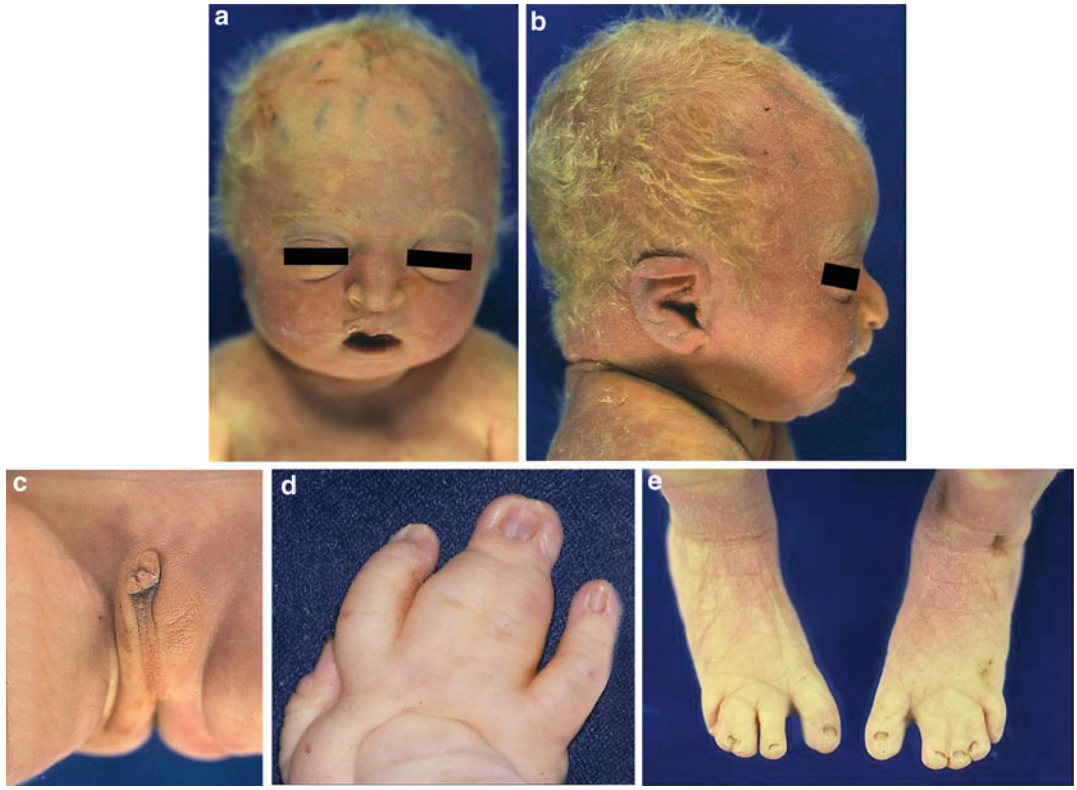

Fig. 1 (**a**–**e**) A newborn (**a**, **b**) with triploidy (69,XXY) showing woolly hair, distinctive facial appearance (epicanthal folds, microphthalmia, beaked nose, small mouth, receding jaw, low-set and malformed ears), partial syndactyly between third-fourth fingers (**d**) and toes (**e**), and ambiguous genitalia (**c**). The infant also had bilateral coloboma and cataracts, short neck, loud continuous heart murmur along the *left* sternal border, and bilateral transverse palmar creases. The infant died at 25 h

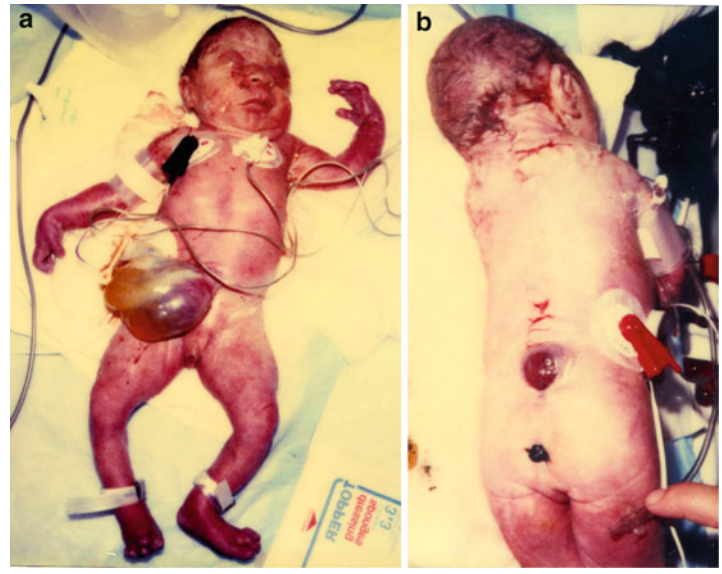

Fig. 2 (**a**, **b**) An infant with triploidy showing abnormal craniofacial features, omphalocele, thick nuchal fold, and lumbosacral meningomyelocele

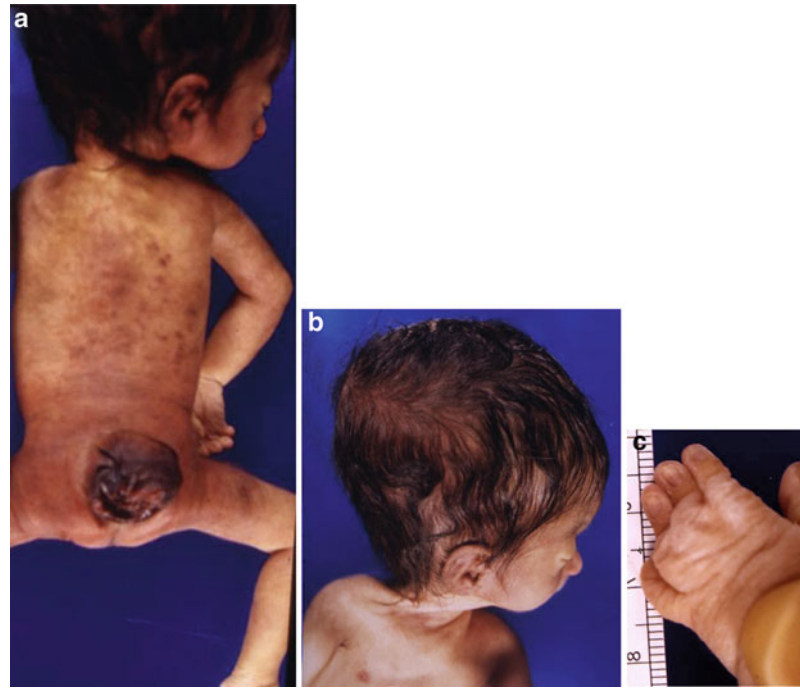

Fig. 3 (**a**–**c**) An infant (**a**, **b**) with triploidy (69,XXX) showing low-set/ malformed ears, syndactyly of two-three-four fingers (**c**), spina bifida, and pulmonary hypoplasia at autopsy. The infant also had a large ventricular septal defect

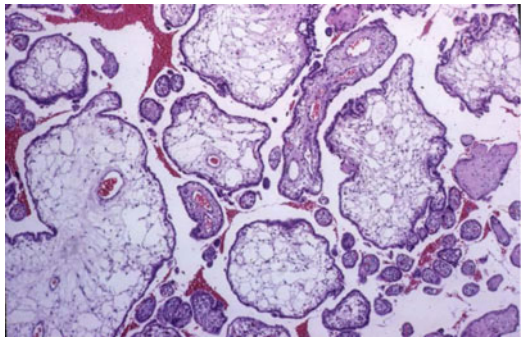

Fig. 4 Partial mole of triploidy placenta. Many villi are enlarged, hydropic, and hypovascular. Prominent infolding and nests of trophoblastic cells in the villous stroma are seen in other areas

Fig. 5 A G-banded karyotype showing 69,XXX

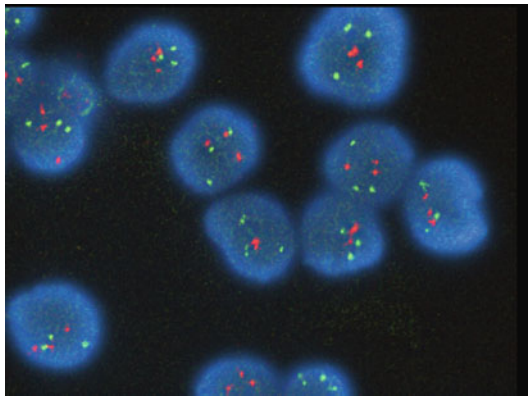

Fig. 6 Triploidy for all chromosomes shown by multicolor FISH on interphase cells. Three copies of chromosome 13 (*green*) and chromosome 21 (*orange*) are shown here

Trismus-Pseudocamptodactyly Syndrome

Contents

The trismus-pseudocamptodactyly syndrome, a relatively rare hereditary disorder, is characterized by inability to open the mouth fully, pseudocamptodactyly, mild foot deformities, and mild short stature. This malformation syndrome was first reported by Hecht and Beals and Wilson et al. in 1969 (Hecht and Beals 1969; Wilson et al. 1969). The term Dutch-Kentucky syndrome was coined for trismus pseudocamptodactyly by Mabry et al. (1974), because the earliest affected member was a young Dutch girl who emigrated to the Southern United States soon after the American Revolution.

Synonyms and Related Disorders

Autosomal dominant distal arthrogryposis type 7 (trismus-pseudocamptodactyly syndrome); Dutch-Kentucky syndrome; Hecht syndrome; Hecht-Beals syndrome

Genetics/Basic Defects

1. Inheritance
    1. Autosomal dominant: multiple affected individuals from a family (O'Brien et al. 1984)
    2. High penetrance
    3. Variable expression (Ter Haar and Van Hoof 1974; Robertson et al. 1982; Tsukahara et al. 1985)
2. Caused by a single mutation, p.R674Q, in *MYH8* (myosin heavy chain 8) gene (Toydemir et al. 2006a; Minzer-Conzetti et al. 2008)
3. Genetic basis of disease in a family with autosomal dominant core-rod myopathy and in three families with autosomal dominant distal arthrogryposis type 7 (trismus-pseudocamptodactyly syndrome) (Mabry et al. 1974; Davidson et al. 2013)
    1. Surprisingly, affected individuals in all four families share a unique three base pair deletion (c.20_22del) in TPM2 (β-tropomyosin).
    2. This dominant mutation results in deletion of a highly conserved amino acid (p.K7del).
    3. The molecular consequences of this mutation were explored using simulated modeling and by expression studies in the zebrafish, in which the mutation appears to disrupt intermolecular interactions and alter mutant TPM2 distribution.

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4. The findings expand the clinical, pathological, and pathomechanistic spectrum of TPM2-related disorders.

4. Pathogenesis
    1. Possible mechanisms of trismus
        1. The shortened lengths of certain mastication muscles presumed to be responsible for the clinical manifestations
            1. Temporalis muscle
            2. Internal pterygoid muscle
            3. Masseter muscle
        2. Enlarged coronoid processes
            1. Resulted from tension exerted by short temporal muscle tendon units
            2. Impinging on the body of the zygomatic bone and inner margin of the arch, thereby limiting mandibular excursion
        3. Secondary to an abnormal ligament between the maxilla and that of the mandible anterior to the masseter muscles
        4. Fibrotic abnormality of the masseter muscle mass in the vicinity of the ascending ramus
    2. Pseudocamptodactyly of fingers
        1. More appropriate term than camptodactyly since it is
            1. Not associated with progressive deformities
            2. Not associated with fixed joint contractures
        2. Caused by a shortening of the flexor digitorum profundus muscle tendon units, involving all fingers
    3. Foot deformities explainable by a shortening of the various muscle tendon groups in the leg and foot
    4. Several individuals with this mutation also had a so-called variant of Carney complex (a high incidence of myxomas, skin pigmentation disorders, endocrine tumors, or overactivity in schwannomas that manifest with cardiac myxomas and spotty skin pigmentation) (Veugelers et al. 2004), suggesting that the pathogenesis of trismus-pseudocamptodactyly syndrome and Carney complex might be shared. However, none of the individuals with trismus-pseudocamptodactyly syndrome studied had features of Carney complex, and p.R674Q was not found in 49 independent cases of Carney complex that were screened. The findings show that distal arthrogryposis syndromes share a similar pathogenesis and are, in general, caused by disruption of the contractile complex of muscle (Toydemir et al. 2006a).
    5. The trismus found in trismus-pseudocamptodactyly syndrome can also be present in Freeman-Sheldon syndrome (also known as distal arthrogryposis type 2A) and Sheldon-Hall syndrome (also known as distal arthrogryposis type 2B) (Hall et al. 1982). Both of these conditions are caused by mutations in the *MYH3* gene (Toydemir et al. 2006b), confirming the hypothesis that the distal arthrogryposis syndromes are caused by aberrant function of the contractile complex of fast-twitch myofibers.

Clinical Features

1. Highly variable expression
2. Two main clinical features (Chen et al. 1986, 1992)
    1. Limited excursion of the mandible
        1. Trismus (restricted opening of the mouth)
            1. Limited mouth opening and shortened flexor muscle-tendon units (Markus 1986)
            2. A leading symptom of trismus pseudocamptodactyly syndrome (Hertrich and Schuch 1991)
            3. Present at birth and persisting throughout life
            4. Greatly variable degree of restricted opening of the mouth
            5. The mouth opening is measured between the incisal edges of the central upper and lower incisors (in millimeter).

6. Children: less than the value for normal children (36.6 ± 5.7 for age 7 years to 47.2 ± 6.4 for age 18 years)
7. Adults: less than the value for normal adults (53.8 ± 6.5 for males, 50.4 ± 5.9 for females)

2. Mastication problems
3. Feeding problems with inadequate caloric intake
4. Swallowing difficulty (dysphagia)
5. Difficulty with dental care
6. Delayed in speech development
7. Difficulty in endotracheal intubation for general anesthesia

2. A flexion deformity of the fingers
   1. Clenched fists may be present at birth.
   2. Typically crawling on the knuckles later in infancy
   3. Occurring with wrist extension (pseudocamptodactyly) which is reversed by wrist flexion
   4. Flexion of the fingers when the hand is dorsiflexed in minimally affected patients
   5. Pronounced flexion with ulnar deviation of the fingers in severely affected patients

3. Other clinical features
   1. Lower extremity and foot deformities (5% of cases)
      1. Mild calcaneovalgus
      2. Equinovarus
      3. Metatarsus varus
      4. Camptodactyly
      5. Vertical talus
      6. Hammertoe deformities
      7. Shortening of both the gastrocnemiae and hamstring muscles
   2. Soft-tissue syndactyly occasionally present
   3. Mild short stature
   4. Facial asymmetry, ptosis, downslanting palpebral fissures and multiple joint involvement, with bilateral hip dysplasia, reduced elbow supination, vertical tali and talipes in addition to the classical findings of trismus and pseudocamptodactyly (Minzer-Conzetti et al. 2008)

4. Differential diagnosis of restricted mouth opening and/or (pseudo)camptodactyly
   1. Restricted mandibular opening caused by
      1. Intra-articular processes
         1. Trauma
         2. Infection
         3. Ankylosis
      2. Extra-articular processes
         1. Soft tissue and bony obstructions
         2. Neurologic disorders such as tetanus
   2. Trismus in temporomandibular joint dysfunction
   3. Trismus caused by hypoplasia and fibrosis of the muscles around the mouth in Freeman-Sheldon syndrome
   4. Trismus and camptodactyly in patients with distal arthrogryposis who may have hyperextension of the metacarpophalangeal joints but also have contractures of the hips and feet, and short stature
   5. Trismus with a fixed facies secondary to hypoplasia or atrophy of small muscle fibers in Schwartz-Jampel syndrome
   6. A new arthrogryposis syndrome with facial and limb anomalies
      1. An autosomal dominant disorder
      2. Small mouth and jaw with limited jaw movement in infancy
      3. Associated with short stature and severe flexion contractures of the hands and feet
   7. Digitotalar syndrome
      1. An autosomal dominant disorder
      2. Flexion deformities
      3. Ulnar deviation and narrowing of the fingers
      4. Soft-tissue webbing causing abnormal positions of the thumbs
      5. A vertical talus

Diagnostic Investigations

1. Radiography
   1. Enlargement of the coronoid processes
   2. Normal hands and forearms
2. Manometry for demonstrating abnormal swallowing

3. Histology of the affected muscles showing presence of fibrous tissue along with some muscle atrophy
4. Molecular genetic testing of *MYH8* mutations

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased unless a parent is affected (a mildly affected parent may be missed) or has germinal mosaicism (Bonapace et al. 2010)
   2. Patient's offspring: 50%
2. Prenatal diagnosis: not been reported but possible in family at risk by *MYH8* mutation analysis of fetal DNA obtained from amniocentesis of CVS, provided the mutation has been previously identified in the affected family member
3. Management
   1. Use a flattened nipple to assist feeding in infancy.
   2. Anesthetic implications (Browder et al. 1986)
      1. Limited excursion of the mandible
      2. Potentially difficult or impossible to apply artificial ventilation and endotracheal intubation
      3. Inhalational anesthesia with spontaneous breathing (Vaghadia and Blackstock 1988) recommended for minor surgery
      4. Bullard laryngoscope, an excellent device for intubating patients with limited mouth opening (Lano and Werkhaven 1997)
      5. Fiber-optic nasotracheal intubation (Seavello and Hammer 1999)
      6. Needs for emergency tracheostomy and cricothyrotomy
   3. Surgical release in the severe cases of trismus
      1. Bilateral coronoid amputation to resolve the trismus. The procedure was successful and the patient achieved normal function (Carlos et al. 2005).
      2. Bilateral coronoidotomies (Lefaivre and Aitchison 2003; Gasparini et al. 2008; Balkin et al. 2015) with excision of accessory fibrous tissue
      3. Bilateral excision of hypertrophic coronoid processes
      4. Surgical release of the shortened muscle-tendon units
      5. Ongoing physical therapy with postsurgical stretching of the jaw opening on a daily basis to avoid relapse
   4. Surgical flexor slide-through procedure on the flexion tendons of the forearms

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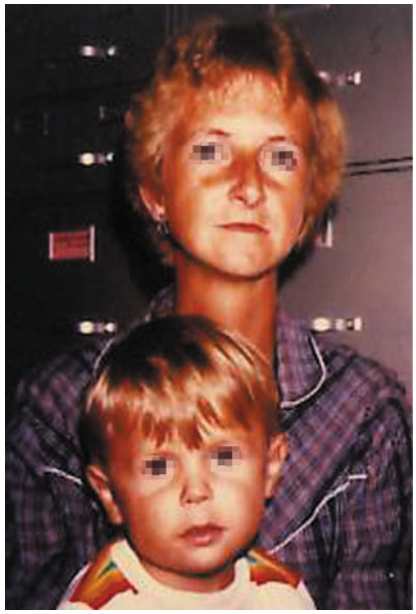

Fig. 1 Facial appearance of a child and his mother with trismus pseudocamptodactyly

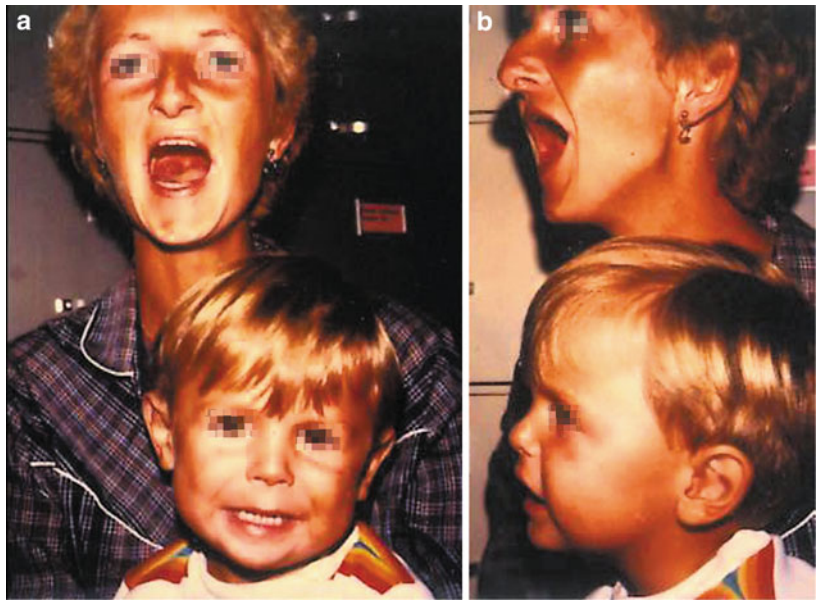

Fig. 2 (**a**, **b**) Front and lateral views of the child and his mother illustrating maximal abilities to open their mouth. The mother and the child both had *MYH8* mutations (p.R674Q)

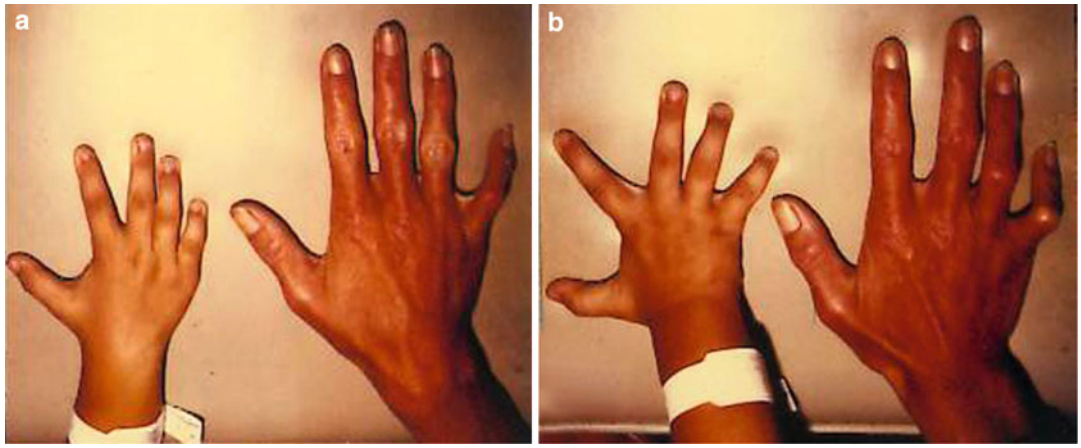

Fig. 3 (**a**, **b**) Hands of the child and his mother demonstrating no contractures of fingers on neutral positions (**a**) but flexion contractures of fingers on dorsiflexion (**b**). Interphalangeal webbings are also seen

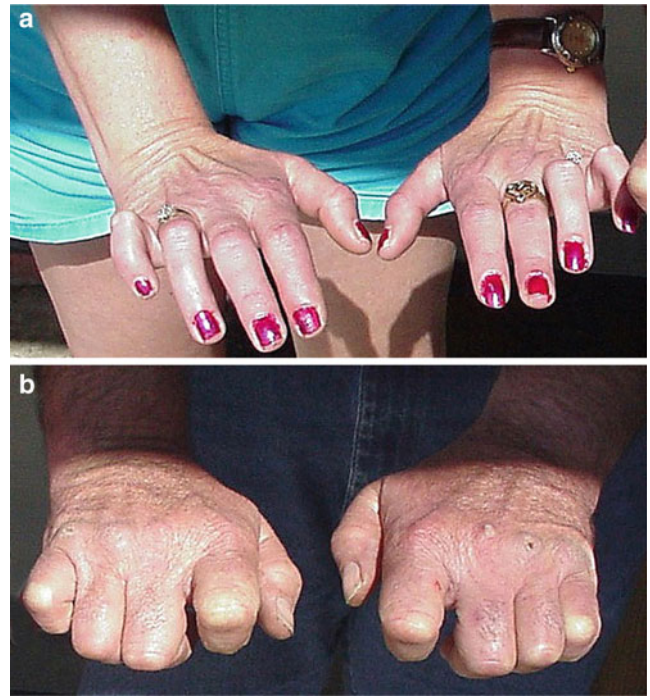

Fig. 4 (**a**, **b**) Marked flexion contractures of fingers on dorsiflexion in the mother (**a**) and her brother (**b**)

Fig. 5 Affected father and son in different family showing trismus and flexion contractures of fingers on dorsiflexion

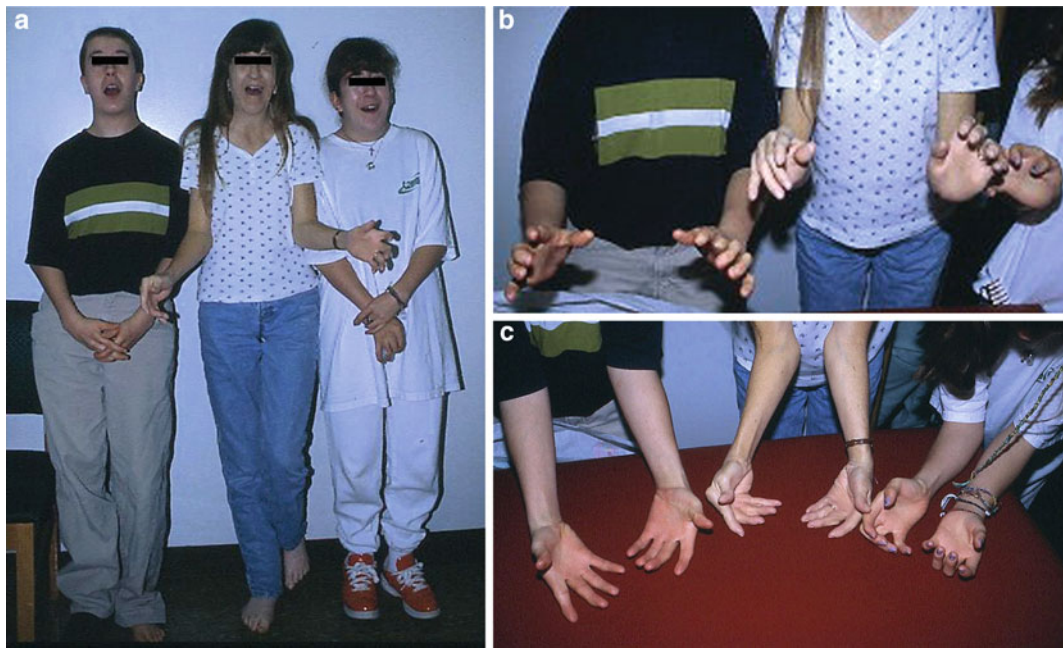

Fig. 6 (**a**-**c**) Affected three individuals in two generations in a different family showing trismus (**a**) and flexion contractures of fingers on dorsiflexion (**b**, **c**)

Trisomy 13 Syndrome

Contents

In 1960, Patau et al. first recognized the relation of trisomy 13 to a clinical syndrome. Incidence is estimated to be 1/4,000–1/10,000 live births. The prevalence at birth was 1 per 29,374 based on liveborn and stillborn probands (Goldstein and Nielsen 1988).

Synonyms and Related Disorders

Mosaic trisomy 13; Partial trisomy 13; Patau syndrome; Translocation trisomy 12

Genetics/Basic Defects

1. Trisomy 13
    1. Mechanism: due to meiotic nondisjunction
        1. Maternal origin of the extra chromosome (90%)
        2. Stage of nondisjunction: mostly maternal meiosis I (vs. meiosis II in trisomy 18)
        3. Paternal origin of the extra chromosome (10%): The majority is primarily postzygotic mitotic errors.
    2. Frequency: 75% of cases
2. Translocation trisomy 13
    1. Mechanism: de novo (75%) or familial transmission (25%)
    2. Frequency: 20% of cases
    3. Trisomy 13 due to t(13;13): The structural abnormalities are usually isochromosomes originating in mitosis.
    4. Despite a maternal origin of the trisomy 13, we cannot therefore infer anything about the parental origin of the chromosomes 13 and 14 involved in the translocation in the de novo t(13q14q) case nor for the two t(13;13) chromosomes showing a meiotic origin of the trisomy (Robinson et al. 1996).
3. Mosaic trisomy 13
    1. Mechanism: due to postzygotic (postfertilization) mitotic nondisjunction
    2. Frequency: 5% of cases
    3. Variable phenotype from full trisomy to near normal (Delatycki and Gardner 1997)
    4. Variable mental retardation with longer survival
    5. Trisomy 13/triploidy mosaicism: a rare event

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4. Partial trisomy 13
    1. Partial trisomy of proximal segment with nonspecific clinical features and little similarity to full trisomy 13
    2. Partial trisomy of distal segment with specific clinical features

Clinical Features

1. General
    1. Low birth weight
    2. Thrombocytopenia
2. CNS
    1. Severe mental retardation
    2. Holoprosencephaly
    3. Seizures
    4. Central apnea
    5. Natural history of psychomotor development: clearly functioning in the severe to profound developmentally handicapped range, children did achieve some psychomotor maturation and always continued to learn (Baty et al. 1994b)
    6. A range of developmental skills are attainable for children with trisomy 13 (Bruns 2015)
3. Craniofacial abnormalities (Taylor 1968)
    1. Microcephaly
    2. Wide sagittal sutures
    3. Wide fontanels
    4. Scalp defect (aplasia cutis congenita, 50%)
    5. Capillary hemangioma of the forehead
    6. Ocular abnormalities
        1. Microphthalmia/anophthalmia
        2. Colobomas
        3. Retinal dysplasia
    7. Cleft lip/palate
    8. Abnormal auricles
    9. Low-set ears
    10. Sensorineural and conductive deafness
    11. Recurrent otitis media
    12. Abundant nuchal skin folds: increased nuchal translucency in trisomy 13 fetuses at 10–14 weeks of gestation (Snijders et al. 1999)
4. Cardiovascular abnormalities
    1. Ventricular septal defect
    2. Atrial septal defect
    3. Patent ductus
    4. Coarctation of the aorta
    5. Dextrocardia
5. Gastrointestinal abnormalities
    1. Omphalocele
    2. Malrotation
    3. Umbilical hernia
    4. Inguinal hernia
    5. Accessory spleen
    6. Heterotopic pancreatic tissue
    7. Meckel's diverticulum
    8. Diaphragmatic defects
    9. Large gallbladder
6. Genitourinary abnormalities
    1. Polycystic kidneys
    2. Cryptorchidism
    3. Hypospadias
    4. Bicornuate uteri
    5. Abnormal fallopian tubes
    6. Hypoplastic ovaries
7. Skeletal abnormalities
    1. Polydactyly
    2. Posterior prominence of heel
    3. Flexed fingers
    4. Hypoplasia of pelvis
    5. Shallow acetabulum
    6. Thin posterior ribs
    7. Flexion deformity of large joints
    8. Limb deficiency (5.3%) (Martínez-Frías et al. 2000)
    9. Radial aplasia
    10. Hyperconvex narrow fingernails
8. Dermatoglyphics
    1. Transverse palmar crease
    2. t′
    3. Hallucal arch fibular or loop tibial
9. Others
    1. Thymic cyst
    2. Persistence of fetal hemoglobin
    3. Rarely reported with teratoma (Dorum et al. 2016)
10. Prognosis
    1. Majority of trisomy 13 conceptuses
        1. Abort during pregnancy
        2. Stillborn

2. Twenty-five percent die by 24 h of life
3. Forty-five percent die by 1 month of life
4. Sixty percent die by 6 months of life
5. Seventy-two die by 1 year of age
6. The median survival time was 8.5 days (1-412 days) (Brewer et al. 2002)
7. Usual mode of death: primary apnea (Wyllie et al. 1994)
8. Early mortality was the most common outcome, but 10–13% survived for 10 years. Among children who underwent surgical interventions, 1-year survival was high (Nelson et al. 2016).
9. Survivals up to 11 and 19 years old reported (Redheendran et al. 1981; Zoll et al. 1993)

11. Mosaic trisomy 13
    1. The phenotype ranges
        1. Typical features of trisomy 13
        2. More mild mental retardation or even normal intellectual function (rare), milder physical features, and longer survival
    2. The range in clinical severity is likely due to the varying proportion of trisomy 13 cells and their distribution within the body.
    3. A report of a patient with trisomy 13 mosaicism with hemangiomas and port wine stains, without structural defects (Wieser et al. 2015)
12. Partial trisomy 13 of the proximal segment
    1. Severe mental retardation
    2. Large nose
    3. Short upper lip
    4. Receding mandible
    5. Clinodactyly of the fifth fingers
    6. The findings of persistent fetal Hb and increased number of nuclear projections on neutrophils are consistent findings associated with partial trisomy of a proximal segment of chromosome 13 and are diagnostic for trisomy of a partial segment of chromosome 13 that contains bands 13q12 and 13q14 (Rogers 1984).
13. Partial trisomy 13 of the distal segment
    1. Severe mental retardation
    2. Bushy eyebrows (synophrys) with long incurved lashes
    3. Frontal capillary hemangioma
    4. Long philtrum
    5. Prominent antihelix
    6. Further delineation of the clinical picture of trisomy for the distal segment of chromosome 13: report of three cases (Schinzel et al. 1976)
        1. Common clinical features included normal birth weight, postnatal asphyxia, convulsions, severe psychomotor retardation, normal growth, and a distinct pattern of dysmorphias consisting of trigonocephalic head with prominent metopic suture, long and markedly curved eyelashes, a stubby nose, increased distance between nose and upper lip, high-arched palate, misshapen ears with virtually absent lobules and prominent anthelices which are curved in a sharp angle, and hemangiomata.
        2. Features present in two cases were microcephaly, long and narrow fingers with convex nails, and hexadactyly.
    7. The physical features of polydactyly and hemangioma have been mapped to bands 13q31 and 13q32→13qter and provide a differential diagnosis for a distal trisomic segment of chromosome 13 that may include bands 13q22→13qter (Rogers 1984).
14. Phenotype-karyotype correlation in patients trisomic for various segments of chromosome 13 (Tharapel et al. 1986)
    1. Persistence of fetal hemoglobin (Hb F), increased projections of polymorphonuclear leucocytes (PMN), depressed nasal bridge, cleft lip/palate, and clinodactyly were more frequent in patients with proximal trisomy 13.
    2. In the distal trisomy group, the common features included haemangioma, bushy eyebrows, long curled eyelashes, prominent nasal bridge, long philtrum, thin upper lip, highly arched palate, and hexadactyly.
    3. In addition, several other features were common to both the groups, often showing

inconsistency even when the same segment was in trisomy.

Diagnostic Investigations

1. Cytogenetic studies
   1. Conventional technique
   2. FISH of interphase cells for rapid diagnosis
   3. Parental karyotyping in case of translocation trisomy 13
   4. Trisomy 13 mosaicism
2. Echocardiography for cardiovascular anomalies
3. EEG: hypsarrhythmia
4. Neurosonographic diagnosis of thalamic/basal ganglia vasculopathy in trisomy 13: an important diagnostic aid (Chabra et al. 1997)
   1. A linear, branching, echogenic pattern in the thalamus/basal ganglia
   2. Doppler evaluation of the thalamus/basal ganglia confirmed these linear echogenicities to be of vascular origin.
5. CT/MRI for central nervous system anomalies
6. Radiography
   1. Wide anterior fontanel
   2. Presence of a cervical rib
   3. Absence of the 12th rib
   4. Anomalies of rib morphology
   5. Low acetabular angle
   6. Long distal phalanges
   7. Cranial bone abnormalities in case of holoprosencephaly
   8. Vertebral fusions (Kjaer et al. 1997)
   9. Clefting of the vertebral bodies
   10. Abnormal postsphenoid component of the sphenoid bone
   11. Agenesis of the nasal bones
7. Placenta: Partial molar change of the placenta may rarely occur in trisomy 13 (Has et al. 2002).
8. Pathology of trisomy 13 syndrome (Moerman et al. 1988)
   1. Eight patients showed abnormal development of the forebrain and midline facial structures (holoprosencephaly).
   2. Cardiovascular malformations were invariably present, the leading malformation being an infundibular ventricular septal defect often in combination with dextroposition of the aorta and abnormalities of the semilunar valves.
   3. Histological abnormalities giving evidence of organ dysplasia were observed in the central nervous system, eyes, pancreas, kidneys, and ovaries.
9. Gross anatomical dissections (Colacino and Pettersen 1978; Pettersen et al. 1979)
   1. A muscle phenotype which includes the absence of palmaris longus, palmaris brevis, plantaris, and peroneus tertius; the presence of pectorodorsalis muscles and muscles from the central tendon of the diaphragm to the pericardium near the pulmonary veins; and variations in the extensor indicis, extensor carpi radialis longus and brevis, biceps, and suprahyoid muscles is discussed.
   2. The brain defects which include absent olfactory bulbs and tracts and hypoplastic commissures are compared to those defects seen in cases of alobar holoprosencephaly wherein severe defects of the ethmoid bone are concomitants.

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. Trisomy 13: about 1 in 4,000
      2. De novo translocation: about 1 in 4,000
      3. Familial translocation: 5–15%
      4. Mosaicism: 1 in 4,000
   2. Patient's offspring: not surviving to reproductive age
2. Prenatal diagnosis
   1. Prenatal ultrasonography (Benacerraf et al. 1988; Nyberg and Souter 2001; Tongsong et al. 2002): prevalence of ultrasound abnormalities (91%) (Lehman et al. 1995)
      1. General
         1. IUGR (48%)
         2. Single umbilical artery
         3. Polyhydramnios (15%)

4. Oligohydramnios (12%)
2. Cranium and CNS abnormalities (58%)
   1. Holoprosencephaly (39%)
   2. Neural tube defects
   3. Lateral ventricular dilatation without holoprosencephaly (9%)
   4. Enlarged cisterna magna or Dandy-Walker variant (15%)
   5. Microcephaly (12%)
   6. Linear branching echogenicity of the thalamus or basal ganglia (representing vasculopathy)
   7. Choroid plexus cyst
3. Facial anomalies
   1. Cyclopia
   2. Proboscis
   3. Hypotelorism
   4. Hypoplastic midface
   5. Cleft lip/palate (36%)
   6. Micrognathia
4. Neck anomalies
   1. Nuchal thickening
   2. Cystic hygroma
   3. Hydrops
   4. Lymphangiectasia
5. Chest/cardiac abnormalities
   1. Diaphragmatic hernia
   2. Ventricular septal defect
   3. Hypoplastic left heart
   4. Echogenic chorda tendineae (30%)
6. Renal abnormalities (33%)
   1. Echogenic kidneys
   2. Pyelectasis
   3. Enlarged kidneys
   4. Hydronephrosis
7. Abdominal abnormalities
   1. Omphalocele
   2. Echogenic bowel (6%)
   3. Bladder exstrophy
8. Limb abnormalities (33%)
   1. Clenched and overlapping digits
   2. Polydactyly
   3. Radial aplasia
   4. Short femur length
   5. Talipes equinovarus
   6. Rocker bottom feet
9. Trisomy 13 can resemble a triploid partial mole in utero without the potential long-term risk to the mother of persisting trophoblastic disease, as villous molar changes can obviously develop without trophoblastic dysplasia (Jauniaux et al. 1998).
10. Trisomy 13 should be included in the differential diagnosis when preeclampsia associated with hydropic changes of the placenta (partial hydatidiform mole) occurs early in gestation (Curtin et al. 2001).

2. A prospective validation study of screening for trisomies 21, 18, and 13 by a combination of maternal age, fetal nuchal translucency, fetal heart rate, and serum free ß-hCG and PAPP-A at 11+0 to 13+6 weeks' gestation in 108,982 singleton pregnancies: detected 90, 97, and 92% of trisomies 21, 18, and 13, respectively, as well as >90% of cases of monosomy X, >85% of triploidies, and >30% of other chromosomal abnormalities, at false positive rates of 4% (Santorum et al. 2016).
3. Chromosome analyses
   1. Amniocentesis
   2. Prenatal diagnosis of mosaicism for triploidy and trisomy 13 (Phelan et al. 2001)
      1. The infant had features common to both trisomy 13 and triploidy: intrauterine growth retardation (IUGR), small abnormal ears, cleft palate, and a small jaw. In addition, he had complete cutaneous syndactyly of fingers 3 and 4 and partial syndactyly of the toes, as seen in triploidy.
      2. Mixoploidy for trisomy 13 and triploidy was confirmed postnatally in blood, skin, and placenta.
      3. Examination of chromosome heteromorphisms and DNA markers suggested the presence of two maternal contributions in the triploid cell line.
      4. In addition, the extra chromosome 13 in the trisomic cell line was derived from the mother.
   3. CVS, followed by amniocentesis or fetal blood sampling, to differentiate between

confined placental mosaicism and true fetal karyotypic abnormality (Smith et al. 1999)
4. Nonmosaic trisomy 13 in the villus mesenchyme indicated the presence of a trisomic cell line in the fetus proper (Hahnemann and Vejerslev 1997)
5. Fetal cells isolated from maternal blood (Oosterwijk et al. 1998) using either flow sorting or magnetic sorting
6. Fetal blood sampling may have a role in mosaic trisomy 13 as the risk for abnormal outcome increases with positive confirmation (Wallerstein et al. 2000).
7. Noninvasive prenatal screening for fetal trisomies 21, 18, 13, and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA (Porreco et al. 2014)
8. A positive cell-free fetal DNA testing result may not be representative of the fetal karyotype because of placental mosaicism. Cytogenetic analysis should be performed when abnormal cell-free fetal DNA test results are obtained (Liu et al. 2014).
9. Noninvasive prenatal detection of trisomy 13 using a single nucleotide polymorphism- and informatics-based approach: accurately detects trisomy 13-affected fetuses noninvasively and with high calculated accuracy (Hall et al. 2014).

4. Dilemma for genetic counseling with trisomy 13 mosaicism (Delatycki et al. 1998)
    1. Infrequent occurrence
    2. Single-cell pseudomosaicism (3.3%)
    3. Multiple-cell pseudomosaicism (4%)
    4. Often represents pseudomosaicism or confined placental mosaicism
    5. Prenatal diagnosis of mosaic trisomy 13 by amniocentesis in which no prenatal ultrasound abnormalities were noted (Eubanks et al. 1998)
    6. True fetal mosaicism (in the context of low-level single-digit percentage mosaicism): not necessarily associated with congenital defects and/or mental abnormalities
    7. An optimistic approach in case of normal ultrasonography and absence of trisomy 13 cells in the fetal blood
    8. Possibility of adverse phenotype and intellectual function in case of true low-level fetal mosaicism
3. Management
    1. Feedings
        1. Nasal tube feeding
        2. Oral gastric tube feeding
        3. Gastrostomy feeding
    2. Home oxygen therapy and home mechanical ventilation (Ishitsuka et al. 2015)
    3. Nissan fundoplication for gastresophageal reflux
    4. Risk for anesthesia
    5. Early intervention programs
    6. Seizure control
    7. Monitor apneic spells
    8. Treat infections
    9. Symptomatic treatment for heart failure
    10. Cardiac operation rarely performed
    11. No adverse reactions attributable to immunization (Baty et al. 1994a)
    12. Treatment decisions in a stable gray zone: If survival rates are low but not too low, neurocognitive impairment is severe but not total, and treatment is not so burdensome as to be inhumane, then parental values should drive decisions (Lantos 2016).
    13. Children with a postnatal diagnosis were treated “as any other children” until the diagnosis, which may give them a survival advantage, independent of palliative care. Rigorous transparency regarding specific interventions and outcomes may help personalize care for these children (Janvier et al. 2016).
    14. Shared decision making integrated with pathways approach is a model that demonstrates professional commitment beyond the most immediate crisis or decision point. This model, which incorporates ethically grounded decision making, guides clinicians and families from the time of

initial diagnosis, through the remainder of the care of the child and family (Andrews et al. 2016).

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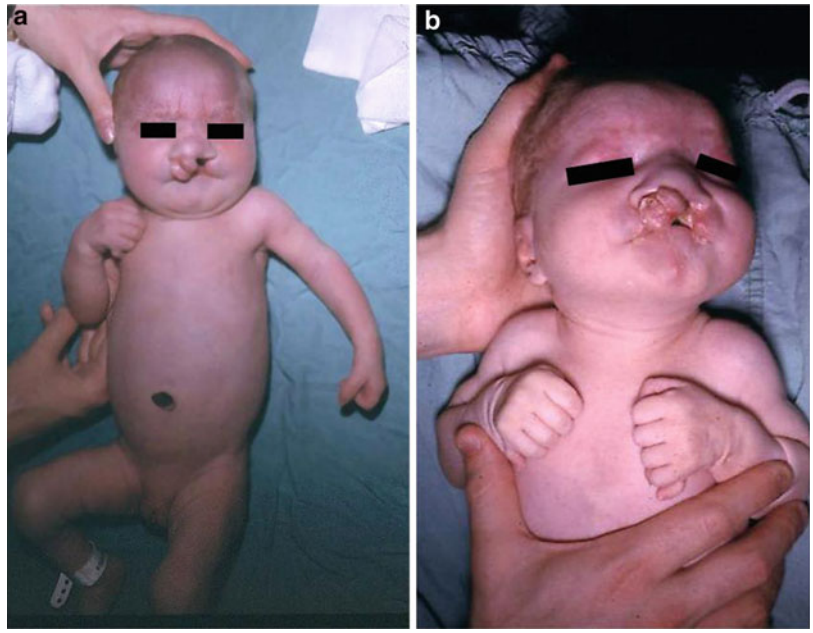

Fig. 1 (**a**, **b**) An infant with trisomy 13 showing microcephaly, microphthalmia, forehead hemangioma, cleft lip/palate, and postaxial polydactyly

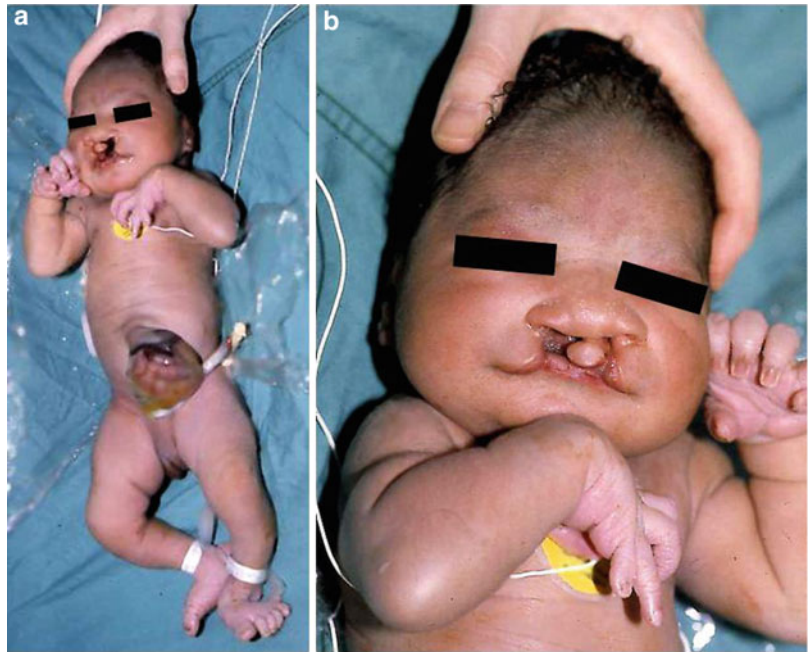

Fig. 2 (**a**, **b**) An infant with trisomy 13 showing microcephaly, microphthalmia, cleft lip/palate, and omphalocele

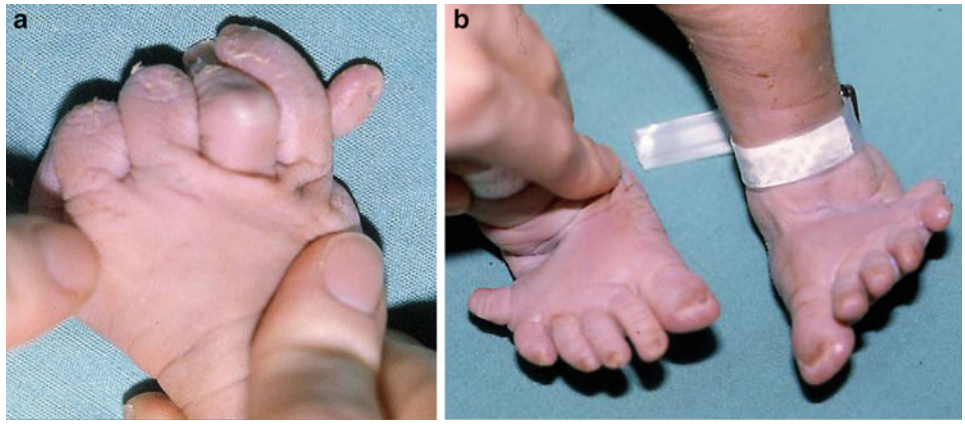

Fig. 3 (**a**, **b**) Postaxial polydactyly of the hand and the feet in an infant with trisomy 13

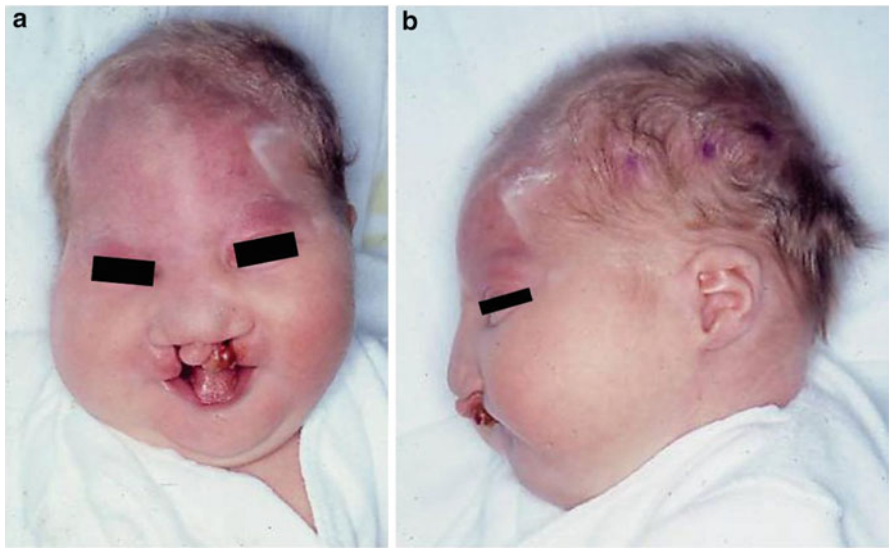

Fig. 4 (**a**, **b**) An infant with trisomy 13 showing microcephaly, forehead hemangioma, upslanted palpebral fissures, cleft lip/palate, and short neck

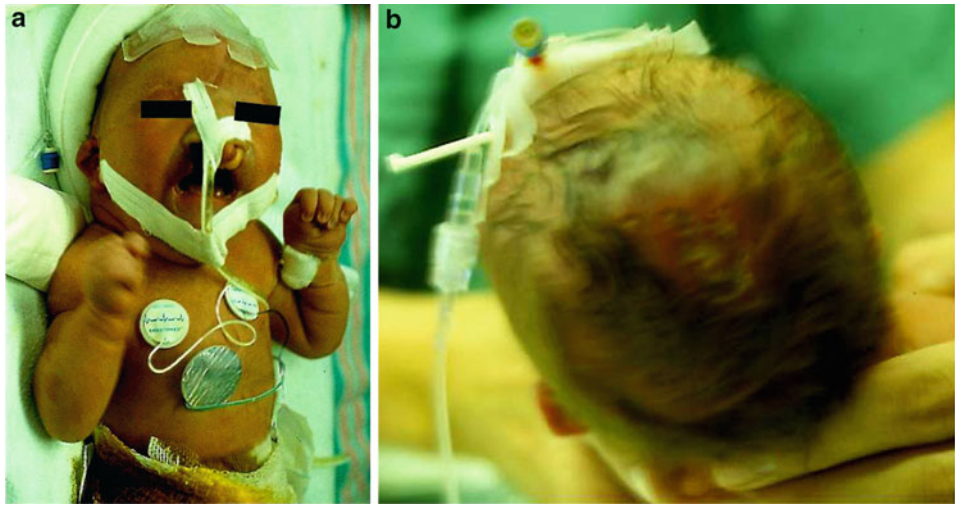

Fig. 5 (**a**, **b**) An infant with trisomy 13 showing scalp defect on the vertex

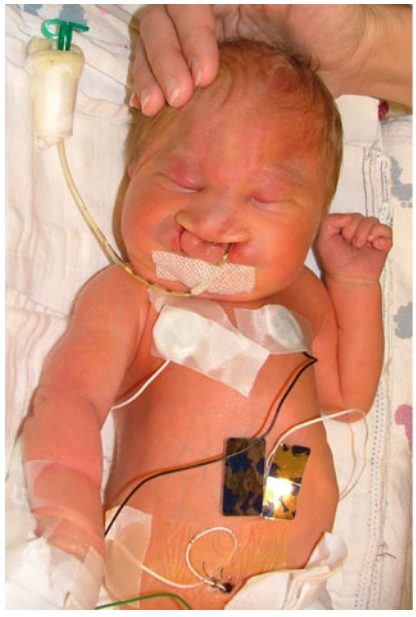

Fig. 6 Another infant with trisomy 13 showing microphthalmia and cleft lip/palate

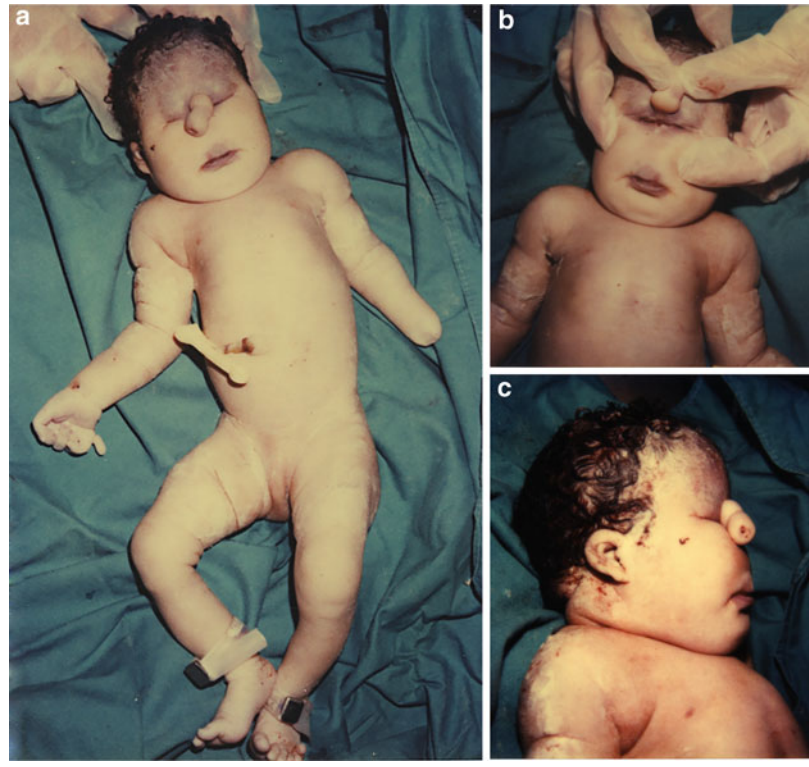

Fig. 7 (**a**–**c**) A neonate with trisomy 13 showing ethmocephaly, transverse reduction of the left forearm, and polydactyly of the right hand and both feet

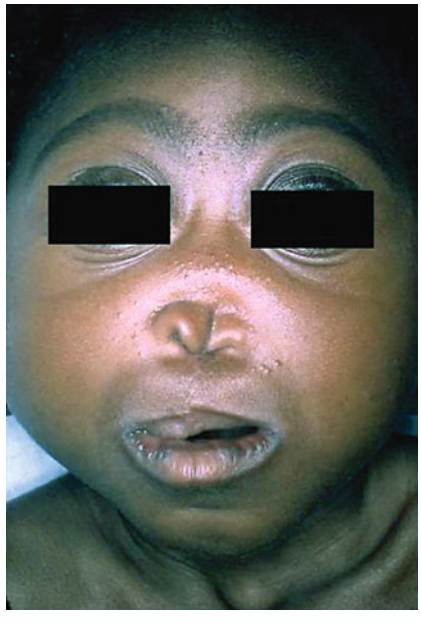

Fig. 8 A child with trisomy 13 associated with premaxillary dysgenesis, hypotelorism, cleft nose, and smooth philtrum

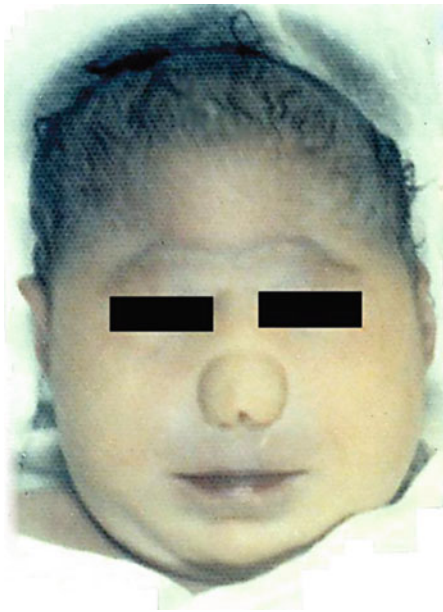

Fig. 9 An infant with trisomy 13-Klinefelter syndrome showing hypotelorism and a single nostril (holoprosencephaly)

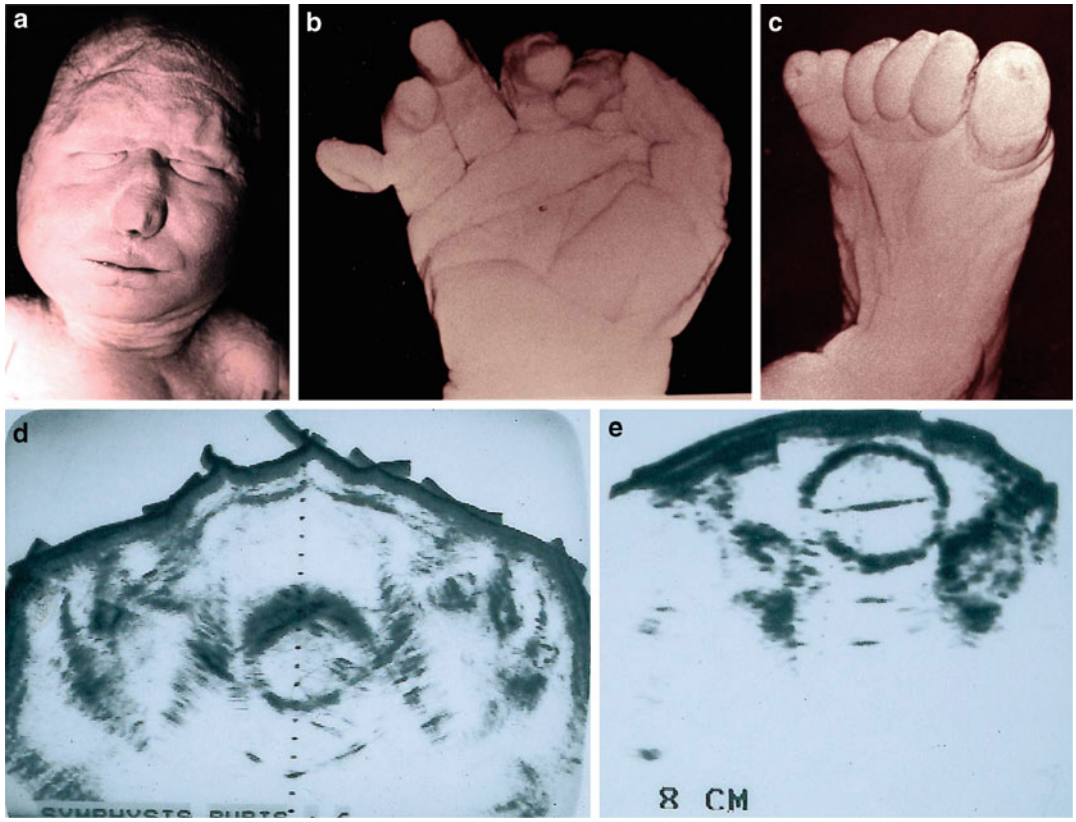

Fig. 10 (**a**–**e**) A neonate with trisomy 13 showing similar facial features (**a**). In addition, the infant has polydactyly (**b**, **c**). Prenatal ultrasound examination showed microcephaly, scalp edema, and holoprosencephaly (**d**) (a normal ultrasound at the same gestation is given here) (**e**)

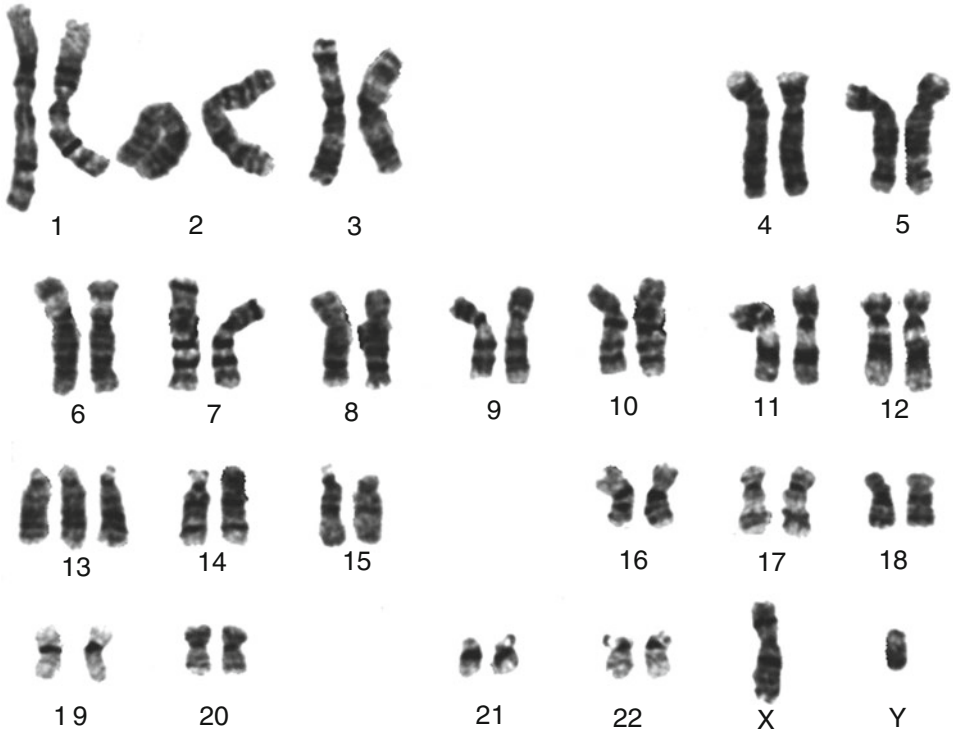

Fig. 11 Trisomy 13 karyotype (G-banded)

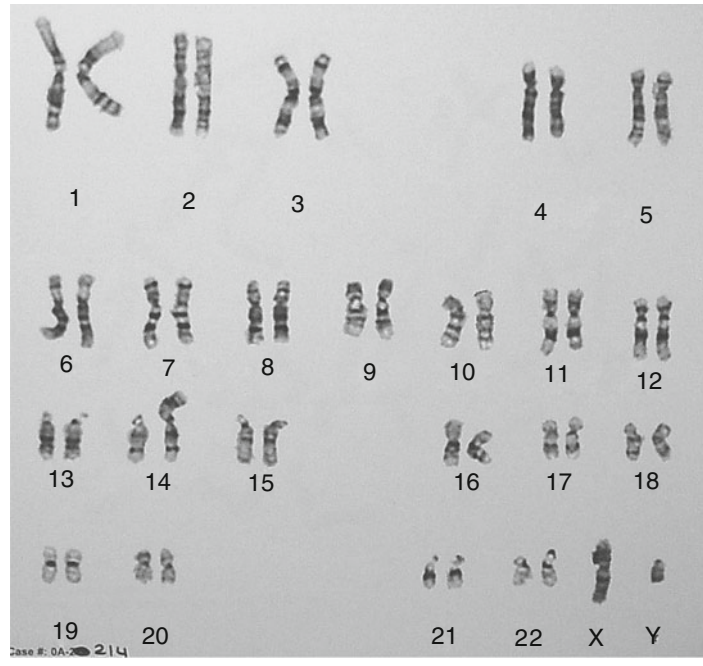

Fig. 12 Translocation of trisomy 13 karyotype [t (13q;14q)]

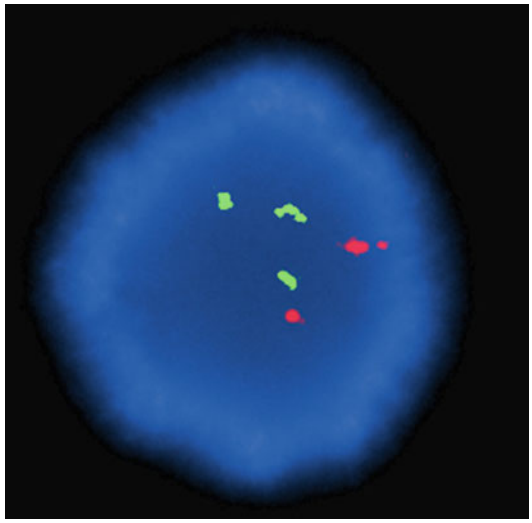

Fig. 13 Trisomy 13 shown by FISH analysis of interphase cells with three copies of the green signal (LSI 13/SpectrumGreen) representing three chromosome 13s and two copies of the red signal representing two chromosome 21s (LSI 21/SpectrumOrange)

Trisomy 18 Syndrome

Contents

Edwards et al. and Smith et al. independently described trisomy 18 syndrome in 1960 (Edwards et al. 1960; Smith et al. 1960). It is the second most common autosomal trisomy after trisomy 21. Prevalence is approximately 1 in 6,000–8,000 live births.

Synonyms and Related Disorders

Edwards syndrome

Genetics/Basic Defects

1. Caused by an extra chromosome 18 resulting from nondisjunction in meiosis (Bugge et al. 1998)
   1. Maternal origin of an extra chromosome 18 in 90% of cases
   2. An error in maternal meiosis II is the most frequent cause of nondisjunction for chromosome 18, unlike all other human trisomies that have been studied, which show a higher frequency in maternal meiosis I.
   3. Increased incidence with advanced maternal age
2. Types of trisomy 18
   1. Full trisomy 18 in 95% of cases
   2. Rare mosaicism and translocation cases: translocation trisomy giving rise to partial trisomy 18 syndrome
   3. Trisomy 18 mosaicism with a mild phenotype (Collins et al. 1995)
3. Preponderance of females with trisomy 18 in liveborns (sex ratio 0.63) (sex ratio defined as the number of males divided by the number of females) compared to fetuses diagnosed prenatally (sex ratio 0.90) indicating a prenatal selection against trisomy 18 males after the time of amniocentesis (Nicolaidis and Petersen 1998)
4. The smallest extra region necessary for expression of serious anomalies of trisomy 18: Two critical regions, one proximal (18q12-q21.2) and one distal (18q22.3-qter), which work jointly to produce the typical trisomy 18 phenotype.

Clinical Features

1. Prenatal history (Chen 2011)
   1. Maternal polyhydramnios possibly related to defective fetal sucking and swallowing reflexes in utero

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Oligohydramnios secondary to renal defects
3. Disproportionately small placenta
4. Single umbilical artery
5. Intrauterine growth retardation
6. Weak fetal activity
7. Fetal distress

2. Clinical history
   1. Apneic episodes
   2. Poor feeding
   3. Marked failure to thrive
3. Detailed clinical features (Taylor 1968)
4. Physical growth: profound growth retardation
5. Central nervous system (CNS)
   1. Inevitable profound delay in psychomotor development and mental retardation (100%)
   2. Natural history of psychomotor development: clearly functioning in the severe to profound developmentally handicapped range, children did achieve some psychomotor maturation and always continued to learn (Baty et al. 1994b)
   3. Neonatal hypotonia followed by hypertonia
   4. Jitteriness
   5. Apnea
   6. Seizures
   7. Malformations
      1. Microcephaly
      2. Cerebellar hypoplasia
      3. Meningoencephalocele
      4. Meningomyelocele
      5. Anencephaly
      6. Hydrocephaly
      7. Holoprosencephaly
      8. Arnold-Chiari malformation
      9. Hypoplasia or aplasia of the corpus callosum
      10. Defective falx cerebri
      11. Frontal lobe defect
      12. Abnormal gyri
      13. Migration defect
      14. Arachnoid cyst
6. Cranial
   1. Microcephaly
   2. Elongated skull
   3. Narrow bifrontal diameter
   4. Wide fontanels and cranial sutures
   5. Prominent occiput
7. Facial
   1. Microphthalmia
   2. Ocular hypertelorism
   3. Epicanthal folds
   4. Short palpebral fissures
   5. Iris coloboma
   6. Cataracts
   7. Corneal clouding
   8. Abnormal retinal pigmentation
   9. Short nose with upturned nares
   10. Choanal atresia
   11. Micrognathia/retrognathia
   12. Microstomia
   13. Narrow palatal arch
   14. Infrequent cleft lip and cleft palate
   15. Low-set, malformed ears (faun-like with flat pinnae and a pointed upper helix)
   16. Other uncommon but relevant abnormalities (Rosa et al. 2013)
      1. Microtia (18%)
      2. Orofacial clefts (12%)
      3. Preauricular tags (10%)
      4. Facial palsy (4%)
      5. Encephalocele (4%)
      6. Absence of external auditory canal (2%)
      7. Asymmetric face (2%)
8. Skeletal
   1. Severe growth retardation
   2. Characteristic hand posture, with clenched hands with the index finger overriding the middle finger, and the fifth finger overriding the fourth finger
   3. Camptodactyly
   4. Radial hypoplasia or aplasia
   5. Thumb aplasia
   6. Syndactyly of the second and third digits
   7. Arthrogryposis
   8. Rocker-bottom feet with prominent calcanei
   9. Talipes equinovarus
   10. Hypoplastic nails
   11. Dorsiflexed great toes
   12. Short neck with excessive skin folds

13. Short sternum
14. Narrow pelvis
15. Limited hip abduction
16. Scoliosis (Ries et al. 1990)
17. Severe kyphoscoliosis and tendency to spontaneous fracture of long bones emerging later

9. Cardiac malformations in more than 90% of infants with trisomy 18
    1. Ventricular septal defects
        1. Present in about two-thirds of cases
        2. Large defect unlikely to undergo spontaneous closure
    2. Polyvalvular heart disease pulmonary and aortic valve defects)
    3. Double outlet right ventricle
    4. Atrial septal defects
    5. Patent ductus arteriosus
    6. Overriding aorta
    7. Coarctation of aorta
    8. Hypoplastic left heart syndrome
    9. Tetralogy of Fallot
    10. Transposition of great arteries
    11. Endocardial fibroelastosis
    12. Persistent left superior vena cava
    13. Absent right superior vena cava
    14. Dextrocardia
10. Pulmonary
    1. Pulmonary hypoplasia
    2. Abnormal lobation of the lung
11. Gastrointestinal
    1. Omphalocele
    2. Malrotation of the intestine
    3. Ileal atresia
    4. Common mesentery
    5. Meckel diverticulum
    6. Esophageal atresia with or without tracheoesophageal fistula
    7. Diaphragmatic eventration
    8. Prune belly anomaly
    9. Diastasis recti
    10. Abnormal lobulation of the liver
    11. Absent or hypoplasia of gallbladder
    12. Absent appendix
    13. Accessory spleens
    14. Exstrophy of cloaca
    15. Pyloric stenosis
    16. Common mesentery
    17. Megacolon
    18. Imperforate or malpositioned anus
    19. Pilonidal sinus
    20. Umbilical, inguinal, or diaphragmatic hernias
12. Genitourinary
    1. Micromulticystic kidneys
    2. Double ureters
    3. Megaloureters
    4. Hydroureters
    5. Hydronephrosis
    6. Horseshoe kidneys
    7. Ectopic kidney
    8. Unilateral renal agenesis
    9. Cryptorchidism, hypospadias, and micropenis in males
    10. Hypoplasia of labia and ovaries, bifid uterus, hypoplastic ovaries, and clitoral hypertrophy in females
13. Endocrine
    1. Thymic hypoplasia
    2. Thyroid hypoplasia
    3. Adrenal hypoplasia
14. Dermatoglyphics
    1. Increased number of simple arches (6 or more) on the finger tips
    2. Transverse palmar crease
    3. Increased atd angle
    4. Clinodactyly of the fifth fingers with a single flexion crease
15. Prognosis
    1. Approximately 95–97.5% of conceptuses with trisomy 18 die in embryonic or fetal life.
    2. Only 30% of live fetuses at midtrimester amniocentesis surviving to term.
    3. Five to ten percent of affected children survive beyond the first year.
    4. The chance of survival to 1 month, 1 year, and 10 years is 70%, 10%, and 1%, respectively (Weber et al. 1964).
    5. Rare reports of long survival into teens (Surana et al. 1972; Smith et al. 1978; Mehta et al. 1986) and 20s (Smith et al. 1989).
    6. High mortality rate secondary to cardiac and renal malformations, feeding

difficulties, sepsis, and central apnea caused by CNS defects.
7. Severe psychomotor and growth retardation invariably present for those who survive beyond infancy.
8. Milder nonspecific phenotype in mosaic trisomy 18 correlates with the proportion of normal cells in the body.
9. Older individuals with trisomy 18 are at risk to develop a Wilms tumor (Carey and Barnes 2016).

Diagnostic Investigations

1. Conventional cytogenetic study to detect full trisomy, mosaic trisomy, or rare translocation type trisomy 18
2. Trisomy 18 mosaicism: clues to the diagnosis (Bass et al. 1982)
    1. Because of his prolonged survival and an atypical phenotype, skin fibroblast cultures from a new biopsy were established at age 18, and only normal 46,XY cells were observed, while peripheral blood lymphocytes still demonstrated 47,XY, + 18.
    2. This patient and six others with trisomy 18 mosaicism illustrate the advisability of looking for such a pattern in individuals whose phenotype in early life is not fully consistent with the trisomy 18 syndrome.
3. Echocardiographic features (Alizad and Seward 2000)
    1. Ventricular septal defect
    2. Atrial septal defect
    3. Patent ductus arteriosus
    4. Pulmonary stenosis
    5. Tetralogy of Fallot
    6. Bicuspid aortic valve
    7. Transposition of the great vessels
    8. Coarctation of the aorta
4. Barium swallow for gastrointestinal anomalies
5. Ultrasound for genitourinary anomalies
6. Skeletal radiography
    1. Phocomelia
    2. Absent radius
    3. Tight flexion of the fingers with second over the third and the fifth over the fourth
    4. Talipes equinovarus
    5. Short sternum
    6. Hemivertebrae
    7. Fused vertebrae
    8. Short neck
    9. Scoliosis
    10. Rib anomaly
    11. Dislocated hips
    12. Pattern of malformations in the axial skeleton in human trisomy 18 fetuses (Kjaer et al. 1996)
        1. Malformations occurred in the occipital field in all fetuses. This was a characteristic notching, either unilateral or bilateral, of the basilar part of the occipital bone.
        2. Nasal bones were abnormal in 8 cases, either absent or hypoplastic.
        3. Malformations were found in the thoracic and/or lumbosacral field in 7 fetuses.
        4. A single abnormality was found in the cervical spine in one fetus.
7. Histopathological study of temporal bone (auditory organ) (Tadaki et al. 2003)
    1. External ear: arctation or atresia of external acoustic meatus (38%)
    2. Middle ear
        1. Anomalies of auditory ossicles (61%)
            1. Incus or malleus
            2. Stapes
        2. Absence or aberration of tensor tympani muscle or its tendon (31%)
        3. Complete absence or hypoplasia of stapedial muscle or its tendon (28%)
    3. Inner ear
        1. Hypoplasia of the ductus semicirculares (37%)
        2. Shortened cochlea (22%)
        3. Anomalies of stria vascularis (22%)
        4. Absence or hypoplasia of lymphatic valve in utricle (21%)
        5. Enlargement of canaliculus cochleae (11%)
    4. Facial nerve: geniculate ganglion cells displaced into the internal auditory meatus (53%)

8. Anatomical analysis of the developmental effects 18-trisomy syndrome (Bersu and Ramirez-Castro 1977)
    1. Of the usual muscles of facial expression, occipitofrontalis and the auricular and nasal muscles were hypoplastic in all eight bodies and each subject showed extensive fusion of the muscles around the corner of the mouth.
    2. There was a supernumerary muscle band that extended from the region near the corner of the mouth to the occipital attachment of trapezius.
    3. The otomandibular region showed a variable spectrum of muscular, skeletal, arterial, and salivary gland variations bilaterally. Three of the bodies had infrahyoid muscle variations.
    4. Abnormalities of the upper and lower limbs (Ramirez-Castro and Bersu 1978)
        1. Muscle variations concentrated along the radial margin of the forearm and hand, the absence of the definitive musculocutaneous nerve in all of the limbs, and reductions of the radial artery
        2. The characteristic flexion deformities of the fingers seem to be due to a displacement of the tendons of extensors digitorum and digiti minimi.
9. Thirty-one autopsy cases of trisomy 18 (Kinoshita et al. 1989)
    1. Cardiovascular anomalies were consistently present; ventricular septal defect and patent ductus arteriosus being the most common malformations.
    2. Various other internal malformations including the Arnold-Chiari malformation were observed.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. De novo full trisomy 18: 1% or less.
        2. Low-grade parental mosaicism has been reported in two occasions in sporadic cases of trisomy 18.
        3. A parent being a balanced carrier of a structural rearrangement: increased recurrence risk pending on the type of structural rearrangement and the pattern of segregation.
    2. Patient's offspring: unlikely to survive to reproduction
2. Prenatal diagnosis
    1. Prenatal screening in families without history of trisomy 18 using maternal serum markers
        1. Low human chorionic gonadotropin hCG) and low unconjugated estriol (uE3) in maternal serum during midtrimester: useful predictors for an increased risk for trisomy 18 (Leporrier et al. 1996)
        2. Possible future first-trimester biochemical screening for trisomy 18: reduced levels of pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (beta-hCG) at 8–13 weeks gestation. The mean MOM in affected pregnancies was 0.25 for PAPP-A and 0.34 for free beta-hCG.
        3. First-trimester screening for trisomy 18 using a combination of maternal age, PAPP-A, and beta-hCG: reported to achieve a detection rate of 76.6% with a false-positive rate of 0.5% (Biagiotti et al. 1998)
        4. Noninvasive prenatal screening for fetal trisomies 21, 18, 13, and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA (Porreco et al. 2014)
        5. A prospective validation study of screening for trisomies 21, 18, and 13 by a combination of maternal age, fetal nuchal translucency, fetal heart rate, and serum-free ß-hCG and PAPP-A at 11+0 -13+6 weeks' gestation in 108,982 singleton pregnancies: detected 90, 97, and 92% of trisomies 21, 18, and 13, respectively, as well as >90% of cases of monosomy X, >85% of triploidies, and

>30% of other chromosomal abnormalities, at false positive rates of 4% (Santorum et al. 2016).

2. Prenatal ultrasonography (Benacerraf et al. 1988; Nyberg et al. 1993; Shields et al. 1998; Kroes et al. 2014; Niknejadi et al. 2014): The majority of fetuses with trisomy 18 have detectable structural abnormalities.
    1. First-trimester sonographic findings (Sepulveda et al. 2010)
        1. Nuchal translucency (77–91%) (Nicolaides et al. 1992)
        2. Absent/hypoplastic nasal bone (53%)
        3. Generalized subcutaneous edema (49%)
        4. Omphalocele (21%)
        5. Abnormal posturing of hands (6%)
        6. Megacystis (4%)
        7. Cardiac defect (4%)
        8. Pleural effusions (4%)
        9. Echogenic yolk sac (4%)
    2. Oligohydramnios/polyhydramnios (12%)
    3. Intrauterine growth retardation (29%)
    4. Two-vessel umbilical cord (40%)
    5. CNS
        1. Abnormally shaped fetal head (strawberry or lemon) (43%)
        2. Microcephaly
        3. Dandy-Walker malformation (posterior fossa enlargement associated with cerebellar hypoplasia)
        4. Enlarged cisterna magna
        5. Choroid plexus cysts (43%)
        6. Neural tube defects (9%)
    6. Micrognathia
    7. Thickened nuchal skin fold
    8. Cystic hygroma or lymphangiectasia (14%)
    9. Omphalocele (20%)
    10. Esophageal atresia
    11. Cardiac defects (37%): septal defects with polyvalvular disease
    12. Diaphragmatic hernia
    13. Renal anomalies (9%)
        1. Polycystic kidneys
        2. Horseshoe and ectopic kidneys
    14. Limb abnormalities
        1. Clenched hands with overlapping index finger (89%): a tell-tale signs of trisomy 18 (Lam and Tang 1999)
        2. Forehand and hand abnormalities such as a short radial ray
        3. Rocker-bottom feet
        4. Club feet
    3. 3D/4DUS offers diagnostic advantages for most anomalies associated with trisomy 18, especially anomalies of the extremities and face (Zheng et al. 2008).
    4. Amniocentesis or CVS by conventional cytogenetic or FISH techniques
        1. Straight trisomy 18
        2. Trisomy 18 mosaicism: 54% risk for an abnormal outcome, including phenotypically abnormal offspring, IUGR, or fetal demise. The risk is increased with increasing percentage of amniotic fluid trisomic cell line.
    5. Culturing fetal hematopoietic stem-progenitor cells from maternal blood during pregnancy: a new strategy holding great promise for noninvasive prenatal genetic diagnosis
    6. Trisomy diagnosis from single cells using multiple STR markers for either preimplantation genetic diagnosis or, potentially, diagnosis from fetal cells isolated from maternal blood (Findlay et al. 1998)
3. Management (Carey 2000)
    1. Genetic counseling in prenatally diagnosed trisomy 18 (Adler and Kushnick 1982)
        1. Traumatic experience in the lives of all couples having a fetus with trisomy 18
        2. Emotional upheaval persisting for variable time periods after the diagnoses and the decisions concerning the pregnancy outcomes
    2. When prenatal or neonatal diagnosis of trisomy 18 is made, the counseling of the family should be realistic, but not desolate. The parents can find it difficult to accept the lack of certainty of the newborn situation, but they have to be prepared for both the probability of death and the possibility of living (Carey 1992). Because the parents

have to make practical decisions concerning resuscitation, surgery, and life support (Cereda and Carey 2012)

3. Medical care of trisomy 18 infants
    1. Supportive
    2. Treat infections
        1. Otitis media
        2. Upper respiratory infections (bronchitis, pneumonia)
        3. Urinary tract infections
    3. No adverse reactions attributable to immunization (Baty et al. 1994a)
    4. Nasogastric and gastrostomy supplementation for feeding problems
    5. Orthopedic management of scoliosis secondary to hemivertebrae
    6. Primarily medical management of congenital heart disease
    7. Diuretic and digoxin for congestive heart failure
    8. Referral for early intervention including physical and occupational therapy
    9. Psychosocial management: Discuss implications, possible outcomes, and available supportive services in the community.
    10. Severe developmental delay exhibited by long-term survivors presenting the greatest challenge to parental coping during the childhood years
    11. Informed and empathetic care to families undergoing a complex grieving process that combines both the reactive grief predominant in chronic illness and the preparatory grief associated with impending death (Van Dyke and Allen 1990)
    12. According to Janvier et al. (2012), parents expressed concerns that interventions were not being offered due to their child's diagnosis.
    13. A range of developmental skills is noted with strengths in the language and communication, gross and fine motor, and social-emotional domains including indicating preferences, exploration of objects, and a range of voluntary mobility. These results serve to expand the knowledge base on developmental status for these groups and advance the need to further explore developmental abilities rather than focus on deficits (Bruns 2015).
    14. A substantial number of patients with trisomy received surgery and were then discharged home, but, of these, a considerable number required home medical care. This included home oxygen therapy, home mechanical ventilation, and tube feeding (Ishitsuka et al. 2015).
    15. Children with a postnatal diagnosis were treated "as any other children" until the diagnosis, which may give them a survival advantage, independent of palliative care. Rigorous transparency regarding specific interventions and outcomes may help personalize care for these children (Janvier et al. 2016).
    16. Evidence for greater provision of necessary and aggressive medical interventions for children with trisomy 18. It is hoped that perceptions regarding children with trisomy 18 will become more positive and interventions more widely offered and provided to this group (Donovan et al. 2016).
4. Surgical care of trisomy 18 infants: Because of the extremely poor prognosis, surgical repair of severe congenital anomalies such as esophageal atresia or congenital heart defects (Embleton et al. 1996) is not likely to improve the survival rate of infants and should be discussed with families.

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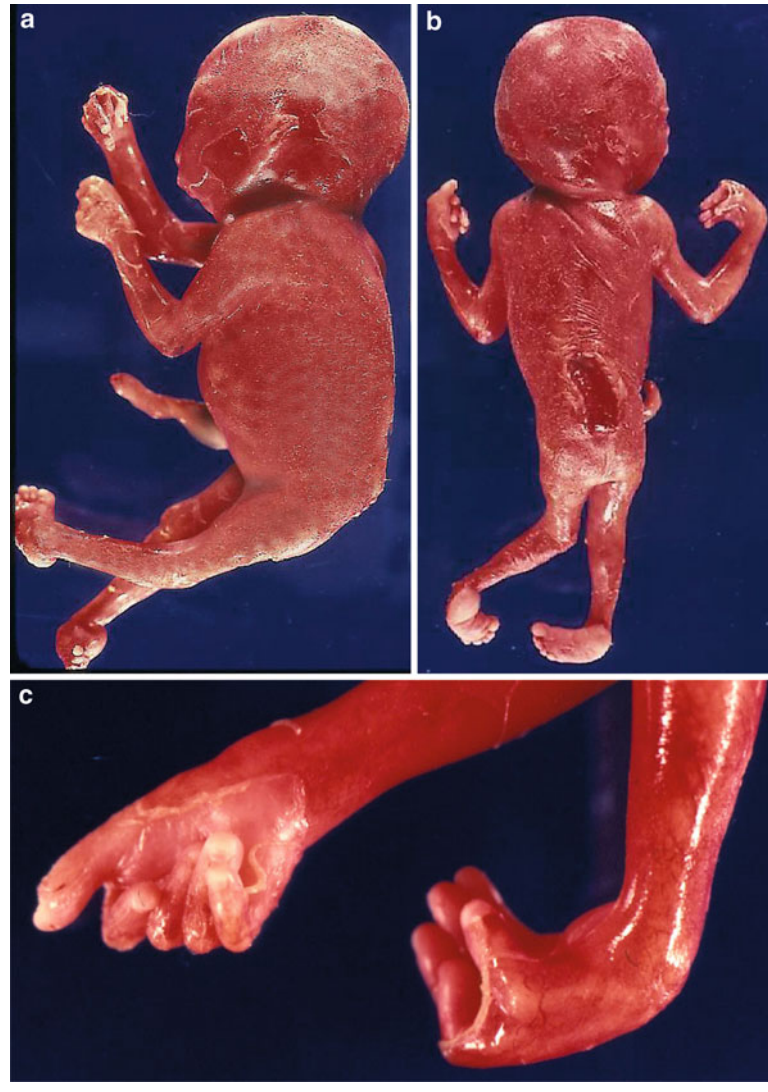

Fig. 1 (**a**–**c**) A fetus (**a**, **b**) with trisomy 18 showing malformed and low-set ears, characteristic finger clenching pattern (**c**), spina bifida, hyperextended knee, and talipes equinovarus

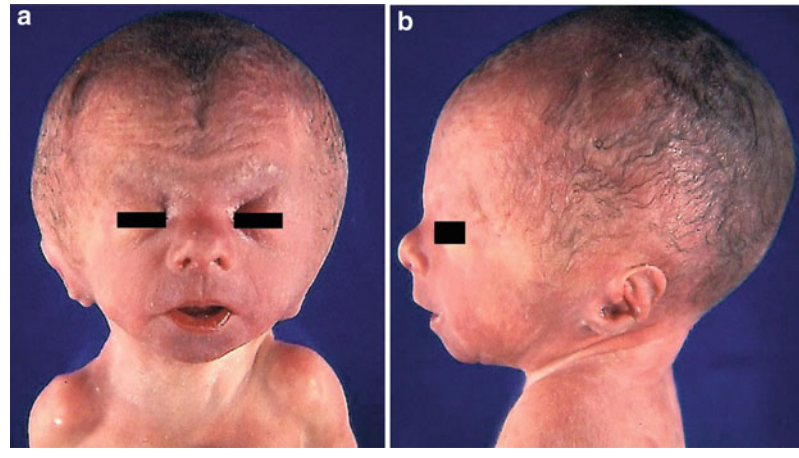

Fig. 2 (**a**, **b**) An infant with trisomy 18 showing small eyes, microstomia, low-set/malformed ears, and short neck

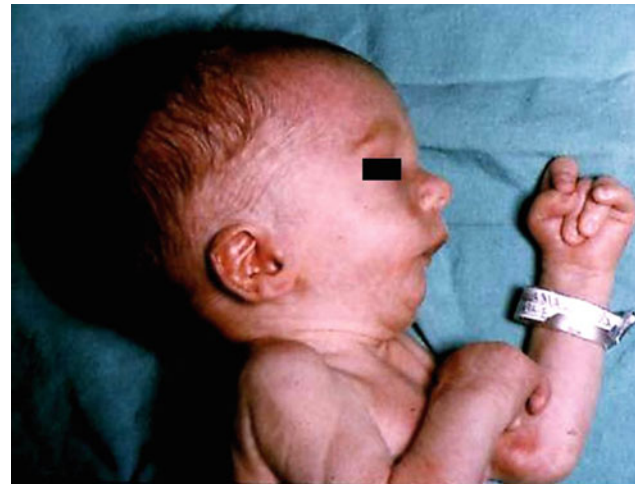

Fig. 3 An infant with trisomy 18 showing micro/retrognathia, short neck, and characteristic finger grasping pattern

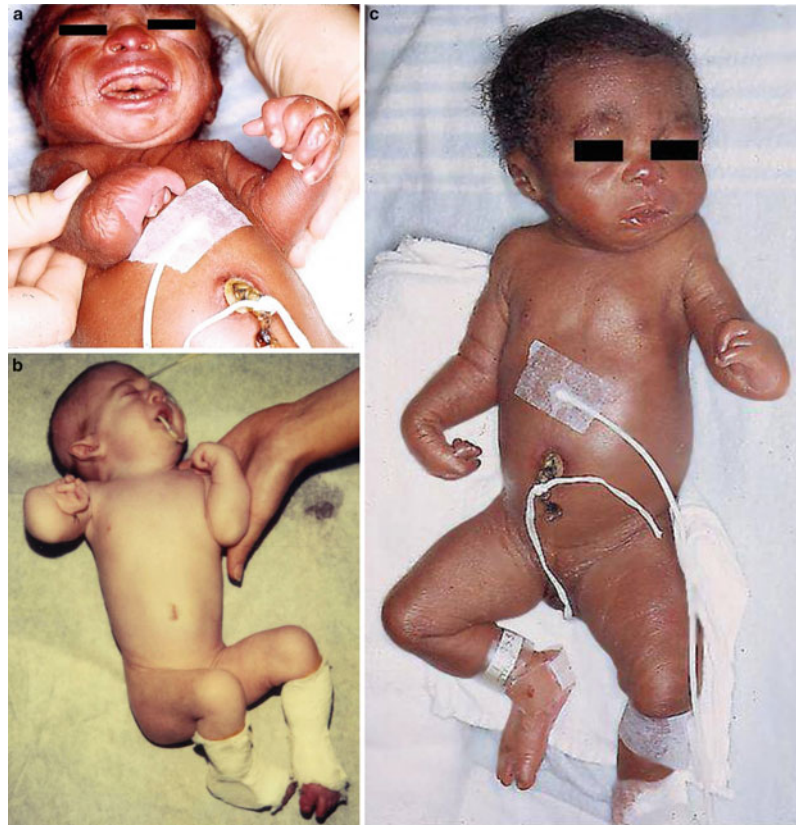

Fig. 4 (**a**–**c**) Three infants with trisomy 18 showing reduction malformations of the upper extremities

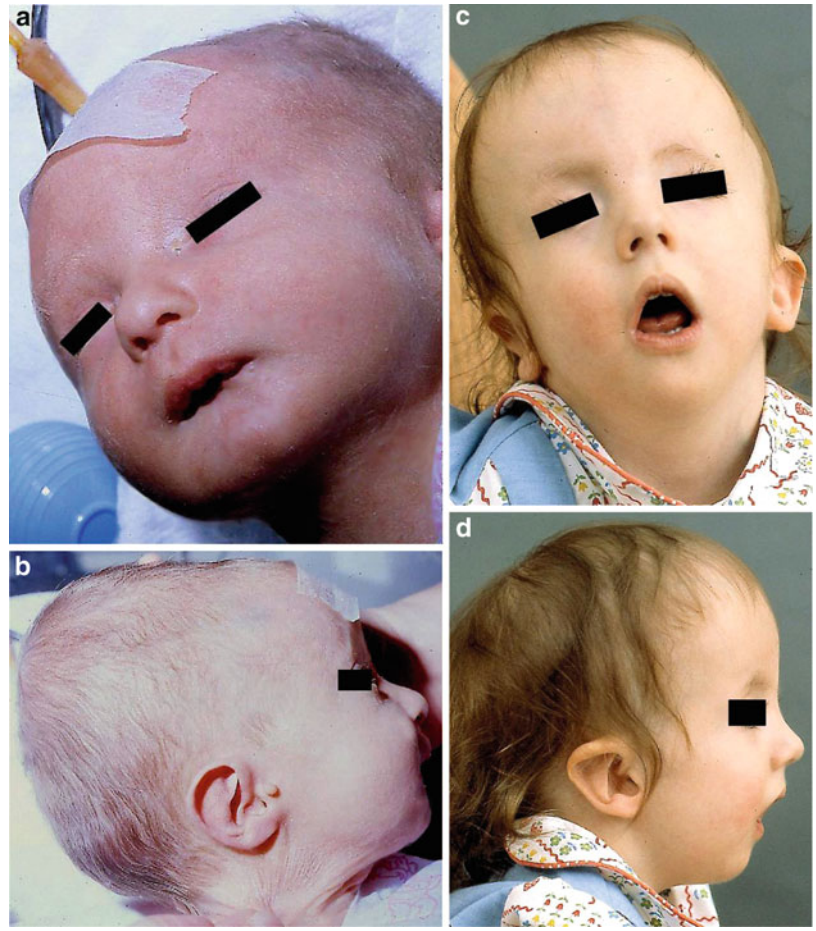

Fig. 5 (**a**–**d**) Two infants with trisomy 18 showing small eyes, micro/retrognathia, and low-set/malformed ears

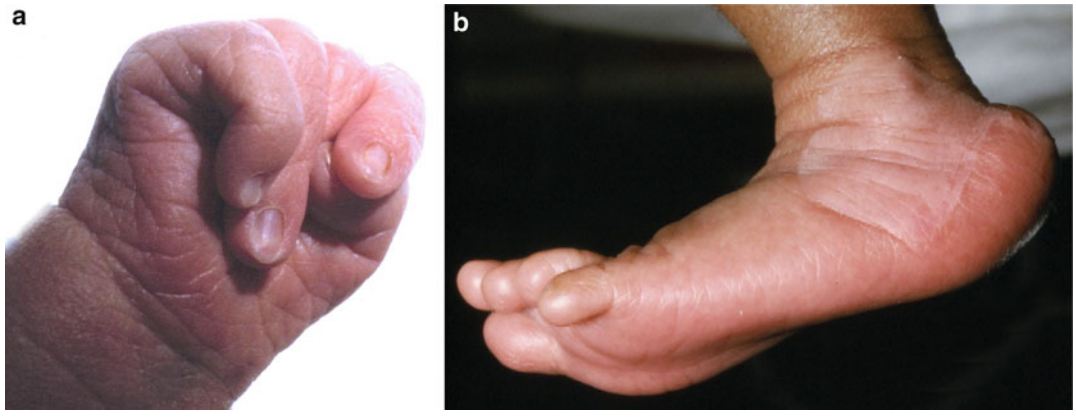

Fig. 6 (**a**, **b**) Typical hand grasping pattern (*left*) and rocker-bottom feet with prominent calcaneus (*right*) observed in trisomy 18

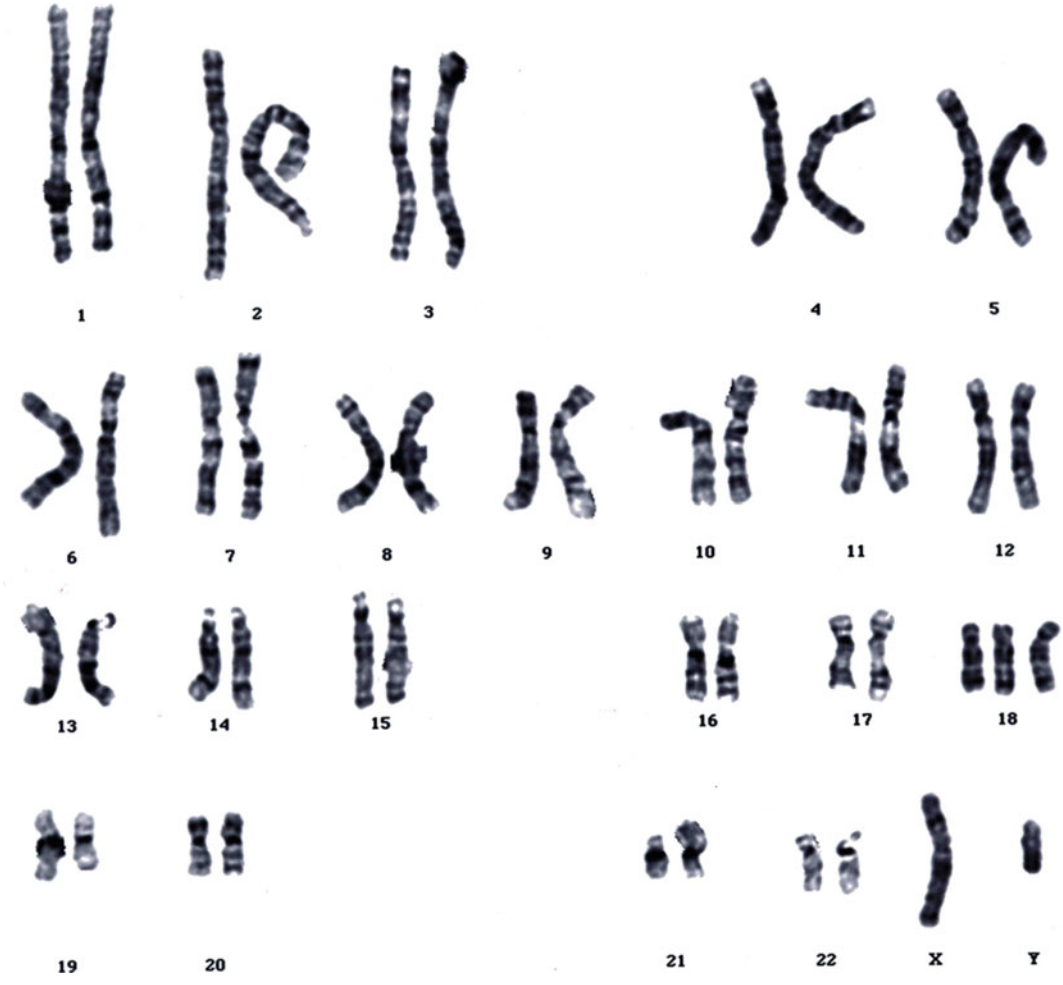

Fig. 7 Trisomy 18 karyotype (47,XY,+18)

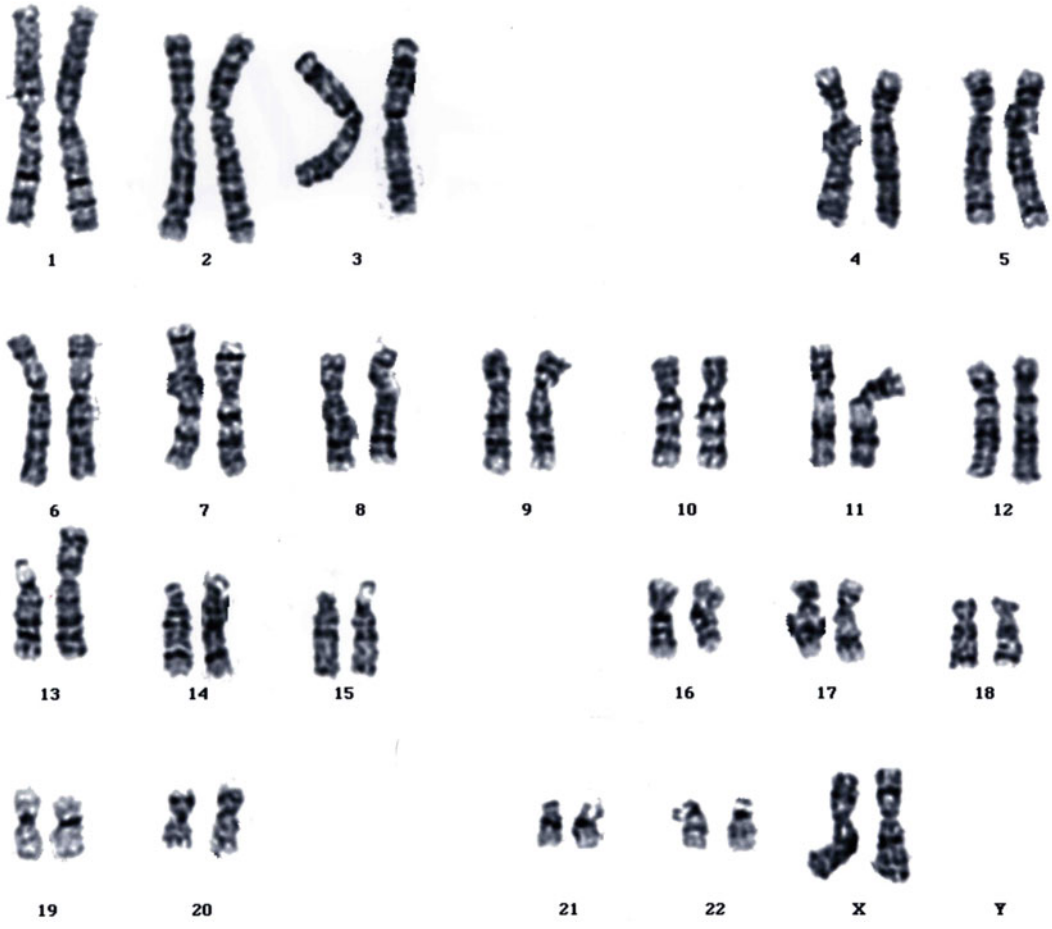

Fig. 8 Translocation trisomy 18 karyotype [46,XX,+18,der(13)t(13;18)(q10;q10)]

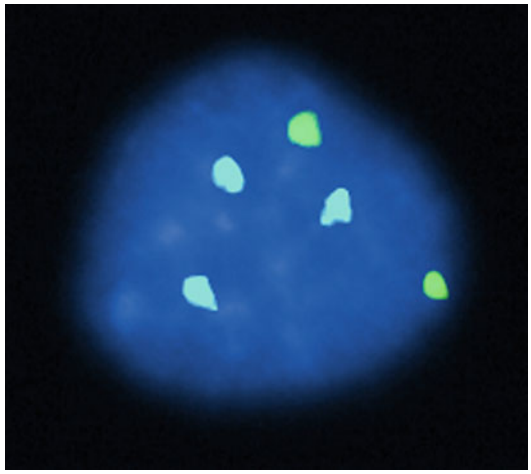

Fig. 9 Trisomy 18 shown by FISH (CEP X/SpectrumGreen, CEP 18/SpectrumAqua, Vysis/Abbott) on an uncultured amniocyte. Three copies of the aqua signal are present in the cells (CEP 18). Two copies of the green signal (CEP X) confirm a female fetus

Trisomy 8 Mosaicism Syndrome

Contents

In 1971, de Grouchy et al. (1971) first described trisomy 8 mosaicism which was further delineated by Fryns et al., Sanchez and Yunis, Schinzel, and Riccardi in 1977. This syndrome, also known as Warkany syndrome, is a well-recognized syndrome despite its phenotypic variability.

Synonyms and Related Disorders

Warkany syndrome

Genetics/Basic Defects

1. Trisomy 8 mosaicism: chromosome complement mosaic for chromosome 8 (presence of a chromosomally normal cell line in addition to the trisomic 8 cell line) (Fineman et al. 1975)
    1. A case of trisomy 8 mosaicism detected prenatally in a single clone of amniotic fluid culture, and confirmed on fetal blood and on peripheral lymphocytes after birth.
    2. A follow-up was performed over 3 years, showing a clinically normal female with cognitive, neuropsychological, and linguistic development in a normal range (Camurri and Chiesi 1991).
2. Origin of trisomy 8 mosaicism
    1. Different from the common autosomal trisomies that usually result from maternal meiotic errors.
    2. Trisomy 8 in spontaneous abortions: meiotic origin in the majority of cases.
    3. Postzygotic (mitotic) nondisjunction error in a diploid conceptus: the most likely origin of trisomy 8 in the live-born population.
    4. Postzygotic (mitotic) nondisjunction error in a diploid conceptus, followed by nonrandom distribution of aneuploid cells between the different compartments.
    5. Affected fetuses usually show a pattern of absence, or low levels of trisomy in cytotrophoblast cells (STC villi), high levels in extraembryonic mesoderm (LTC villi), and again low levels of trisomic cells in AF cells and/or fetal blood lymphocytes.
    6. LTC villi are more likely to reflect the true fetal chromosomal constitution than STC villi.
    7. The chromosomal mechanisms accounting for the WS include either literal trisomy 8 (aneuploidy), usually if not always with

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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mosaicism, or translocation leading to partial trisomy 8 (8q2). In addition, some patients with mosaic trisomy 8 may not have the Warkany syndrome (Riccardi 1977).

8. A report on a mildly dysmorphic male patient with partial low-level trisomy 8 mosaicism due to a pseudoisodicentric chromosome 8 with normal 6.0 SNP microarray and high resolution chromosome analyses in lymphocytes. The aneuploidy was detected in fibroblasts and confirmed by FISH in lymphocytes. This report elaborates further the clinical variability seen in trisomy 8 mosaicism (Leon et al. 2011).

Clinical Features

1. Wide range of phenotypic variation ranging from normal individual to severe malformation syndrome (Fineman et al. 1975; Kurtyka et al. 1988; Agrawal and Agrawal 2011) and cytogenetic expression (Jordan et al. 1998; Udayakumar and Al-Kindy 2013)
2. Central nervous system (Habecker-Green et al. 1998)
    1. Intelligence: range from normal to mental retardation
    2. Agenesis of the corpus callosum
    3. Arrhinencephaly
3. Craniofacial features
    1. Skull
        1. Asymmetrical skull
        2. Microcephaly
        3. Hydrocephaly
        4. Prominent forehead
        5. Flattened occiput
        6. Low posterior hairline
    2. Eyes
        1. Ocular hypertelorism
        2. Deep-set eyes
        3. Strabismus
        4. Corneal clouding
        5. Cataracts
        6. Amblyopia
    3. Nose
        1. Plump nose with broad base
        2. Prominent nares
    4. Mouth
        1. Micrognathia
        2. Everted lower lip
        3. High palate
        4. Cleft soft palate
    5. Low-set and malformed ears
4. Chest
    1. Pectus excavatum
    2. Widely spaced nipples
5. Heart: congenital heart disease
6. Gastrointestinal tract
    1. Meckel diverticulum
    2. Hirschsprung disease
    3. Anal anomalies
7. Genitourinary tract
    1. Cryptorchidism
    2. Unilateral renal agenesis
    3. Wilms tumor
    4. Ureteral anomalies
    5. Perineal anomalies
    6. Inguinal hernia
    7. Genital hypoplasia in males
8. Skeletal system
    1. Short stature
    2. Abnormal clavicle
    3. Absent or dysplastic patellae
    4. Joint contracture or limitation
    5. Vertebral anomalies
    6. Narrow pelvis
    7. Rib anomalies
    8. Scoliosis
    9. Camptodactyly of second through fifth fingers and toes
9. Skin
    1. Deep palmar skin furrows
    2. Deep plantar skin furrows: a hallmark of the syndrome
10. Neoplasia in individuals with trisomy 8 mosaicism (Habecker-Green et al. 1998)
    1. Leukemia
    2. Wilms tumor
    3. Cystic renal tumors
    4. Gastric Leiomyosarcoma
    5. Gestational trophoblastic disease

11. Fertility: an increased risk of infertility for males and females with trisomy 8 mosaicism (Habecker-Green et al. 1998)
12. Life expectancy: usually normal

Diagnostic Investigations

1. Necessary to perform both karyotyping and FISH to detect low mosaic trisomy 8
2. Traditional cytogenetic diagnosis
    1. Detection of mosaic trisomy 8 from various tissue.
    2. Abnormal cell line tends to decrease from lymphocytes with time (Jordan et al. 1998).
    3. In older patients, aneuploidy can sometimes be demonstrated in fibroblast cultures only.
3. Interphase fluorescent in situ hybridization (FISH) using a chromosome 8 centromere-specific probe
4. Array comparative genomic hybridization (array-CGH)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: recurrence risk not increased
    2. Patient's offspring
        1. An increased risk of spontaneous abortion for trisomic conceptuses
        2. Fetuses with complete trisomy 8: nonviable
        3. Chromosomally normal pregnancies possible
2. Prenatal diagnosis
    1. Ultrasonography (Gün et al. 2012)
        1. Bilateral renal pyelectasis
        2. Single umbilical artery
        3. Polyhydramnios
        4. Axial view of the head demonstrating the "teardrop sign" in the lateral ventricle (ventriculomegaly)
        5. Agenesis of corpus callosum
        6. 3D surface rendering of the fetal dysmorphic face
            1. Prominent forehead and ears
            2. Hypertelorism
            3. Broad-based nose
            4. Large mouth
            5. Large head
    2. Prenatal cytogenetic diagnosis of mosaicism
        1. Metaphase analysis of cultured cells from either amniotic fluid or chorionic villi (Guichet et al. 1995): currently the standard technique (analysis of 30 colonies needed to exclude 10% mosaicism with a 95% confidence level)
        2. Interphase fluorescent in situ hybridization (FISH) with a centromere-specific probe: to further define the level of mosaicism
        3. The application of interphase FISH to uncultured amniocytes is better than cordocentesis in prenatal confirmation of trisomy 8 mosaicism (Chen et al. 2012).
        4. Array comparative genomic hybridization (array-CGH): enables faster results than standard cell culture and metaphase analysis (capable of detecting mosaicism at levels as low as 7%)
        5. A report of a case of a fetus mosaic for trisomy of the entire long arm (q) of chromosome 8 without additional chromosomal aberrations (Wood et al. 2008).
            1. The diagnosis was made by amniocentesis performed following an 18 week sonogram that showed multiple fetal anomalies.
            2. Mosaicism for trisomy 8q was confirmed by routine karyotyping and fluorescent in situ hybridization (FISH) analysis.
            3. The case proved useful for testing the sensitivity of array comparative genomic hybridization (array-CGH) with respect to segmental trisomy in the presence of chromosomal mosaicism.
3. Problems in genetic counseling (Rodriguez et al. 2013)
    1. Prediction of phenotype difficult since clinical severity is not related to the level of mosaicism

2. Problems in detecting trisomy 8 mosaicism in chorionic villi (Klein et al. 1994)
    1. Do not necessarily reflect a constitutional mosaicism of the fetus
    2. Most likely represent confined placental mosaicism (a chromosomally abnormal cell line limited to the trophoblast tissue and/or extraembryonic mesoderm, with a normal karyotype in the fetus proper)
    3. In large published series of amniotic fluid chromosome analysis, 0.2% of cases are mosaic, and in addition, up to 8% of cases have single or multiple cell pseudomosaicism (Hsu et al. 1992)
    4. Possible false-negative cases of trisomy 8 mosaicism in short-term culture villi, as well as cultured amniotic fluid cells (Schneider et al. 1994; Hanna et al. 1995)
    5. Follow-up investigations in fetal blood cells recommended when trisomy 8 mosaicism is encountered in chorionic villi
    6. Very low-level trisomy 8 mosaicism may be compatible with a normal phenotype
3. Difficulties in the prenatal diagnosis of trisomy 8 mosaicism (van Haelst et al. 2001)
    1. When found in chorionic villi, it mostly represented confined placental mosaicism, while in a case of true fetal trisomy 8 mosaicism, the cytotrophoblast cells showed a normal karyotype. So, the cytotrophoblast compartment of chorionic villi is a poor indicator of the presence or absence of fetal trisomy 8 mosaicism.
    2. Follow-up investigations including amniocentesis and especially fetal blood sampling are required to come to a definite prenatal diagnosis of trisomy 8 mosaicism.
4. Problems in detecting trisomy 8 mosaicism in amniotic fluid
    1. Amniocentesis: not the best way to reveal trisomy 8 mosaicism
    2. Cases of missed trisomy 8 mosaicism reported (Tsai et al. 2014)
3. Management
    1. Mostly supportive.
    2. A report of a patient with constitutional mosaic trisomy 8 syndrome and infantile spasms, who became seizure free after treatment with adrencorticotropic hormone and clonazepam (Datta et al. 2010).
    3. Constitutional trisomy 8 mosaicism (CT8M) in a healthy bone marrow donor: Confirmation of first reported donor origin trisomy 8 (Uddin et al. 2010). The diagnosis of CT8M in the donor was completely serendipitous as it was only identified after the recipient developed donor-derived T8, post-transplant (Frey et al. 2008).
    4. Surgical management may be needed for those individuals with major malformations.
    5. While taking into consideration the natural prognosis, underlying malformations, and surgical benefits and risks, the indications for cardiac surgery in patients with mosaic trisomy 8 should be carefully individualized (Hasegawa et al. 2016).

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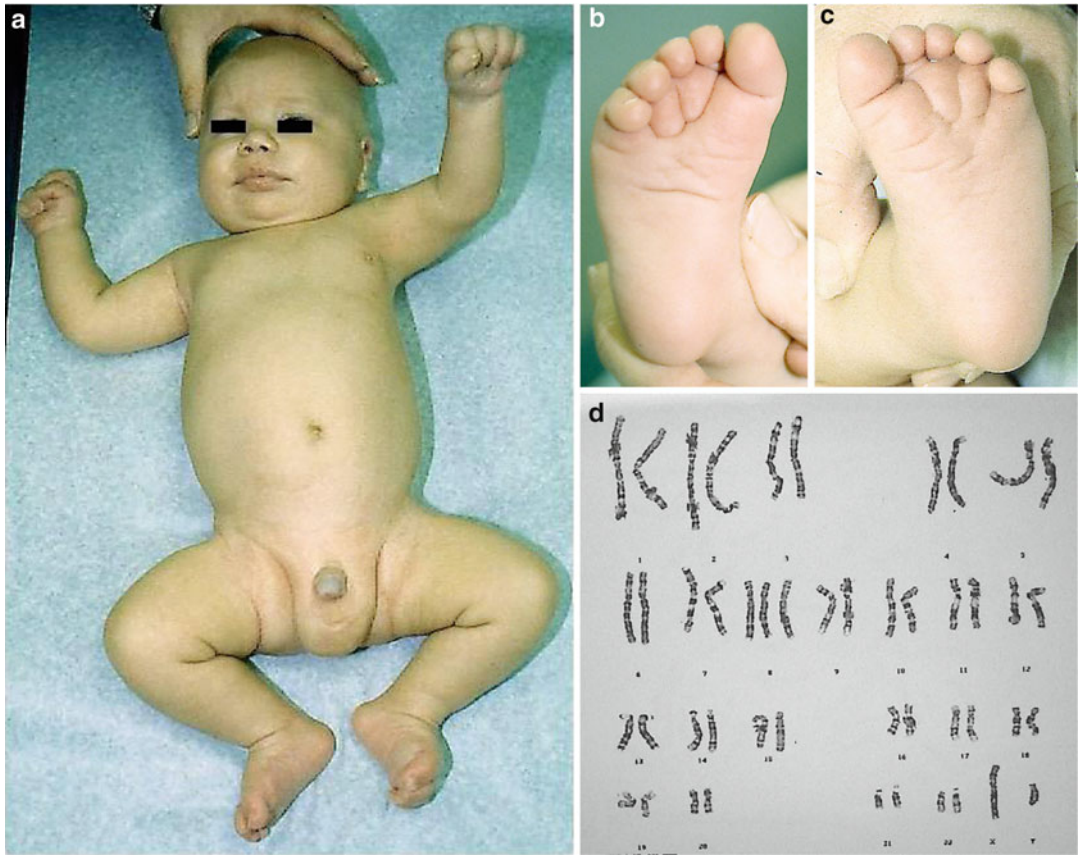

Fig. 1 (**a**–**d**) An infant boy with trisomy 8 mosaicism showing typical craniofacies (prominent forehead, ocular hypertelorism, plump nose with broad base, micrognathia) (**a**) and characteristic deep plantar skin furrows (**b**, **c**). Chromosome analysis showed trisomy 8 mosaicism (only trisomy 8 karyotype is shown here) (**d**)

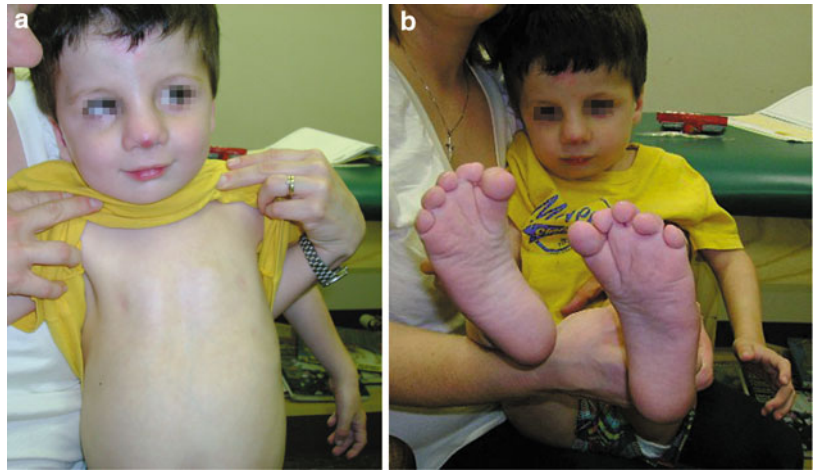

Fig. 2 (**a**, **b**) A 2-year-and-6-month-old boy with trisomy 8 mosaicism showing typical craniofacial features (prominent forehead, ocular hypertelorism, plump nose with broad base, micrognathia) (**a**) and characteristic deep plantar furrows in both feet (**b**)

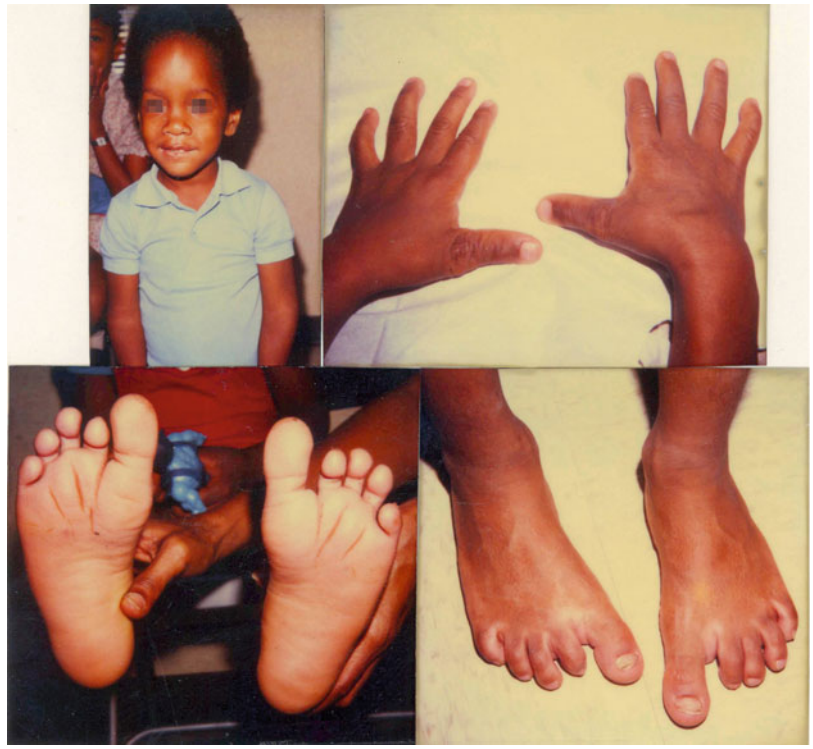

Fig. 3 Another child with trisomy 8 mosaicism with typical phenotype

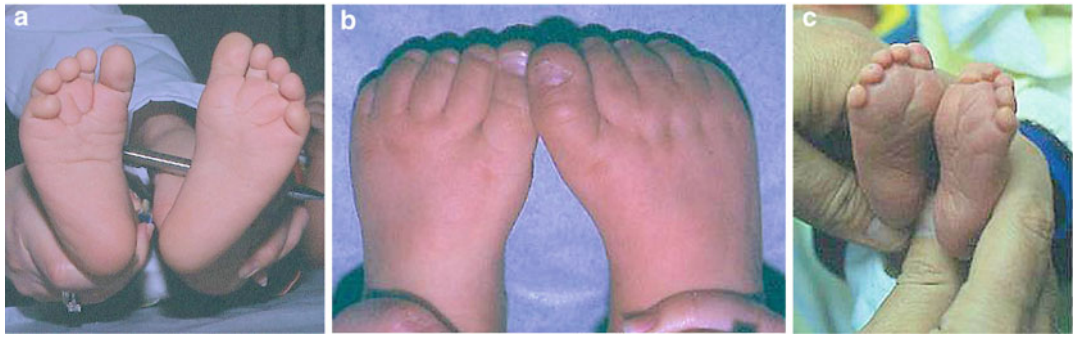

Fig. 4 (**a**–**c**) Two infants (**a**, **b**, **c**) with trisomy 8 mosaicism showing characteristic deep plantar furrows in both feet

Tuberous Sclerosis

Contents

Tuberous sclerosis is the second most common neurocutaneous syndrome after neurofibromatosis. The term "tuberous sclerosis" derived from the "tubers" (swellings or protuberances) and areas of "sclerosis" (hardening) of the cerebral gyri that calcifies with age. The classic description of the syndrome includes Bogt's triad: mental retardation, seizures, and adenoma sebaceum (a misnomer) or facial angiofibromas. Tuberous sclerosis affects about 1 in 6,000 newborns (Osborne et al. 1991).

Synonyms and Related Disorders

Tuberous sclerosis complex

Genetics/Basic Defects

1. Inheritance
   1. Autosomal dominant
      1. Almost complete penetrance
      2. Extremely variable in its manifestations and severity (Northrup et al. 1993)
   2. Sporadic (new mutations) in two thirds of cases
2. Caused by mutations in either of the following two tuberous sclerosis complex (*TSC*) genes (Jones et al. 1997, 1999; O'Callaghan and Osborne 2000; Curatolo et al. 2008)
   1. *TSC1* (Fryer et al. 1987)
      1. Located on chromosome 9q34 (Haines et al. 1991; van Slegtenhorst et al. 1998).
      2. Encodes protein, hamartin (TSC1), a protein implicated in regulating cell adhesion via interactions with cortical actin filaments and a plasma membrane binding protein ezrin-radixin-moesin, part of a Rho-mediated signaling pathway.
      3. Approximately 50% of tuberous sclerosis families show linkage to *TSC1*.
      4. Mutations occurrence: 10–15% of sporadic cases.
      5. Most described mutations in the *TSC1* gene result in a truncated protein (Young et al. 1998).
      6. Phenotype: less severe
   2. *TSC2* (Kandt et al. 1992; Henske et al. 1995)
      1. Located on chromosome 16p13.3 (European Chromosome 16 Tuberous Sclerosis Consortium 1993)
      2. Encodes protein, tuberin (TSC2), a protein implicated in regulating cytoplasmic vesicle transport to the cell membrane

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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3. Approximately 50% of families show linkage to *TSC2*.
4. Mutation occurrence: 75–80% of sporadic cases
5. Many mutations in the *TSC2* gene are large (contiguous) deletions, which may involve the *PKD1* gene, resulting in a severe phenotype called very early onset polycystic kidney disease.
6. Phenotype: more severe

3. Both *TSC1* and *TSC2*
   1. Have properties consistent with tumor suppressor genes functioning according to Knudson's "two-hit" hypothesis (Green et al. 1994; Yeung 2003).
   2. The clinical variability occurs secondary to the random nature of the second "hit" in individuals carrying a germ line mutation.
   3. Loss of heterozygosity for *TSC1* or *TSC2* gene
      1. Suggests that one mutation is acquired embryonically and another is acquired later on somatically (two-hit hypothesis).
      2. Observed in 41% of all hamartomas including renal angiomyolipomas, cardiac rhabdomyomas, and subependymal giant cell astrocytomas.
4. Hamartin and tuberin (van Slegtenhorst et al. 1998)
   1. Widely expressed in the brain
   2. May interact as part of a cascade pathway that modulates cellular differentiation, tumor suppression, and intracellular signaling
5. Mosaicism in tuberous sclerosis reported
   1. Somatic mosaicism: The mutation is not found in all cell lines.
   2. Gonadal mosaicism (Rose et al. 1999): The mutation found only in gonadal cells and is therefore transmitted to offspring while parents are spared from any disease manifestation.
6. Genotype-phenotype correlations (Dabora et al. 2001)
   1. Overlap of many clinical features exists among the patients with *TSC1* and *TSC2* mutations.
   2. Sporadic patients with TSC1 mutations
      1. On average, milder phenotypic manifestations compared with patients with TSC2 mutations
      2. Lower frequencies of seizures
      3. Lower frequencies of moderate to severe mental retardation
      4. Fewer subependymal nodules and cortical tubers
      5. Less severe kidney involvement
      6. No retinal hamartomas
      7. Less severe facial angiofibroma
   3. Some features are rare or not seen at all in *TSC1* patients.
      1. Grade 2–4 kidney cysts or angiomyolipomas
      2. Forehead plaques
      3. Retinal hamartomas
      4. Liver angiomyolipomas
   4. Both germ line and somatic mutations are less common in TSC1 than TSC2.
   5. Patients without mutation
      1. Milder than patients with TSC2 mutations
      2. Somewhat distinct from patients with TSC1 mutations

Clinical Features

1. Characteristic cutaneous features (virtually 100% of cases) (Nevin and Pearce 1968; Schwartz et al. 2007)
   1. Hypomelanotic macules ("ash-leaf spots") (87–100% of cases) (Fitzpatrick 1991)
      1. One of the earliest skin lesions (often present at birth)
      2. Commonly on trunk and buttocks, rarely on the face, and best appreciated by the Wood's fluorescence lamp
      3. Not specific to tuberous sclerosis because they are seen in unaffected children
      4. Smaller depigmented spots over the anterior shins: characteristically distributed in a "confetti" fashion (clustered skin lesions with a reticulated appearance)
   2. Shagreen patches (a form of collagenomas) (20–80%)

1. Elevated discolored skin lesions commonly over lumbosacral region, observed in about 21% of patients
2. Age at presentation: birth to adulthood

3. Facial angiofibromas (adenoma sabaceum) (47–90%)
   1. One of the most common and specific cutaneous manifestations - Multiple facial angiofibromas are a pathognomic features of TSC (Trauner et al. 2003)
   2. Causing the most disfigurement among the skin lesions
   3. Red to brown nodules, observed over the nose and cheeks in bilaterally symmetrical butterfly distribution. Rarely segmental tuberous sclerosis may present as unilateral facial angiofibromas.
   4. Age of presentation
      1. Usually appear after 2 years of age
      2. Increase in size and number of facial angiofibromas with time
      3. Observed in about 80% of adults with tuberous sclerosis
   5. Chance of small and discrete papules of facial angiofibromas to become confluent and fungating lesions
4. Forehead fibrous plaque (15%)
   1. Large fibromas without angiomatous appearance on the scalp or the forehead areas
   2. Yellowish-brown or skin-colored plaques of variable size and shape usually located on the forehead or scalp
   3. Present at any age and can be seen at birth or early infancy
5. Periungual fibromas (17–87%)
   1. Skin-colored or reddish nodules seen on the lateral nail groove, nail plate, or along the proximal mail folds
   2. More commonly found on the toes than on the fingers
   3. Characteristically appear during puberty and persist through life
6. Café au lait spots: seen in 15–30% of patients with tuberous sclerosis
7. "Confetti-like" macules (2.8%)
   1. Multiple, 1–2 mm white spots symmetrically distributed over extremities
   2. Present at the second decade or adulthood
8. Molluscum fibrosum pendulum (skin tags) (23%)
   1. Multiple soft pedunculated skin growths on neck, rarely in axilla or groin
   2. More common during first decade of life, rarely during infancy

2. CNS abnormalities (the most common manifestations of the disorder)
   1. Epilepsy
      1. The major neurologic manifestation, affecting 85% of patients
      2. Onset usually at few months of age
      3. Typically with initial classic hypsarrhythmia and infantile spasms (Yeung 2002), which transform into adult-type partial complex or tonic-clonic seizures
      4. Carries a poor prognosis with cognitive impairment
      5. Intractable seizures
   2. Presence of cortical "tubers" (O'Callaghan 2008)
      1. A pathognomonic sign.
      2. Tubers are developmental abnormalities of the cerebral cortex.
      3. The lesions have lost the normal six-layered laminar architecture of the cerebral cortex and contain dysplastic neurones, astrocytes, and characteristic giant cells.
      4. Tubers can be identified in fetal life and persist throughout life.
      5. Tubers do not increase in number after birth, although they may become more visible on magnetic resonance imaging as the brain myelinates in the first 2–3 years of life.
   3. Subependymal nodules (abnormal neuronal and glial elements): the most common cerebral lesion
   4. Cortical or subcortical white matter tubers (70% of cases)
      1. Composed of abnormal giant astrocytes.
      2. Found in 90% of patients with tuberous sclerosis.

3. Large cortical tubers may occasionally block the foramen of Monro resulting in hydrocephalus.
5. Subependymal giant cell astrocytomas
    1. The most common CNS tumors (6–14%).
    2. Subependymal nodules, small hamartoma lining the ventricles, may calcify.
    3. A radiologically confirmed cortical tuber or calcified subependymal nodule are highly suggestive of tuberous sclerosis.
    4. Rare malignant transformation of these astrocytomas, accounting for 25% of deaths in tuberous sclerosis.
6. Other abnormalities
    1. Cerebral atrophy
    2. Cerebral infarct
    3. Cerebral aneurysm
    4. Arachnoid cyst
    5. Chorea (rare manifestation) (Sha et al. 2009)

3. Developmental disorders (>50%) (Curatolo et al. 1991; Gutierrez et al. 1998)
    1. Childhood
        1. Learning disabilities
        2. Behavioral problems
        3. Pervasive developmental disorder
        4. Autism more common in childhood (Gillberg et al. 1994; Baker et al. 1998)
        5. Hyperactivity or attention deficit hyperactivity disorder (ADHD)
        6. Aggression
    2. Adulthood: mental retardation present in less than 50% of the affected individuals
4. TSC-associated neuropsychiatric disorders (Hunt and Dennis 1987; Ng et al. 2015)
    1. Behavioral
        1. Sleep disturbances
        2. Aggressive behaviors
        3. Temper tantrums
        4. Depressed mood
    2. Psychiatric
        1. Attention-deficit hyperactivity disorder
        2. Autism or autism spectrum disorder
        3. Depressive disorders
        4. Anxiety disorders
    3. Intellectual
        1. May function within normal range
        2. Severe to profound impairment of global intellectual ability
    4. Academic
        1. Reading skills
        2. Writing and spelling
        3. Mathematical skills
    5. Neuropsychological
        1. Attention deficits (selective attention, sustained attention, and attention switching)
        2. Executive deficits (planning, poor sequencing, perseveration)
        3. Receptive and expressive language deficits
        4. Memory deficits (working memory, episodic memory)
        5. Visuospatial deficits
    6. Psychosocial
        1. Psychological impact of disorder
        2. Self-esteem
        3. Family stressors
        4. Resillience factors
5. Ocular involvement (at least 50% of the patients)
    1. Retinal and optic nerve astrocytic hamartomas (the most frequent manifestations)
    2. Retinal phakoma
        1. Astrocytomas of the retina
        2. Often called “mulberry lesions”
        3. Absence of the normal “red reflex” in the newborn suggests the presence of retinal phakoma.
    3. Visual loss resulting from
        1. Macular hamartoma
        2. Vitreous hemorrhage
        3. Papilledema or optic atrophy secondary to intracranial tumors
    4. Rare sector hypopigmentation of the iris, vitiligo, or poliosis of the eyelid and eyelashes
6. Dental involvement: important findings
    1. Pitting of the dental enamel
        1. Invariably present in the permanent teeth
        2. Seen in the primary (deciduous) teeth (30%)

3. Rarely produce symptoms
2. Gingival angiofibromas (50% of children; 70% of adults)

7. Neoplasms affecting heart, kidneys, lungs, and other organ systems
   1. Cardiac rhabdomyomas (Caldemeyer and Mirowski 2001)
      1. The commonest cardiac tumors of childhood and are often associated with TSC
      2. The earliest diagnostic finding in some patients detected on prenatal sonography
      3. Detected by echocardiography, rarely causing problems
      4. Observed in two thirds of affected children. However, more than 80% of children with cardiac rhabdomyomas have tuberous sclerosis.
      5. Usually resolve spontaneously or regress with age
      6. A rare cause of prenatal and neonatal cardiac failure, mostly from dysrhythmias
      7. Rare tumor obstruction to cardiac valves or chambers
   2. Renal cysts or angiomyolipomas (70–80% of patients) (Stillwell et al. 1987; Ewalt et al. 1998; Martignoni et al. 2003)
      1. Bilateral multiple renal angiomyolipomas (70%)
         1. Diagnostic of tuberous sclerosis
         2. Renal angiomyolipomas are benign tumors but contain vascular tissue, which may cause bleeding, hypovolemic shock, and renal failure.
      2. Epithelial cysts (20%)
      3. Polycystic kidney disease (2–3%)
      4. Rare occurrence of renal cell carcinoma (<1%) (Al-Saleem et al. 1998)
      5. Malignant angiomyolipoma (<1%) (Al-Saleem et al. 1998)
      6. Benign adenomatous hamartoma (oncocytoma) (<1%)
      7. Lymphangioleiomyomatosis of the renal sinus: rare
   3. Pulmonary manifestations (Caldemeyer and Mirowski 2001)
      1. Lymphangio(leio)myomatosis (1–6% of patients) (Strizheva et al. 2001)
         1. Observed almost exclusively in young female patients, suggesting that a hormonal component is involved in the development of pulmonary sequelae (Lendvay and Marshall 2003)
         2. Affects between 26% and 39% of women with TSC
         3. Progressive, diffuse interstitial disease, detected by chest radiographs which show diffuse reticular pattern and multiple cyst lesions in the lungs
         4. Often complicated by pneumothorax from rupture of subpleural pulmonary cysts
         5. The end-stage disease shows "honeycomb" lungs.
         6. No effective treatment that reverse the progression of the lung disease (one of the causes of early mortality in TSC patients (Hancock and Osborne 2002))
      2. Multifocal micronodular pneumocyte hyperplasia (Vicente et al. 2004)
         1. Affects men and women
         2. May accompany lymphangioleiomyomatosis
   4. Hamartomas and polyposis of the stomach, intestine, and colon
      1. Almost never cause significant symptoms
      2. Occasional GI bleeding leading to positive tests for fecal occult blood
   5. Hepatic cysts and angiomyolipomas (up to 24%)
      1. Asymptomatic and nonprogressive
      2. Marked female predominance
   6. Vascular lesions (Salerno et al. 2010)
      1. Aneurysms
         1. Aorta
         2. Pulmonary artery
         3. Intracranial arteries (internal carotid, middle cerebral)
         4. Axillary artery
         5. Subclavian artery
         6. Iliofemoral artery

2. Stenotic-occlusive disease
    1. Aorta
    2. Common iliac artery
    3. Coronary artery
    4. Moyamoya disease
    5. Renal artery
    6. Mesenteric arteries
7. Arterial aneurysms reported in the brain, aorta, and axillary arteries
8. Musculoskeletal manifestations (Bernauer et al. 2001)
    1. Sclerotic and hypertrophic lesions of bone
        1. Mostly an incidental finding
        2. Occasionally palpable and associated with pains
        3. Common locations including calvarium, pelvis, vertebrae, and long bones
    2. Bone lucencies
        1. Nonspecific hamartomas
        2. Found in the phalanges of the hands and feet
        3. Usually asymptomatic
        4. Involvement in two thirds of patients
8. Pregnancy does not increase the risk of developing renal and pulmonary complications in women with tuberous sclerosis (Mitchell et al. 2003).
9. Diagnostic criteria of tuberous sclerosis complex (first proposed in 1992) (Avellino et al. 1997). The presence of one of the primary diagnostic criteria is considered sufficient to diagnose tuberous sclerosis complex.
    1. Primary features
        1. Facial angiofibromas
        2. Multiple ungula fibromas (or periungual fibromas in the absence of trauma)
        3. Cortical tuber (histologically confirmed)
        4. Subependymal nodule or giant cell astrocytomas (histologically confirmed)
        5. Multiple calcified subependymal nodules protruding into the ventricle (radiographic evidence)
        6. Multiple retinal astrocytomas (retinal hamartomas)
    2. Secondary features
        1. Affected first-degree relative
        2. Cardiac rhabdomyoma (histologic or radiographic confirmation)
        3. Other retinal hamartomas or achromic patch
        4. Cerebral tubers (radiographic confirmation)
        5. Noncalcified subependymal nodules (radiographic confirmation)
        6. Shagreen patch
        7. Forehead plaque
        8. Pulmonary lymphangiomyomatosis (histologic confirmation) (lymphangioleiomyomatosis)
        9. Renal angiomyolipoma (radiographic or histologic confirmation)
        10. Renal cysts (histologic confirmation)
    3. Tertiary features
        1. Hypomelanotic macules (three or more ash-leaf spots)
        2. "Confetti" skin lesions
        3. Renal cysts (radiographic evidence)
        4. Randomly distributed enamel pits in deciduous or permanent teeth
        5. Hamartomatous rectal polyps (histologic confirmation)
        6. Bone cysts (radiographic evidence)
        7. Pulmonary lymphangiomyomatosis (radiographic evidence)
        8. Cerebral white-matter "migration tracts" or heterotropias (radiographic evidence)
        9. Gingival fibromas
        10. Hamartoma of other organs (histologic confirmation)
        11. Infantile spasms
    4. Diagnostic criteria
        1. Definitive: either 1 primary, 2 secondary, or 1 primary plus 2 tertiary features
        2. Probable: either 1 secondary plus 1 tertiary or 3 tertiary features
        3. Suspect: either 1 secondary or 2 tertiary features
10. The Tuberous Sclerosis Consensus Conference: devised the above clinical diagnostic criteria in 1998 (Roach et al. 1992, 1998, 1999; Weiner et al. 1998; Lendvay and Marshall 2003)

1. Major features
    1. Facial angiofibromas or forehead plaque
    2. Nontraumatic ungual or periungual fibroma
    3. Hypomelanotic macules (three or more)
    4. Shagreen patch (connective tissue nevus)
    5. Multiple retinal nodular hamartomas
    6. Cortical tuber
    7. Subependymal nodule
    8. Subependymal giant cell astrocytoma
    9. Cardiac rhabdomyoma, single or multiple
    10. Lymphangiomyomatosis
    11. Renal angiomyolipoma
2. Minor features
    1. Multiple, randomly distributed pits in dental enamel
    2. Hamartomatous rectal polyps
    3. Bone cysts
    4. Cerebral white matter radial migration lines
    5. Gingival fibromas
    6. Nonrenal hamartoma
    7. Retinal achromic patch
    8. "Confetti" skin lesions
    9. Multiple renal cysts
3. Diagnostic criteria
    1. Definitive diagnosis: presence of two major features or one major feature plus two minor features
    2. Probable diagnosis: presence of one major feature plus one minor feature
    3. Possible diagnosis: presence of one major feature or two or more minor features

11. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference (Northrup & Krueger 2013)
    1. Genetic diagnostic criteria
        1. The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC).
        2. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al. 2012, 2013).
        3. Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC.
        4. Ten percent to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.
    2. Clinical diagnostic criteria: definite diagnosis (two major features or one major feature with two minor features); possible diagnosis (either one major feature or two minor features)
        1. Major features
            1. Hypomelanotic macules ($\geq$3, at least 5-mm diameter)
            2. Angiofibromas ($\geq$3) or fibrous cephalic plaque
            3. Ungual fibromas ($\geq$2)
            4. Shagreen patch
            5. Multiple retinal hamartomas
            6. Cortical dysplasias (includes tubers and cerebral white matter radial migration lines)
            7. Subependymal nodules
            8. Subependymal giant cell astrocytoma
            9. Cardiac rhabdomyoma
            10. Lymphangioleiomyomatosis (LAM)
            11. Angiomyolipomas ($\geq$2) (A combination of LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis)

2. Minor features
    1. "Confetti" skin lesions
    2. Dental enamel pits (>3)
    3. Intraoral fibromas (≥2)
    4. Retinal achromic patch
    5. Multiple renal cysts
    6. Nonrenal hamartomas

12. Prognosis
    1. The mild form of tuberous sclerosis: live full life without loss of function
    2. The severe form: significant morbidity and mortality from seizures, mental retardation, and associated cardiac, retinal, renal, and pulmonary pathology
    3. Renal disease: the most common cause of death (Shepherd et al. 1991)
    4. Association with sudden death (Byard et al. 2003; Noone et al. 2009)
        1. Cardiac arrhythmia
        2. Epilepsy
        3. Intratumoral hemorrhage
        4. Additional complications
            1. Cardiac outflow obstruction
            2. Obstructive hydrocephalus
            3. Aneurysm rupture
            4. Spontaneous pneumothorax

Diagnostic Investigations

1. Cutaneous evaluation including Wood's lamp
2. Ophthalmologic evaluation for hamartomas
3. Echocardiography to identify rhabdomyomas (Gibbs 1985; Smith et al. 1989; Jozwiak et al. 1994; Tworetzky et al. 2003)
4. ECG for cardiac arrhythmias (Curatolo et al. 1991)
5. EEG for seizures
6. Radiography of the skull (Caldemeyer and Mirowski 2001)
    1. Calcification frequently seen in subependymal nodules and giant cell astrocytomas.
    2. Less commonly seen in cortical and white matter tubers.
    3. Calcification increases with the age of the patient.
7. Plain chest radiographic films: diffuse reticular pattern in lymphangiomyomatosis of the lung
8. Pulmonary CT scan
    1. Diffuse interstitial changes with infiltrates.
    2. Cystic changes.
9. Body CT (Avila et al. 2010)
    1. The number of sclerotic bone lesions seen at body CT is of value in the diagnosis of TSC and in the differentiation of patients with sporadic lymphangioleiomyomatosis from those with TSC/lymphangioleiomyomatosis.
    2. The CT finding of multiple sclerotic bone lesions might be added to the diagnostic criteria of TSC.
10. Renal ultrasound/CT/MRI
    1. Assess angiomyolipomas
    2. Assess renal cysts
11. Neuroimagings by MRI or CT of the brain (Houser et al. 1991; Altman et al. 1988; Baron and Barkovich 1999)
    1. Calcification best detected on computed tomography
    2. Magnetic resonance imaging more sensitive for detecting small subependymal nodules and cortical and white matter tubers, especially when not calcified
        1. Extent and number of cortical tubers
        2. Subependymal gliomas
        3. Dilated lateral ventricles
        4. Hamartomatous foci
        5. Vascular dysplastic lesions such as aneurysms
        6. Identify subependymal giant cell astrocytomas before occurrence of obstructive hydrocephalus
12. Histologic findings
    1. Angiofibromas
        1. Atrophic sebaceous glands with dermal fibrosis and dilation of some capillaries
        2. "Glial" appearance of fibrosis due to the large size and stellate shape of the fibroblasts
        3. Absence of elastic tissue in the angiofibromas
    2. Ungual fibromas
        1. Fibrosis
        2. Rare capillary dilation

3. Shagreen patches
    1. Increased dense sclerotic mass of broad collagenous bundles
    2. Normal collagen bundles sometimes arranged in an interwoven pattern
    3. Reduced elastic tissue
4. Hypopigmented ash leaf macule
    1. Normal melanocytes numbers with decreased pigmentation
    2. Smaller melanosomes with defective melanization by electron microscopy

13. Molecular testing of the TSC1 and TSC2 genes: clinically available (Northrup et al. 2011)
    1. Complicated by the large size of the two genes, the large number of disease-causing mutations, and the high rate of somatic mosaicism (10–25%) (Sampson et al. 1997; Au et al. 1998a, b; Verhoef et al. 1999)
    2. Sequence analysis
    3. Deletion/duplication analysis: A deletion of the two contiguous genes (*TSC2* and *APKD1*) likely responsible if a child with tuberous sclerosis is found to have polycystic kidney disease (Brook-Carter et al. 1994)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. One to 4% recurrence risk (in case of unaffected parents) due to germ line mosaicism and nonpenetrance of the disorder recommend a conservative recurrence risk of 2–3% for families with apparently sporadic tuberous sclerosis due to germline mosaicism (Rose et al. 1999)
        2. Fifty percentage if one of the parent is affected
    2. Patient's offspring: 50%
2. Prenatal diagnosis (Milunsky et al. 2009)
    1. Prenatal ultrasonographic detection of cardiac lesions consistent with rhabdomyoma
        1. Fifty percentage risk for tuberous sclerosis in the fetus
        2. Cardiac rhabdomyomas (Bader et al. 2003)
            1. The most common cardiac tumor diagnosed in utero and in children
            2. Favorable natural history of tumors detected prenatally: Most tumors regress after the third trimester.
            3. In rare cases, there is progression in utero with a fetal demise risk of 4–6%.
    2. Prenatal MRI imaging: 2nd trimester diagnosis of subependymal tubers (Levine et al. 2000)
    3. Prenatal diagnosis/preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.
3. Management (Muller 2001; Franz 2014)
    1. Multidisciplinary team approach
    2. Early intervention programs
    3. Assess intellectual function and educational needs
    4. Psychiatric and behavioral problems (Muzykewicz et al. 2007)
        1. The most common formal diagnoses were anxiety disorders (28%), mood disorders (26%), adjustment disorders (21%), ADHD (21%), and mental disorders not otherwise specified due to general medical condition (42%).
        2. Citalopram demonstrated efficacy in treating anxiety and depression.
        3. Risperidone, in treating problematic behaviors.
    5. Pharmacologic management of behavioral problems
    6. Treat cardiac failure or cardiac arrhythmias
    7. Anticonvulsants for seizure control
        1. Treatment for infantile spasm is difficult because it is often intractable to conventional antiepileptic drugs.
            1. ACTH among other anticonvulsant therapies with variable benefits.
            2. Vigabatrin (Hancock and Osborne 1999).
        2. Early control of seizures has a crucial role in preventing subsequent epileptic

encephalopathy, and in reducing the cognitive/behavioral consequences of seizures, but does not guarantee for a normal mental outcome in children with TSC (Bombardieri et al. 2010).

8. Rapamycin and clinical trials (Orlova and Crino 2010)
    1. Rapamycin
        1. A macrolide antibiotic that has important regulatory effects on cell growth, proliferation, and inflammation via its inhibitory action on mammalian target of rapamycin
        2. Has been used as an immunomodulatory agent following organ transplantation and has a moderate-risk side effect profile
    2. Both preclinical and clinical trial data suggest that rapamycin may provide a possible therapy for TSC: The benefits may only be realized during active therapy.
        1. Reduction of angiomyolipomas volume
        2. Modest improvement of pulmonary function testing
9. Surgical care
    1. Laser treatment of facial angiofibromas
    2. Removal of ungual fibromas by laser, diathermy, liquid nitrogen, or dermabrasion
    3. CSF shunting to relief raised intracranial pressure
    4. Epilepsy surgery (Baumgartner et al. 1997): Unifocal onset seizures and mild to no developmental delay at the time of surgery are predictive of excellent long-term outcome (Jarrar et al. 2004)
        1. Focal cortical resection (tuberectomy)
        2. Lobar or multilobar resection
        3. Corpus callosotomy
    5. Vagus nerve stimulation
    6. A partial nephrectomy or selective embolization preferable to total nephrectomy for treating angiomyolipomata
    7. Cystic renal lesions rarely required surgery
    8. Renal transplantation for end-stage renal insufficiency resulting from replacement of renal parenchyma by angiomyolipomas and growing cysts or from the removal of the kidneys for intractable hemorrhage (Papaioannou et al. 2003)
        1. Offers prolonged survival
        2. Appears to be the treatment of choice in such patients
4. Updated treatment recommendations (de Waele et al. 2014)
    1. Renal manifestations
        1. In the case of angiomyolipomas larger than 3.5–4 cm, renal arterial embolization followed by corticosteroids, or kidneysparing surgery, is used to avoid total nephrectomy.
        2. Pharmacological intervention using mTORi (mammalian target of rapamycin inhibitor) can obviate the need for surgery by reducing angiomyolipoma volume.
    2. Extrarenal manifestations
        1. Traditionally, the management of SEGA (subependymal giant cell astrocytomas) that are growing and/or causing clinical signs of intracranial hypertension or unexplained changes in neurological status or TAND (TSC-associated neuropsychiatric disorders) symptoms was surgical resection.
        2. SEGA surgery is associated with significant morbidity such as hemiparesis, hydrocephalus, intracranial bleeding, infection, precocious puberty, neuropathic headache and cognitive decline, and mortality (6.2%).
        3. Surgical resection should be performed for acutely symptomatic SEGA.
        4. For growing but otherwise asymptomatic SEGA, either surgical resection or treatment with mTORi can be effective. mTORi also have beneficial effects on all the other clinical features of TSC. In selected LAM patients with moderate-to-severe lung disease or rapid progression, treatment with an mTORi may be used to stabilize or improve lung function, quality of life, and functional performance.

5. Everolimus is approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for use in TSC patients with SEGA requiring therapeutic intervention who are not amenable to surgery.
6. Topical treatment of facial angiofibromas with sirolimus has extensively been reported to yield positive results.
7. Recently, it has been demonstrated that everolimus has a partial effect on epilepsy, decreasing the frequency and severity of seizures.

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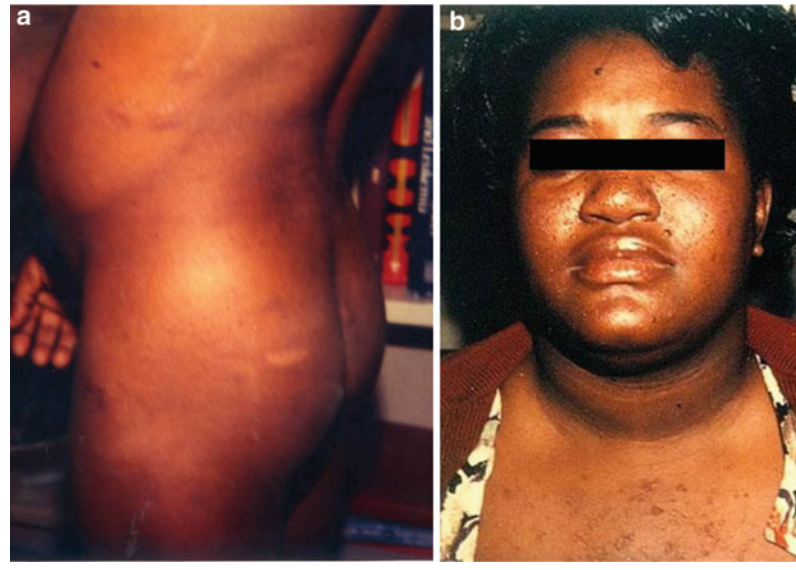

Fig. 1 (**a**, **b**) An ash leaf spot is observed in a child affected with tuberous sclerosis, inherited from his mother who has characteristic facial angiofibromas with symmetrical "butterfly" distribution on the nasolabial folds and cheeks

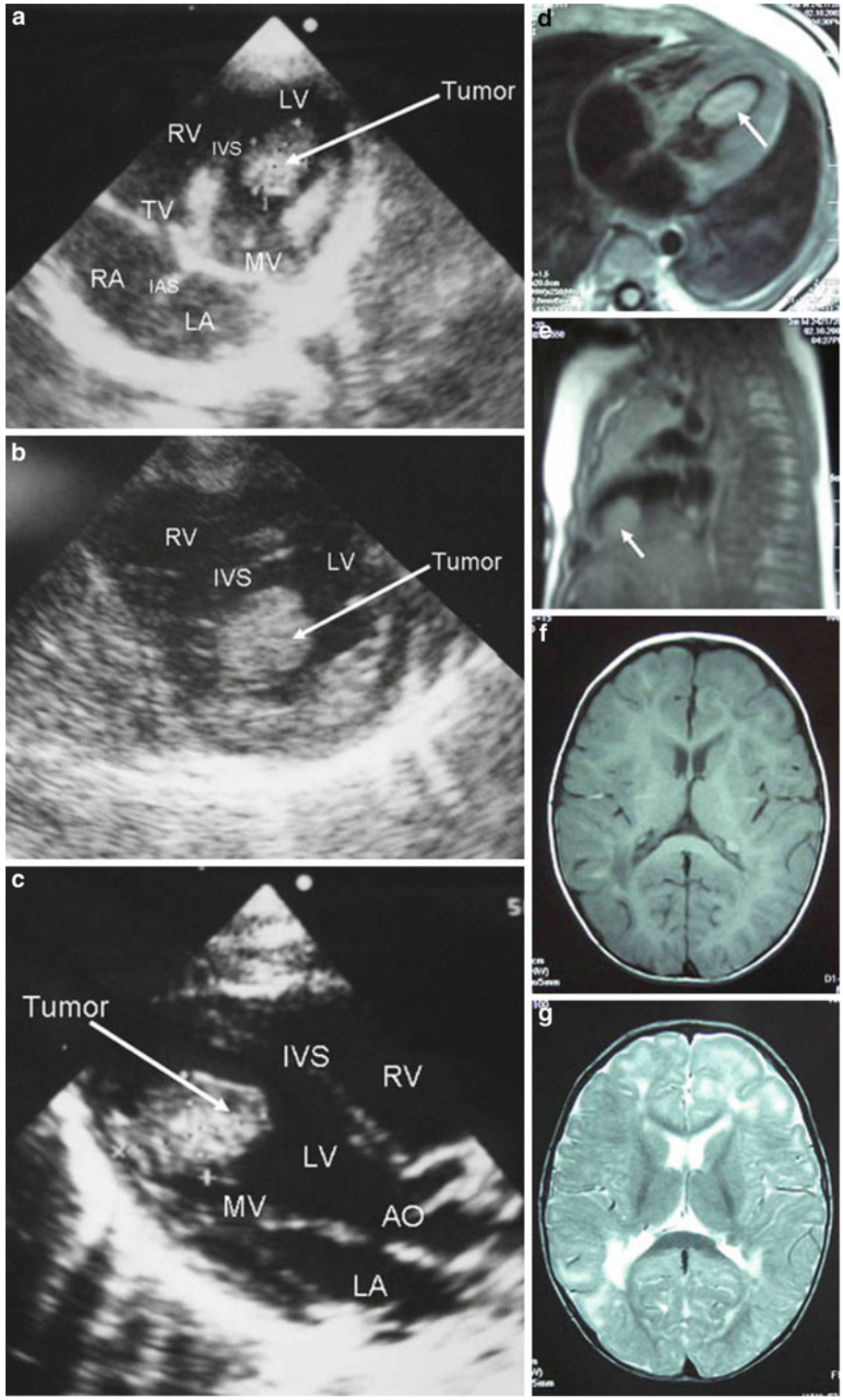

Fig. 2 A 3-month-old infant was found to have small angiofibromatous skin lesions on the cheek, two depigmented spots on the back, and a white round lesion in the left fundus. Echocardiography showed a tumor

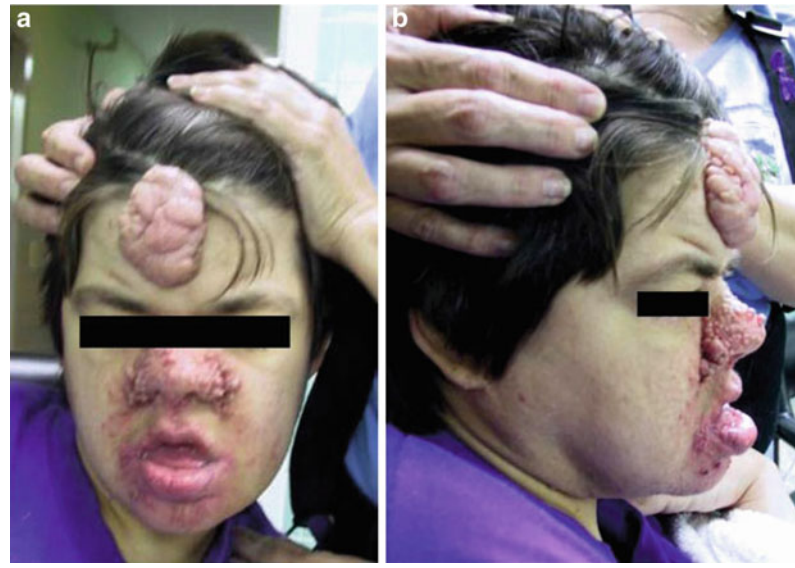

Fig. 3 (**a**, **b**) Severe facial angiofibromas in symmetrical butterfly distribution over nose and cheek with a large forehead plaque. Some angiofibromas have become confluent and fungating lesions

Fig. 2 (continued) (measured 2 × 1 cm) in the left ventricular cavity (**a**, four chamber view; **b**, short axis view; **c**, long axis view). MRI with T1-enhanced images (**d**, **e**) showed the same rhabdomyoma (*arrow*) in the left ventricular cavity. T1-enhanced (**f**) and T2-enhanced (**g**) images of the brain showed many lesions at subcortical white matter indicated by high or low signals. Some lesions can be seen in the periventricular region. Abbreviations: AO *aorta*, IAS *interatrial septum*, IVS *interventricular septum*, LA *left atrium*, LV *left ventricle*, MV *mitral valve*, RA *right atrium*, RV *right ventricle*, TV *tricuspid valve*

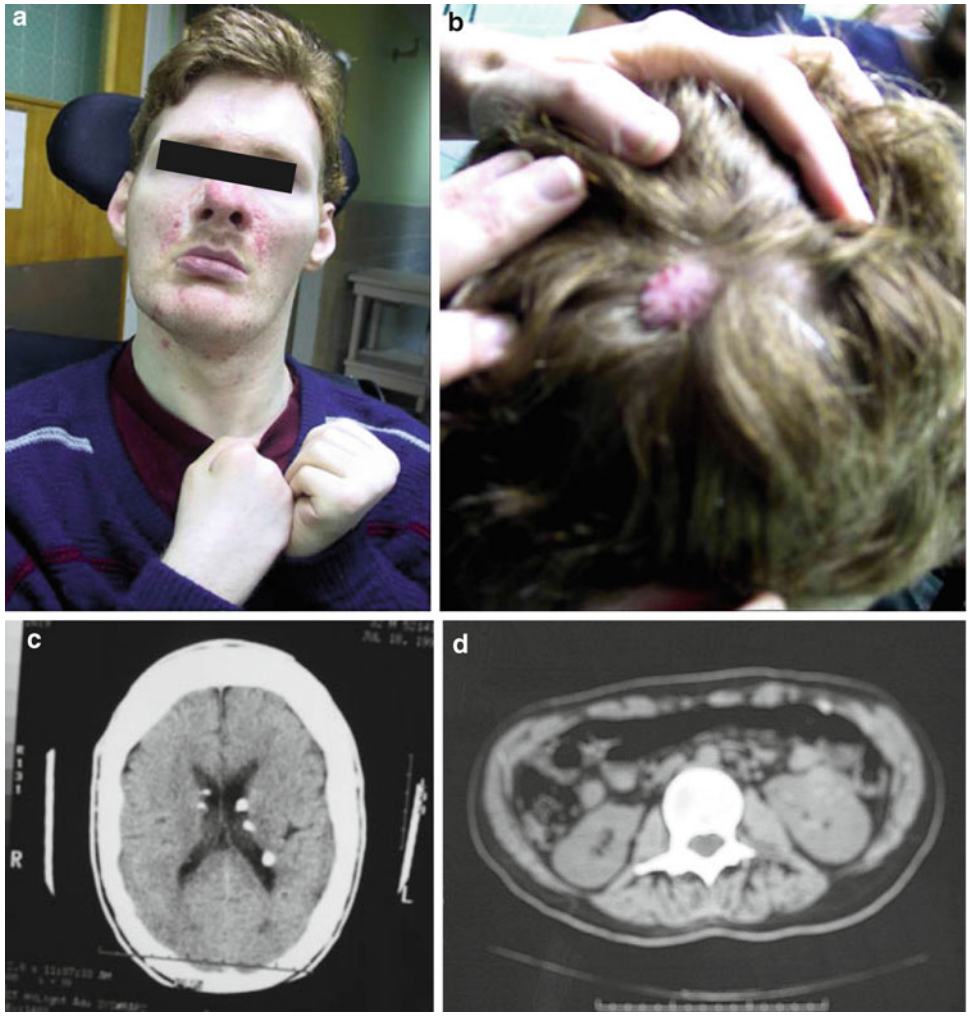

Fig. 4 (**a**–**d**) An adult with tuberous sclerosis showing typical facial angiofibromas and a scalp plaque. CT of the brain showed presence of calcified subependymal nodules. CT scan of the abdomen demonstrates an enlarged left kidney. Histologic examination of the tumor showed renal cell carcinoma

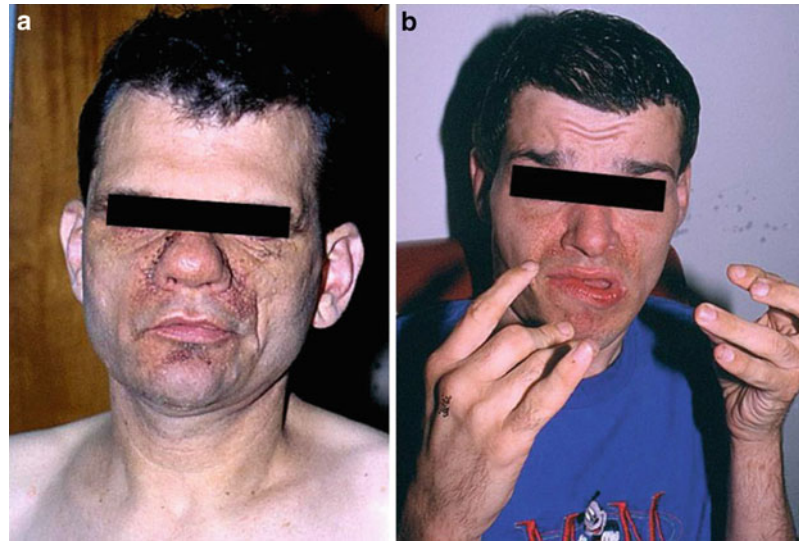

Fig. 5 (**a**, **b**) Two adults with tuberous sclerosis showing typical facial angiofibromas and mental retardation

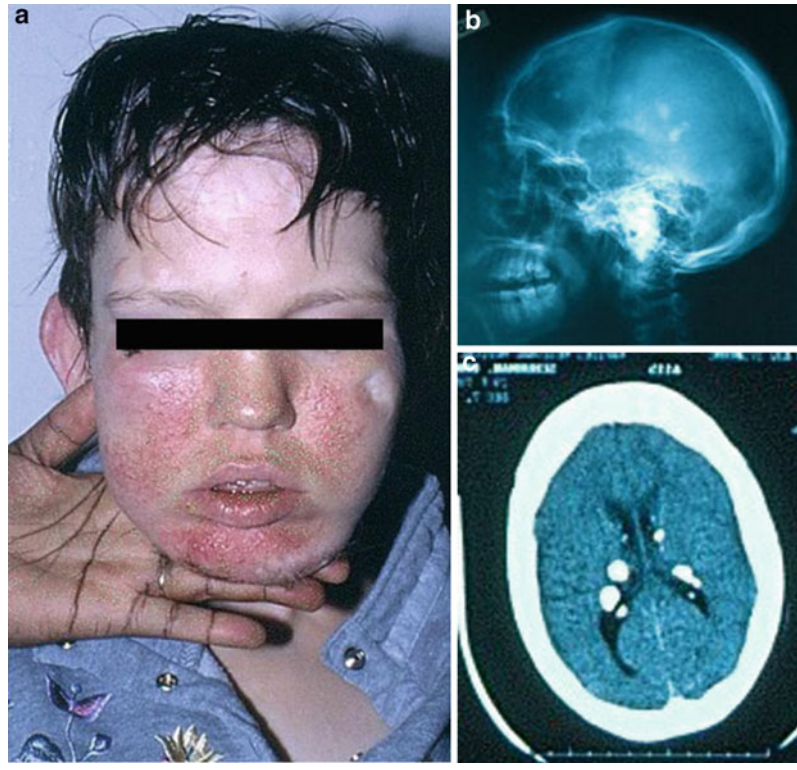

Fig. 6 (**a**–**c**) An adult with tuberous sclerosis with typical facial angiofibromas and mental retardation. A plain skull X-ray film and a CT of the brain demonstrated intracranial calcifications

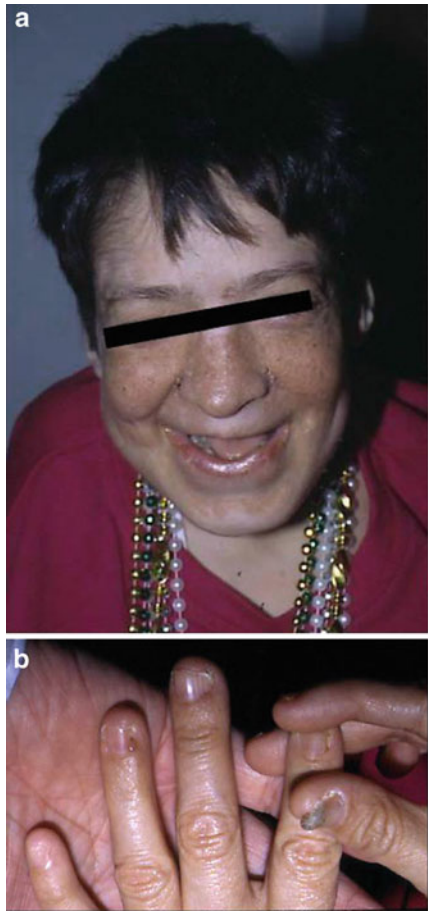

Fig. 7 (**a**, **b**) An adult with tuberous sclerosis showing typical facial features. Periungual (*fourth finger*) and ungual (*thumb*) fibromas were present

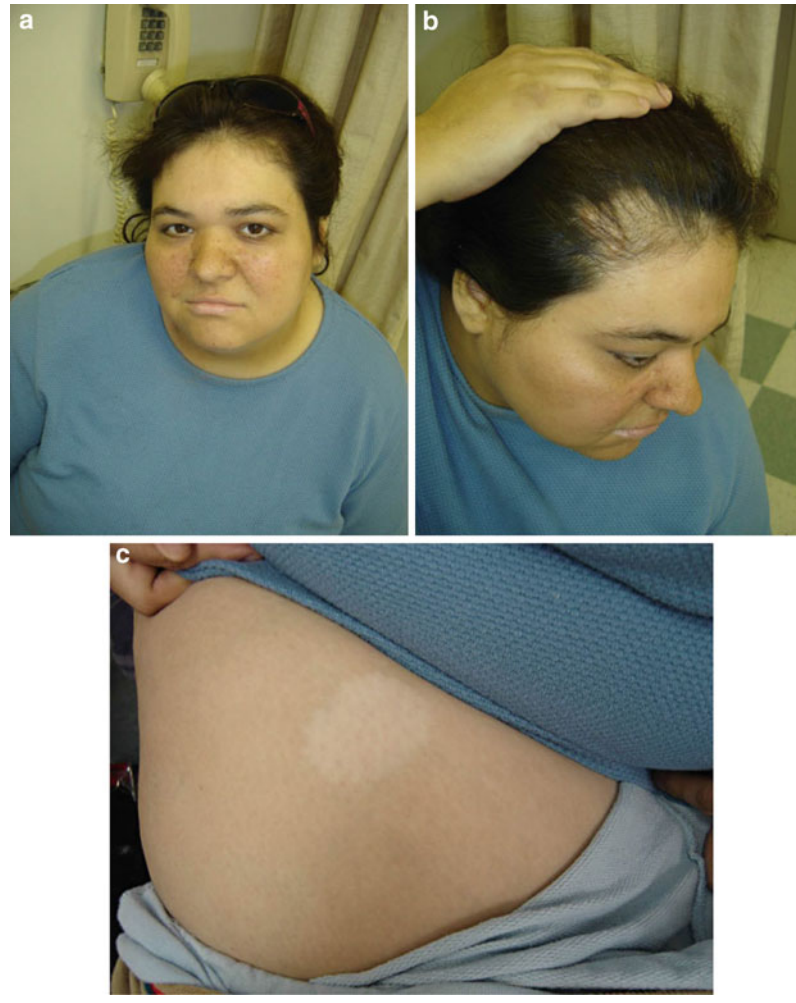

Fig. 8 (**a**–**c**) An adult with tuberous sclerosis showing typical facial angiofibromas, a scalp plaque, and a large depigmented lesion on the back

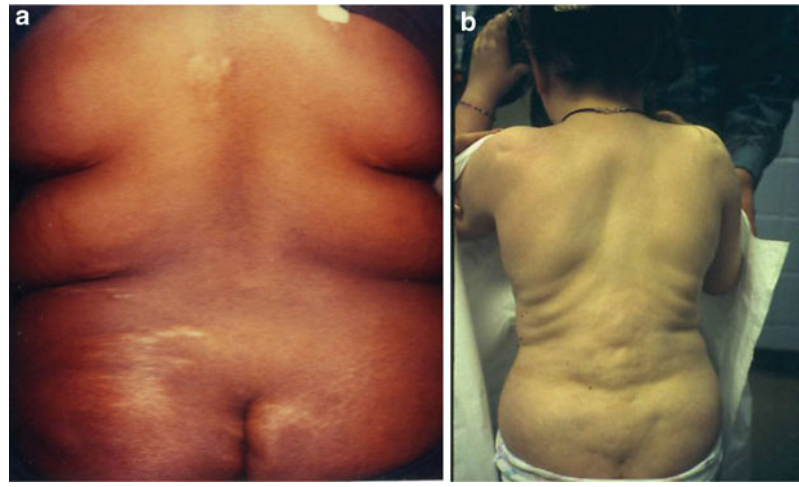

Fig. 9 (**a**, **b**) Shagreen patches are seen in upper back and lower back in two different patients with tuberous sclerosis

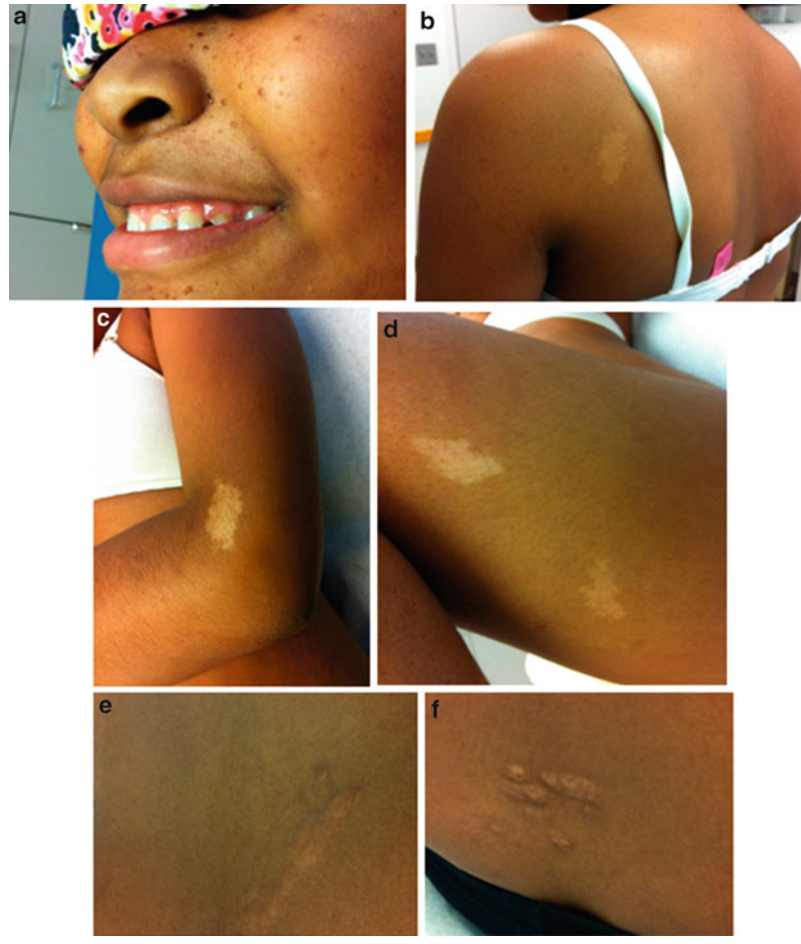

Fig. 10 (**a**–**f**) A 10-year-old female was hospitalized for papilledema and was subsequently diagnosed with the brain tumor (subependymal giant cell astrocytoma). She has tuberous sclerosis with facial angiofibromas (**a**), hypopigmented macules on antecubital, scapular, and leg regions (**b**–**d**), and Shagreen patches in the lumbar and sacral areas (**e**–**f**) (Courtesy of Dr. Susonne Ursin)

Turner Syndrome

Contents

In *1938*, Turner (1938) reported a syndrome of sexual infantilism, short stature, webbed neck, cubitus valgus, and primary amenorrhea in seven female patients. Later in 1954, it was observed that the ovaries were usually replaced by streaks of stroma without follicles; hence, the name gonadal agenesis. Negative sex chromatin was discovered in 1954; only one X chromosome was demonstrated cytogenetically in these patients in 1959.

About 99% of 45,X fetuses abort spontaneously, usually before 28 weeks, and only 1% of these fetuses survive to term. Despite this, Turner syndrome is a relatively common chromosome disorder affecting 1 in 2,500 female live births. About 10% of all spontaneous abortuses have a 45,X karyotype.

Synonyms and Related Disorders

45,X Turner syndrome; 45,X/46,XX mosaic Turner syndrome; 45,X/46,X,r(X) ring chromosome X mosaic Turner syndrome; 46,X,i(X)(q10) isochromosome Xq syndrome.

Genetics/Basic Defects

1. Caused by complete or partial X chromosome monosomy in all or some of the body cells.
2. Short stature and skeletal manifestations (short fourth metacarpals, cubitus valgus, Madelung deformity, high-arched palate, and short neck) are attributed to haploinsufficiency of the *SHOX*, the short-stature homeobox-containing gene on the pseudoautosomal region of the sex chromosomes (Xp22 and Yp11.3). *SHOX* gene is also known as *PHOG* gene (Ellison et al. 1997) for pseudoautosomal homeobox-containing osteogenic gene, lying on the very tip of the short arm of both sex chromosomes (Binder et al. 2000).
3. Involvement of SHOX in idiopathic growth retardation and in the short stature phenotype of Turner syndrome patients (Rao et al. 1997).
4. Estrogens exert a maturational effect on skeletal tissues that are susceptible to premature fusion of growth plates because of haploinsufficiency of *SHOX*, facilitating the

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development of skeletal lesions (Kosho et al. 1999).

5. Chromosome locus (Wolff et al. 2010).
    1. A majority of genes associated with the physical features observed in Turner syndrome are located on Xp (Xp11.2-p22) (Zinn et al. 1998).
    2. Loci contributing to ovarian function reside in Xq (Xq24) (Schlessinger et al. 2002).
6. Karyotype findings associated with Turner syndrome (Wolff et al. 2010)
    1. Prenatal
        1. Approximately 1–2% of conceptuses have a 45,X karyotype.
        2. The fetuses typically have ultrasound findings such as cystic hygroma or nuchal thickening.
        3. A majority of cases with mosaicism for a 45,X cell line and a cell line with a second structurally normal sex chromosome result in the birth of a child with a normal phenotype (Chang et al. 1990; Koeberl et al. 1995).
    2. Postnatal
        1. Apparently nonmosaic monosomy X is found in 45% of patients with Turner syndrome postnatally.
        2. A structural chromosome abnormality or mosaicism for 45,X and another cell line is found in the lymphocytes of the remaining patients with Turner syndrome.
7. Chromosome mosaicism in Turner syndrome (Fernández et al. 1996)
    1. A molecular investigation of 25 patients who had Turner syndrome and who had previously been subject to analysis using cytogenetic techniques.
    2. When in situ hybridization and polymerase chain reaction (PCR) techniques were applied, a larger number of mosaic individuals were observed than were detected by cytogenetic methods.
    3. This was mainly because of the presence of the cell line 46,XX.
    4. The most frequent mosaics.
        1. 45,X/46,XX (36%).
        2. The presence of isochromosomes comprised 24% and fragments 12%.
        5. The patients who had been previously diagnosed with mosaicism displayed a higher complexity in their karyotypes because of the presence of new cellular lines.
        6. The isodicentric X chromosome for the long arm, idic(Xq), gave rise to complex mosaics of up to nine cell lines.
        7. The application of fluorescence in situ hybridization and PCR led to a clearer definition of alterations at the centromeric level and the identification of the nature of chromosome fragments.
8. Review of new data supports the hypothesis that all viable 45,X cases are cryptic mosaics with a rescue cell line, implying an origin by mitotic loss (Hook and Warburton 2014).
9. Presence of Y chromosome material (Wolff et al. 2010).
    1. Mosaicism for a cell line with a normal or abnormal Y chromosome is identified in 6–11% of patients with Turner syndrome with standard cytogenetic techniques.
    2. 45,X/46,XY mosaicism can present with a wide variety of phenotypes (Rosa et al. 2014).
    3. The great majority of structurally abnormal Y chromosomes found in Turner syndrome mosaics contain two copies of virtually all of the functional Y chromosome euchromatin (Robinson et al. 1999).
    4. Risk of developing gonadoblastoma (Page 1994; Cools et al. 2006).
        1. A gonadoblastoma is a neoplasm composed of germ cells and sex cord elements with an excellent prognosis if detected early.
        2. Gonadoblastoma can progress to dysgerminoma with metastatic potential.
        3. A gonadoblastoma susceptibility locus has been proposed for the pericentromeric region of the Y chromosome (Tsuchiya et al. 1995; Lau 1999).
        4. The neoplasm does not appear to correlate with the presence of *SRY*.

5. Presence of occult Y chromosome mosaicism.
    1. Eight percentage of cases detected by molecular or standard cytogenetic techniques: Of these 12% of cases had gonadoblastoma
    2. Zero to four percentage of cases detected by FISH using a probe for the Y centromere (DYZ3) (Hanson et al. 2002; Wiktor and Van Dyke 2005)

10. Pathogenesis (Ogata and Matsuo 1995)
    1. Gonadal dysgenesis: Oocytes undergoing accelerated degeneration during the first meiosis, resulting in loss of nearly all oocytes by late childhood
    2. Somatic stigmata
        1. Lymph fluid stasis caused by lymphatic hypoplasia results in distension of the main and tributary lymphatic ducts and generalized lymphedema.
        2. Distended lymphatics and lymphedema cause mechanical extension of surrounding tissues, giving rise to deformations recognized as lymphatic obstruction stigmata:
            1. Webbed neck
            2. Low posterior hairline
            3. Rotated auricles
            4. Puffy hands and feet
            5. Redundant skin
            6. Nail hypoplasia
            7. Whorl dominant fingertip pattern

11. Phenotype-karyotype correlation
    1. Phenotype results from haploid dosage of genes that are common to the X chromosome that escape X inactivation (Zinn et al. 1993).
    2. Absence or deletion of the short arm of the X chromosome correlates with Turner stigmata (Ogata et al. 2001):
        1. Short stature
        2. Broad chest
        3. Widespread nipples
        4. Webbing of the neck
        5. Peripheral lymphedema at birth
        6. Short fourth metacarpals
        7. Hypoplastic nails
        8. Multiple pigmented nevi
        9. Coarctation of the aorta
    3. Absence or deletion of the long arm of the X chromosome correlates with infertility and gonadal dysgenesis.
    4. The degree of mosaicism correlates with the presence of clinical features of Turner syndrome.
    5. Severe phenotype associates with a small or tiny ring X chromosome which lacks the *XIST* (X-inactive-specific transcript) at Xq13 (Cervantes et al. 2001):
        1. Loss of *XIST* results in functional X disomy for the sequences contained in the ring.
        2. Some r(X), ascertained because of severe phenotypes, undergo X inactivation.
    6. The severe phenotype of females with tiny ring X chromosomes is associated with inability of these chromosomes to undergo X inactivation (Migeon et al. 1994, 2000).
    7. Mental retardation in patients with a small ring X chromosome (Van Dyke et al. 1992).
        1. High risk of mental retardation results from lack of lyonization of the ring X due to loss of the X inactivation center.
        2. Excluding those with a small ring X, mental retardation is not significantly increased in patients with Turner syndrome.
    8. Unexpected mild phenotype in some cases with ring(X) chromosome (Turner et al. 2000).
    9. A comparison of the clinical and cytogenetic findings in nine patients with a ring (X) cell line and 16 45,X patients (Collins et al. 1994).
        1. The ring (X) patients lacked many of the “classic” Turner’s syndrome features and the majority were not karyotyped until after the age of 11, usually because of pubertal failure.
        2. They also showed a reduction in IQ of 11 points compared with the 45,X group.

3. Some ring (X) patients show characteristic facial features
    1. A broad nose with anteverted nostrils
    2. Prominent philtrum
    3. Long palpebral fissures
    4. A wide mouth with a thin upper lip
4. Neither the physical features nor the IQ are related to the parental origin of the chromosome error.
5. In the majority of cases, the ring (X) chromosome was late replicating.

12. Cytogenetic findings in a consecutive series of 478 patients with Turner syndrome (Kleczkowska et al. 1990)
    1. Classic, 45,X karyotype (52.1%)
    2. Mosaic 45,X/46,XX (10.9%)
    3. Mosaic 45,X/47,XXX and other "superfemale" cell lines (4.6%)
    4. Isochromosomes i(Xq) and i(Xp) (16.1%)
    5. Ring chromosomes r(X) (4.4%)
    6. Other structural aberrations of the X chromosome (7.7%)
    7. Mosaic 45,X/46,XY patients (4%)
13. A cytogenetic and molecular study of 211 patients with clinical diagnosis of Turner syndrome (Jacobs et al. 1997)
    1. Cytogenetic study.
        1. 97 patients to have a 45,X constitution
        2. 15 to be 45,X/46,XX or 45,X/47,XXX mosaics
        3. 86 to have a structurally abnormal X
        4. 13 to have a structurally abnormal Y chromosome
    2. Molecular methods were used to look for cryptic X and Y chromosome mosaicism in patients with a 45,X constitution.
        1. Two cryptic X but no cryptic Y mosaics were detected.
        2. In 74% of the 45,X patients, the X was maternal in origin.
        3. The i(Xq)s were approximately equally likely to involve the paternal or maternal chromosome, while the majority of deletions and rings and virtually all the abnormal Y chromosomes were paternal in origin.
        4. The preponderance of paternal errors in Turner syndrome may result from the absence of pairing along the greater part of the XY bivalent during paternal meiosis I, which may make the sex chromosomes particularly susceptible to both structural and nondisjunctional errors during male gametogenesis.
14. Mother and daughter with 45,X/46,X,r(X) (p22.3q28) and mental retardation (Matsuo et al. 2000)
    1. One or more of these MRX (X-linked mental retardation) genes, subject to X-inactivation, are lost from the ring X chromosome.
    2. The reduced expression of the MRX gene (s) caused by random X-inactivation has resulted in mental retardation in the mother and daughter.

Clinical Features

1. Skeletal manifestations (Hall and Gilchrist 1990; Ogata and Matsuo 1995; American Academy of Pediatrics. Committee on Genetics. 1995)
    1. Short stature (100%): an invariant feature in the 45,X Turner syndrome
    2. Characteristic growth pattern
        1. Intrauterine growth retardation
        2. Progressive decline in growth velocity in childhood
        3. Lack of pubertal growth spurt
        4. Delayed growth cessation
    3. Cubitus valgus
    4. Madelung deformity of the wrist (a bayonet-like deformity of the wrist) with decreased extension and supination as a presenting sign of Turner syndrome (Schwartz and Summer 2000)
    5. Hypoplastic nails
    6. Short fourth metacarpals
2. Characteristic craniofacial features
    1. Down slanting of the palpebral fissures
    2. Epicanthal folds
    3. Occasional ptosis and strabismus

4. Midfacial hypoplasia
5. Broad nasal bridge
6. High-arched palate
7. Micrognathia
8. Rotated auricles

3. Teeth
   1. Crowding
   2. Malocclusion
4. Neck
   1. Short and broad neck
   2. Webbed neck (pterygium colli) with low posterior hairline from the resolution of the cystic hygroma that was present in fetal life
5. Chest
   1. Shield chest
   2. Increased internipple distance (Chen et al. 1974)
6. Congenital heart defects (26%) (Subramaniam 1989; Gøtzsche et al. 1994; Mortensen et al. 2012; Granger et al. 2016)
   1. Aortic valve abnormalities (18%)
      1. Bicuspid aortic valve
      2. Partially fused and unicuspid aortic valves
   2. Aortic stenosis
   3. Coarctation of the aorta (10%)
   4. Aneurysm (aortic root dilatation)
   5. Cystic medial necrosis of the aorta
7. Vascular anomalies
   1. Multiple intestinal telangiectasia
   2. Hemangiomas
   3. Lymphangiectasia
   4. Venous ectasias
   5. Intermittent and recurrent gastrointestinal bleeding
   6. Protein-losing enteropathy secondary to gastrointestinal lymphangiomas
   7. Chylous fluid accumulation in the abdomen and chest
8. Lymphatic phenotype in Turner syndrome (Atton et al. 2015)
   1. Peripheral lymphedema in the newborn infant involves dorsum of the hands and feet
   2. The majority of patients presented at birth with four-limb lymphedema, which often resolved in early childhood, but frequently recurred in later life.
   3. The swelling was confined to the legs and hands with no facial or genital swelling.
   4. There was only one case of suspected systemic involvement (intestinal lymphangiectasia).
   5. The lymphoscintigraphy results suggest that the lymphatic phenotype of Turner syndrome may be due to a failure of initial lymphatic (capillary) function.
9. Nail dysplasia
   1. Concave fingernails
   2. Upturned toenails
10. Skin
    1. Redundant skin
    2. Multiple pigmented nevi
    3. Tendency of hypertrophic scarring or keloid formation
11. Gonadal dysgenesis
    1. Sexual infantilism: one of the most common clinical findings
    2. Primary amenorrhea (the rule)
    3. Spontaneous menstruation occurring in about 5% of patients. Some of these women even give birth (3–5%).
    4. Delayed pubertal development in most patients
    5. Up to 30% of patients with at least some pubertal development indicating the presence of follicles in their ovaries in adolescence (Hreinsson et al. 2002)
    6. A high frequency of miscarriage reported among the spontaneous pregnancies of women with Turner syndrome
    7. Progressive ovarian failure
    8. Infertility/sterility
12. Genitourinary lesions
    1. Horseshoe and ectopic kidneys
    2. Ovarian abnormalities (Granger et al. 2016)
       1. Streak ovaries
       2. Ovarian failure
    3. Ureteropelvic obstruction
    4. A double collecting system
    5. A bifid renal pelvis
    6. Hydronephrosis
    7. Vaginal agenesis: rare
13. Hypertension (common even without cardiac or renal malformations)

14. Conductive and sensorineural hearing losses
15. Autoimmune disease
    1. A markedly increased incidence of thyroid antibodies
    2. Lymphocytic thyroiditis (Chen et al. 1978)
    3. Autoimmune hypothyroidism
    4. Impaired serum glucose tolerance in 25–60% of patients
    5. Diabetes mellitus in 5% of patients
    6. An increased incidence of inflammatory bowel disease
        1. Regional enteritis
        2. Ulcerative colitis
    7. Rheumatoid arthritis
    8. Acute hyperthyroidism: rare
16. Patients with Turner syndrome are extraordinarily prone to abnormalities constituting the metabolic syndrome (Gravholt et al. 1998)
    1. Ischemic heart disease, hypertension, and stroke
    2. Dyslipidemia
    3. Insulin-dependent and noninsulin-dependent diabetes mellitus
    4. Obesity
    5. Hyperinsulinemia
    6. Hyperuricemia
17. Abnormal dermatoglyphics
    1. Predominant digital whorls
    2. Distal triradii
18. Psychosocial aspects (Chen et al. 1981)
    1. Significantly higher verbal level than performance level attributed to a specific space-form perception deficit
    2. Arithmetic subtests: most difficult among verbal subtests
    3. Difficulty in performance
        1. Reading
        2. Figure drawing
        3. Geometry
        4. Arithmetic
19. Presence of Y chromosome material in some cases of Turner syndrome
    1. A high risk of developing gonadoblastoma and dysgerminoma
    2. Requiring preventive removal of the dysgenetic gonads
20. Mosaic patients with a structurally abnormal X chromosome
    1. Classic Turner phenotype
        1. X-derived marker in majority of cases
        2. Usually a large ring X chromosome that includes *XIST* not associated with a severe phenotype, although a low IQ or even mental retardation has been observed in some cases
    2. Severe phenotype
        1. Mental retardation
        2. Dysmorphic features uncharacteristic of Turner syndrome
        3. Observed in patients associated with a small or tiny ring X chromosome lacking the *XIST* gene at Xq13
21. Mosaicism in 45,X Turner syndrome (Held et al. 1992)
    1. In vivo selection of structurally altered sex chromosomes exists.
    2. Thus, the observation of apparent nonmosaic 45,X chromosomal complements in liveborn individuals with Turner syndrome does not contradict the hypothesis that some degree of mosaicism is necessary for survival in early pregnancy.
22. Postnatal outcomes of prenatally diagnosed 45,X/46,XX (Tokita and Sybert 2016)
    1. Relative to those diagnosed postnatally, prenatal patients were more likely to have normal growth and normal secondary sexual development, less likely to manifest distinctive Turner syndrome features such as nuchal webbing and edema, and had significantly fewer renal defects.
    2. These differences underscore the need for a nuanced approach to prenatal counseling in cases of 45,X/46,XX mosaicism.

Diagnostic Investigations

1. Endocrine study
    1. Very low estrogen levels.
    2. Elevated pituitary gonadotrophins after puberty.
    3. The majority of Turner syndrome patients suffer from accelerated loss of primordial follicles. Low circulating levels of anti-

Müllerian Hormone (AMH) may predict lack of spontaneous puberty in prepubertal girls and imminent premature ovarian insufficiency in Turner syndrome women with preserved ovarian function (Lunding et al. 2015).

2. Karyotype analyses
    1. 45,X
        1. Observed in 50% of cases
        2. Maternal origin of the X chromosome in two thirds of cases
    2. Structurally abnormal sex chromosome, such as i(Xq)
    3. Mosaicism with a second cell line containing a normal or abnormal X or Y
        1. Most common forms of mosaicism (Saenger et al. 2001)
            1. 45,X/46,XX
            2. 45,X/46,X,i(Xq)
        2. Containing a sex marker chromosome in about 20% of cases
            1. Sex marker chromosome: usually an X chromosome
            2. Second cell line containing a structurally abnormal Y chromosome in 6% of cases
    4. Determination of the chromosomal origin of sex marker chromosomes
        1. Fluorescence in situ hybridization (FISH)
        2. Primed in situ labeling (PRINS) diagnostic for repetitive sequences in specific human chromosomes
    5. Painting probes and libraries and PCR to detect "hidden" mosaicism (Fernández-García et al. 2000; De Oliveira et al. 2009)
        1. Classical alpha-satellite probes for the X (CEP-X) chromosome and Y chromosomes (CEP-Y) (Vysis)
        2. Whole chromosome painting probes (WCP-X, WCP-Y) (Vysis)
        3. XIST-digoxigenin (Oncor) hybridizing specifically to Xq13.2 indicating the X-inactivation center
        4. DXZ4-biotin (Oncor) hybridizing specifically to a cluster of 50–100 copies of a 3-kb repeat in the Xq24 region
        5. Subchromosomal painting libraries (SCPL116 specific for the short arm of the X chromosome, SCPL102 specific for the long arm of the X chromosome)
        6. Using PCR to detect Y chromosome-specific sequences
3. Molecular diagnosis of Turner syndrome (Gicquel et al. 1992)
    1. DNA analysis appears to be a useful and rapid tool in screening for Turner's syndrome.
    2. It could be an alternative to cytogenetic analysis in diagnosing the disorder when severe growth retardation or delayed puberty are not accompanied by a Turner phenotype.
4. Cytogenetic and molecular analysis of sex-chromosome monosomy (Hassold et al. 1988)
    1. The level of mosaicism is much higher among live-born than among spontaneously aborted 45,X conceptions, as has been noted by other investigators (Hook and Warburton 1983).
    2. This suggests that the extraordinarily high in utero lethality of the 45,X condition is largely restricted to those cases lacking a second cell line and implies that most, if not all, live-born 45,X's are mosaics (Hook and Warburton 1983).
    3. This suggestion is supported by recent molecular analyses that have detected Y-chromosome mosaicism among Turner syndrome individuals previously classified as being "pure" 45,Xs on cytogenetic examination (Muller et al. 1987).
    4. Continued use of X chromosome- and Y chromosome-specific probes to study mosaicism will determine the extent to which the presence of a second cell line affects survival of 45,X conceptions.
5. Identification of specific X and Y sequences
    1. Important for establishing phenotype-karyotype correlations
    2. Important for adequate genetic counseling
    3. PCR to identify the presence or absence of specific Y sequences

6. Echocardiography for cardiovascular malformations
7. Renal ultrasound for renal anomalies
8. Radiography (Finby and Archibald 1965; Lesczynki and Kosowica 1965)
    1. Madelung deformity
        1. Prominent and dorsally dislocated but reducible distal ulna
        2. Short and bowed radius
        3. Carpal articular surface of the radius tilted in a volar and ulnar direction producing a triangular configuration and premature fusion of the ulnar side of the radial growth plate
    2. Short fourth metacarpals and metatarsals
    3. Short distal phalanges with tufting
    4. Carpal bone fusion
    5. A coarse, reticular pattern of the carpal bones: more reliable and specific on hand and wrist films (Bercu et al. 1976)
    6. Pes cavus
    7. Irregular tibial metaphyses with mushroom projections on the medial surface of the proximal tibial metaphyses
    8. Spine
        1. Schmorl's nodes (abnormalities of cartilaginous end plates)
        2. Scheuermann's disease of the vertebrae (osteochondrosis of vertebral epiphyses in juveniles)
        3. Scoliosis
        4. Lack of lumbar lordosis
        5. Congenital hip dislocation
    9. Skull
        1. Midfacial hypoplasia
        2. An obtuse cranial base angle
        3. Short cranial base
    10. Osteoporosis
9. Other investigations
    1. Blood pressure measurement for hypertension
    2. Thyroid function
    3. Routine otological and audiologic follow-up of patients with Turner syndrome for conductive and sensorineural hearing loss is warranted from the time of diagnosis (Güngör et al. 2000)
    4. Orthodontic evaluation
    5. Orthopedic evaluation
    6. Glucose intolerance

Genetic Counseling

1. Recurrence risk: The mode of inheritance is sporadic.
    1. Patient's sib: low
    2. Patient's offspring: rarely pass to offspring due to infertility
2. Prenatal diagnosis
    1. Maternal serum screening
        1. Slightly decreased levels of α-fetoprotein and unconjugated estriol
        2. Elevated hCG and inhibin A
    2. Ultrasonographic screening (Hunter et al. 1982)
        1. Fetal hydrops
        2. Increased nuchal translucency
        3. Fetal cystic hygroma
        4. Fetal ascites
        5. Coarctation of the aorta
        6. Left-sided cardiac defects
        7. Brachycephaly
        8. Lymphedema
        9. Renal anomalies
        10. Intrauterine growth retardation
        11. Polyhydramnios
        12. Oligohydramnios
    3. Elevated second-trimester maternal serum β-human chorionic gonadotropin and amniotic fluid alpha-fetoprotein as indicators of adverse obstetric outcomes (high risk of fetal death) in fetal Turner syndrome (Alvarez-Nava et al. 2015)
    4. Karyotype of fetal cells from amniocentesis or CVS using standard cytogenetic, FISH, or microarray analysis
        1. A karyotype consistent with diagnosis of Turner syndrome
        2. Phenotype of the individual cannot be predicted based on the karyotype
        3. Follow laboratory guideline recommendations for prenatal diagnosis of Turner syndrome (Wolff et al. 2010)

3. Management (Sybert 2001; Davenport 2010)
    1. Health supervision: This set of guidelines is designed to assist the pediatrician in caring for the child in whom the diagnosis of Turner syndrome has been confirmed by karyotype (American Academy of Pediatrics. Committee on Genetics 1995).
    2. The prevalence of aortic dilatation and cardiac disease in Turner syndrome is high and the risk of aortic dissection increases with age. This must be carefully followed (Levitsky et al. 2015).
    3. Psychosocial counseling
        1. Degree of parental understanding and appropriate attitudes toward the patient with Turner syndrome depends, in general, on good family relationships, socioeconomic level of the family, and appropriate physician's counseling
        2. Short stature: a major concern when entering school
        3. Pubertal failure and sterility: major concerns to the parents and patients at pubertal age
        4. Webbed neck less frequent concern cosmetically unless that defect is marked and visible
        5. Occasional parental rejection and over protectiveness
        6. Child's adjustment to the disease influenced by parental personalities and their ability to cope with the implications of the syndrome
        7. Development of a high degree of social competency permitting patients to be integrated into a society where they will be self-sufficient and self-sustaining
    4. Psychosocial and sexual functioning in women with Turner syndrome (Pavlidis et al. 1995)
        1. Health status was associated with self-concept.
        2. Sexual satisfaction was related to both a higher frequency of intercourse and a higher self-reported health status.
    5. Bone fragility is recognized as one of the major lifelong comorbidities in TS (Turner syndrome) subjects (Faienza et al. 2016).
        1. The pathogenetic mechanisms responsible of bone impairment remain to be well clarified, although estrogen deficiency and X chromosomal abnormalities represent important factors.
        2. An enhanced spontaneous osteoclastogenesis has been demonstrated to occur in girls and young women with TS before and after pubertal induction with ERT (estrogen replacement therapy).
        3. This process seems to be more active in girls before puberty induction and supported by the high FSH (follicle-stimulating hormone) serum levels observed at prepubertal stage, while in young women on continuous ERT, the effects on osteoclasts seem to be mediated mostly by high RANKL (receptor activator of nuclear factor kappa-B ligand) levels.
        4. We recommended to consider the average age of 9 years as a crucial time point for the introduction of ERT.
        5. In the future, a neutralizing FSH antibody could be useful.
        6. In the meantime, a regimen combining the earlier introduction of ERT with rGH (recombinant growth hormone) treatment in girls with TS could have the effect to reduce FSH levels and to preserve bone health in these subjects.
    6. Estrogen replacement therapy: Current evidence suggests a benefit of ERT and HDL (high density lipoprotein) cholesterol (Clintron et al. 2016)
        1. To induce near normal pubertal development
        2. To prevent osteoporosis
        3. To reduce the risk of developing cardiovascular disease
    7. Growth hormone (GH) therapy (with or without anabolic steroids) for short stature
        1. Standard of care for girls with Turner syndrome (Bondy 2007)
        2. Girls treated with GH at 5.7 years (mean) averaged 7.2 cm taller than those in the control group (Stephure 2005)

3. Recombinant human growth hormone (rGH) has been approved by the Food and Drug Administration for treatment of short stature in Turner and Noonan syndromes (Chacko et al. 2012)

8. TS patients presenting with severe liver atrophy and disturbance of the major portal inflow should be indicated for liver transplantation (Kawabata et al. 2016)
9. Pregnancies among women with Turner syndrome: rare (Hovatta 1999; Cabanes et al. 2010; Mortensen et al. 2010)
    1. The most serious maternal complications
        1. Worsening of preexisting hypertension
        2. Aortic dissection
    2. A high risk of miscarriages and stillbirths among spontaneous pregnancies
    3. Seventy five percentage of spontaneous pregnancies: normal karyotype

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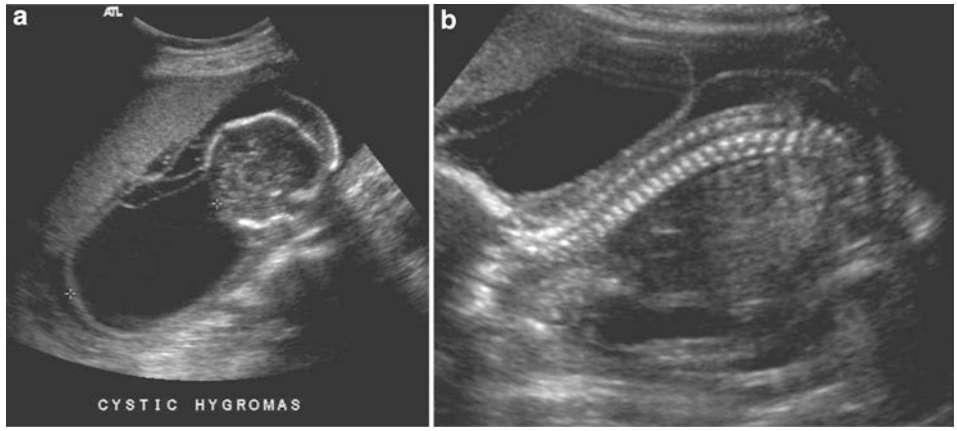

Fig. 1 (a, b) A multiseptated cystic hygroma is observed in a fetus with Turner syndrome at 18 weeks of gestation

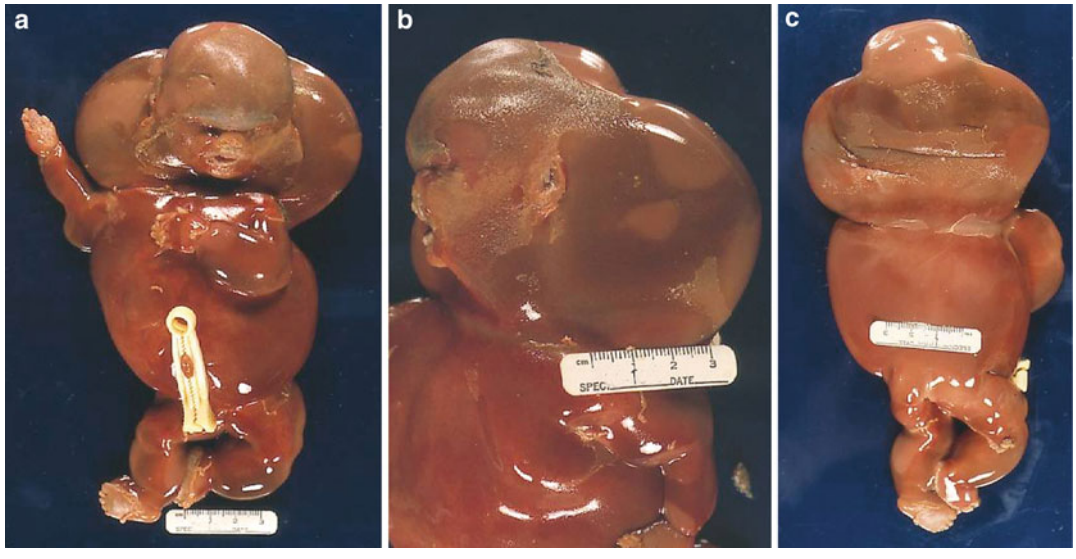

Fig. 2 (a–c) A 45,X fetus showing massive cystic hygroma and hydrops fetalis

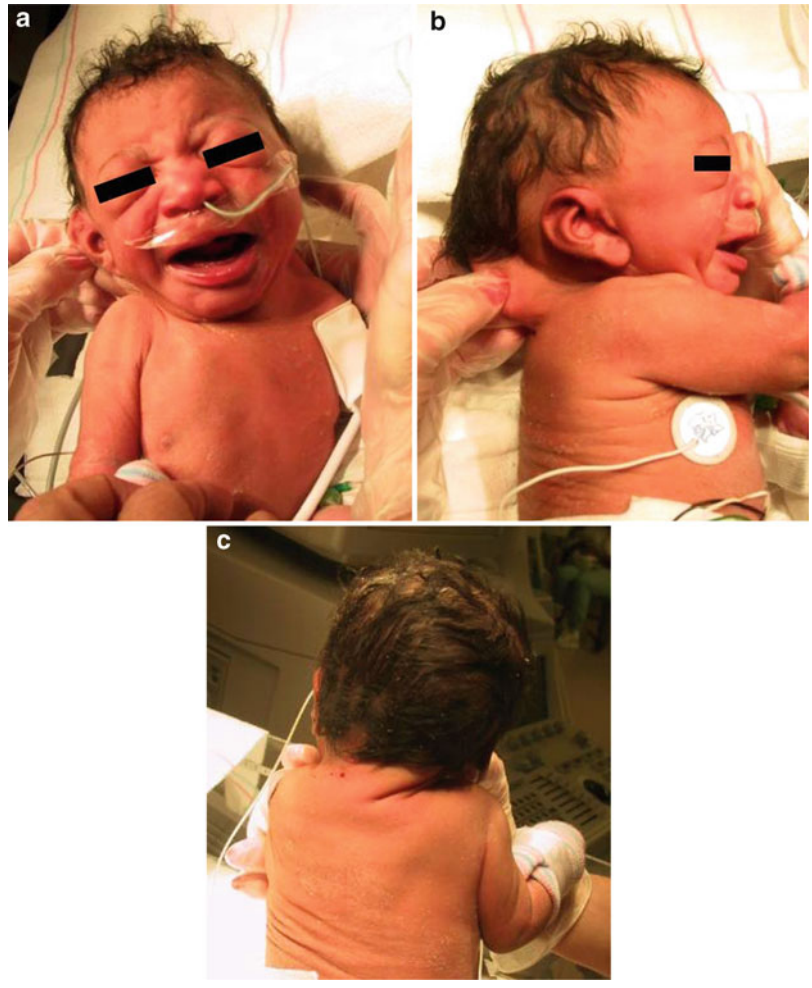

Fig. 3 (a–c) A newborn with 45,X showing classic facial features, webbed neck, shield chest, and wide space between nipples

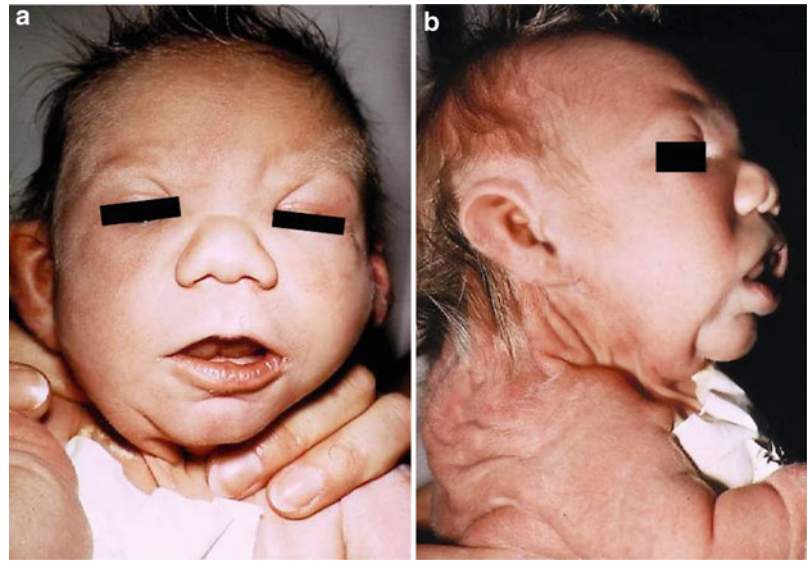

Fig. 4 (a, b) A 45,X newborn with classic facial features (epicanthal folds, down-slanting palpebral fissures, flat nasal bridge, receding chin, low-set/ posteriorly rotated ears) and excessive nuchal skin folds

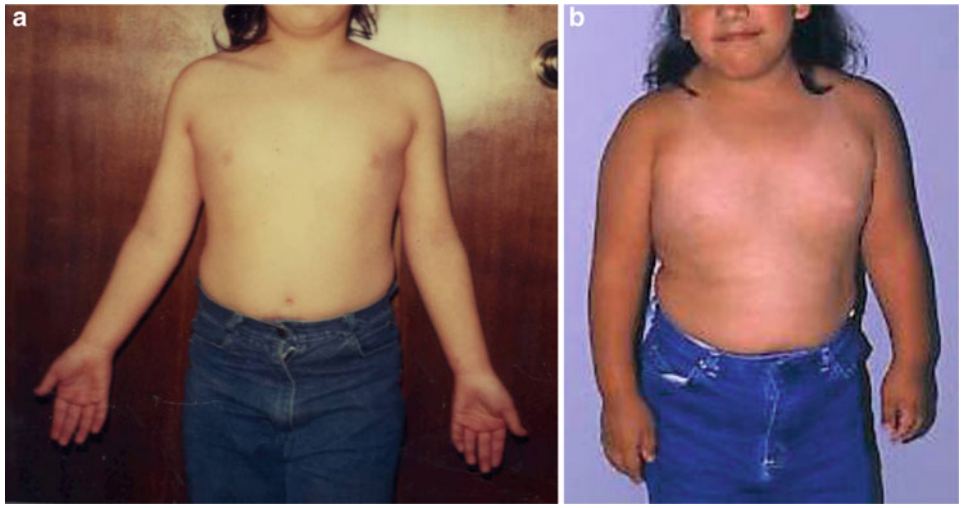

Fig. 5 (a, b) Two patients with Turner syndrome shield chest

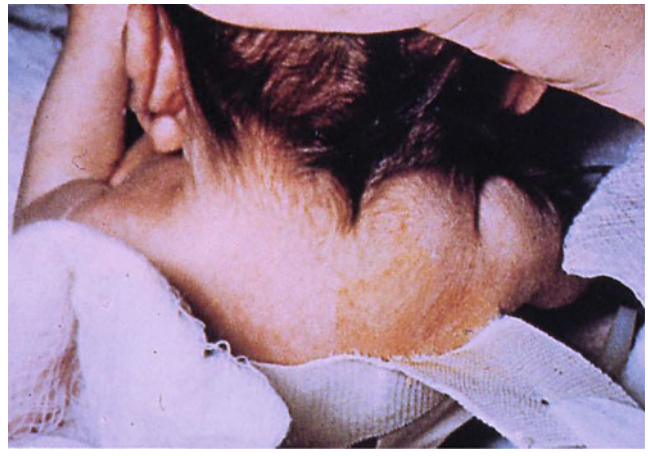

Fig. 6 A patient with Turner syndrome showing short and webbed neck and low hairline

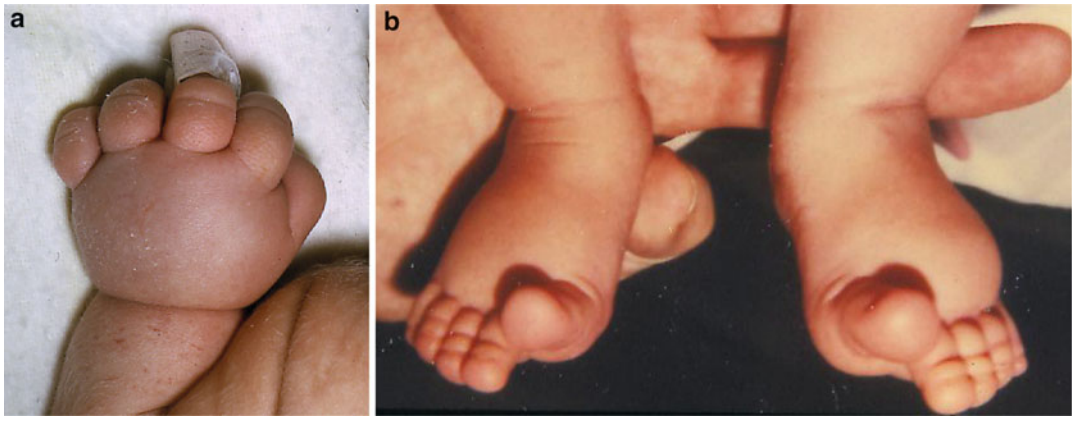

Fig. 7 (a, b) Two 45,X newborns with severe lymphedema of the dorsum of hand and feet and toenail hypoplasia

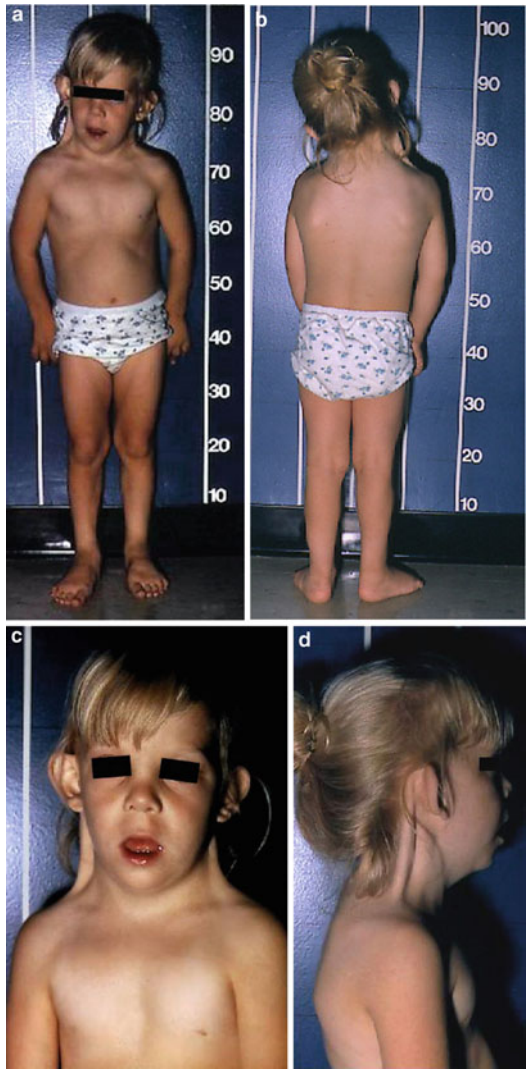

Fig. 8 (a–d) A 45,X girl showing short stature, classic facial features, severe webbed neck, shield-like chest, and widely spaced nipples

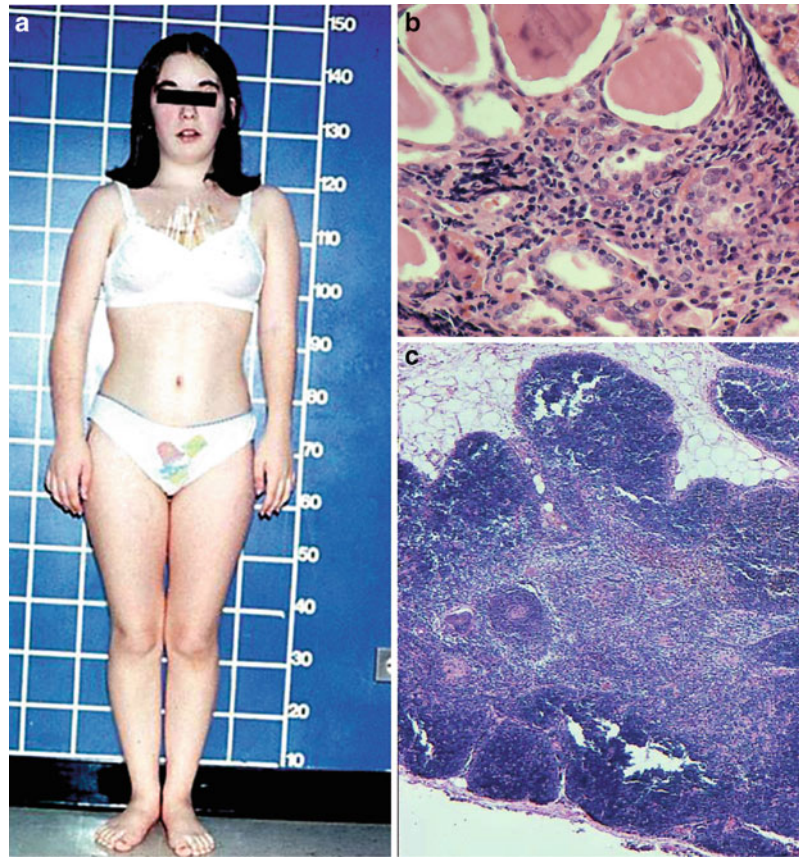

Fig. 9 (a–c) A 45,X/46, XX patient (a) showing short stature, characteristic facial features, webbed neck, lymphocytic thyroiditis (b), and follicular formation of thymus medulla (c)

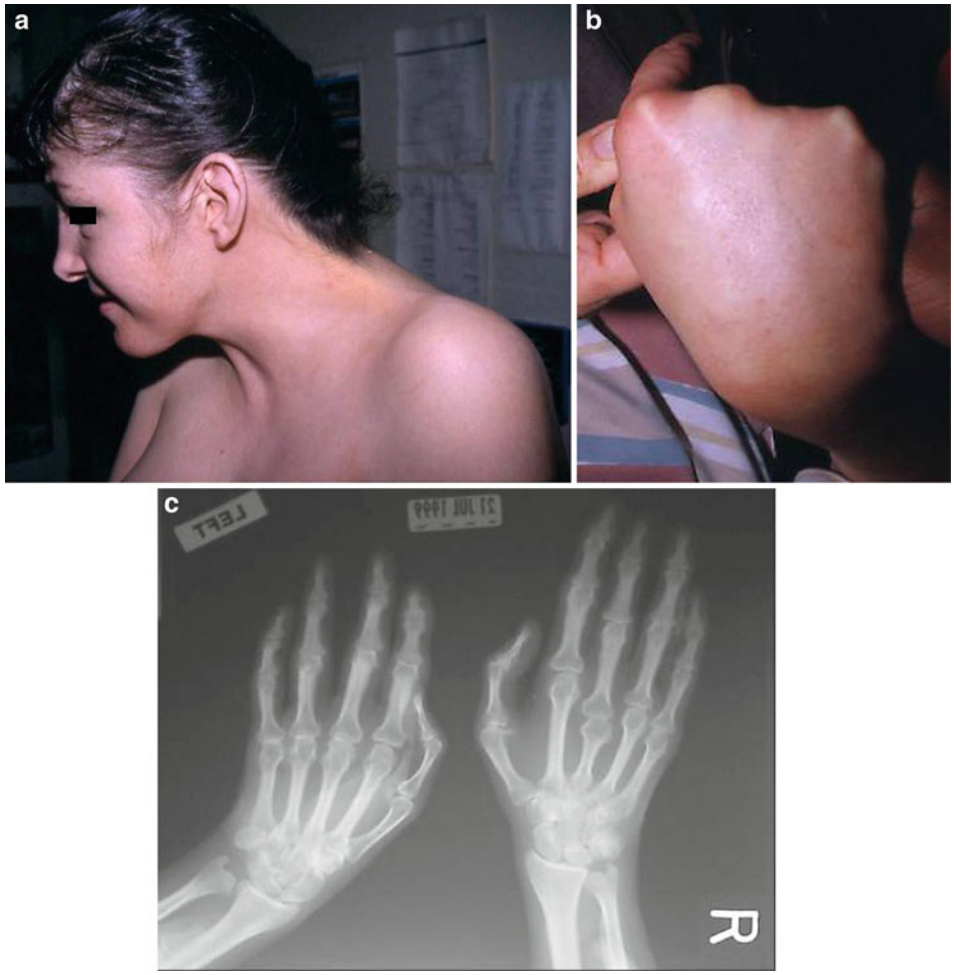

Fig. 10 (a–c) An adult patient with 45,X/46,XX mosaic Turner syndrome showing webbed neck with low posterior hairline (a) and short metacarpals (b), illustrated by hand radiograph (c)

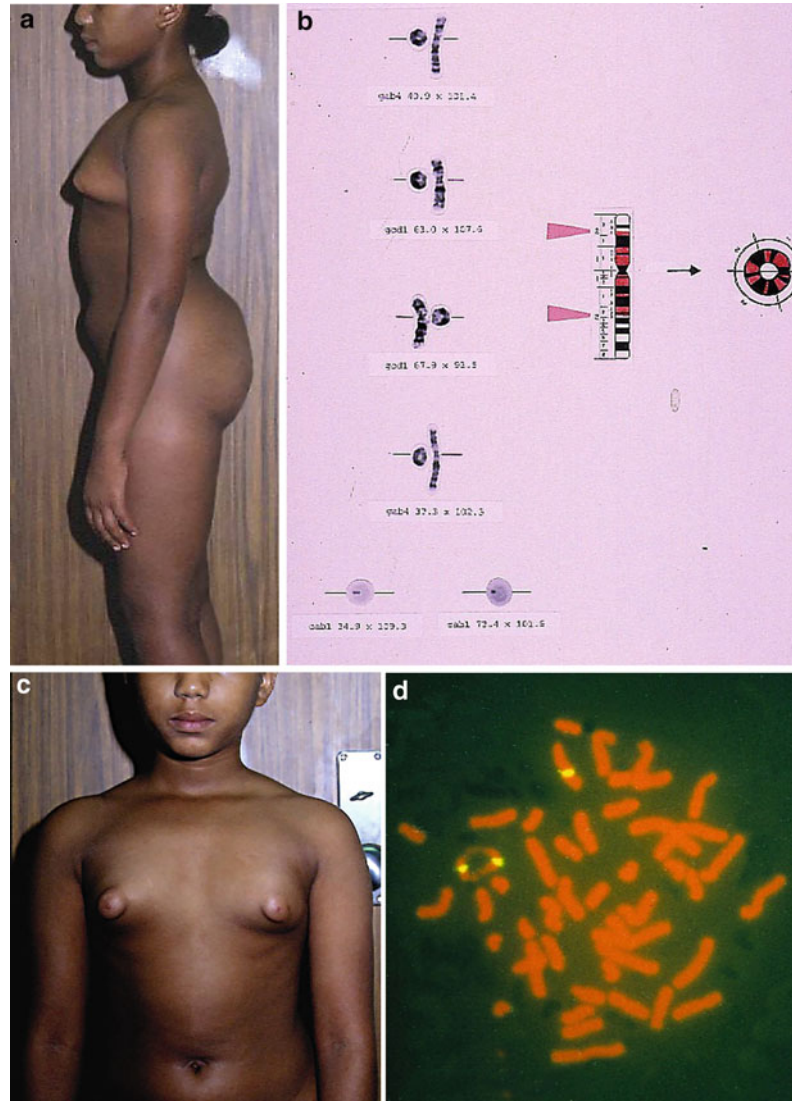

Fig. 11 (a–d) A girl (a, *b*) with 45,X/46,X,r(X) ring chromosome X Turner mosaicism. The ring chromosome is illustrated by partial karyotype with ideogram and FISH (c) with an X chromosome centromeric probe (d)

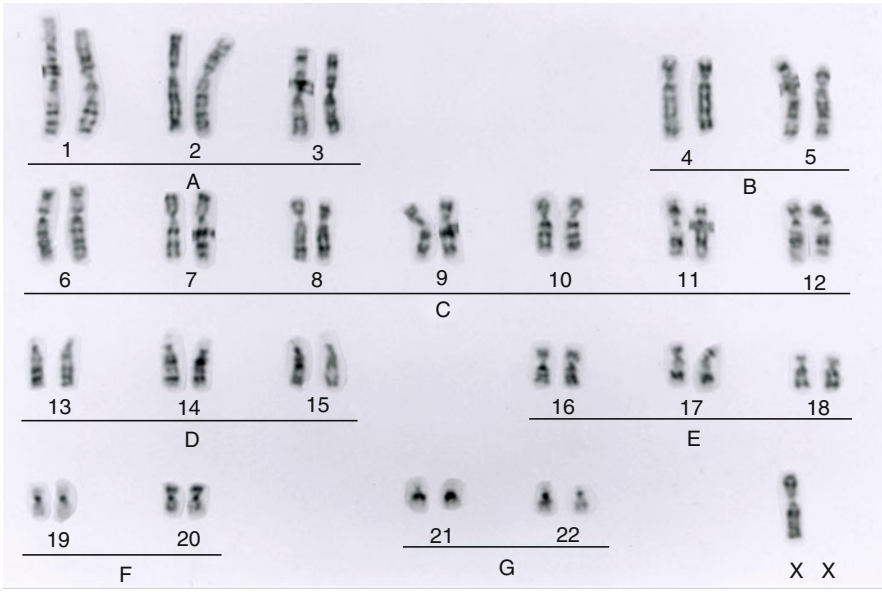

Fig. 12 45,X karyotype

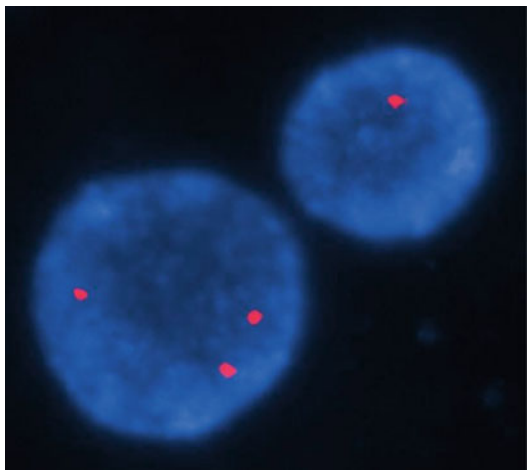

Fig. 13 FISH showing a mosaic fetus with XXX/X (CEP X/SpectrumOrange). Three copies of the orange signal are in the XXX cells and one copy in the monosomy X cells

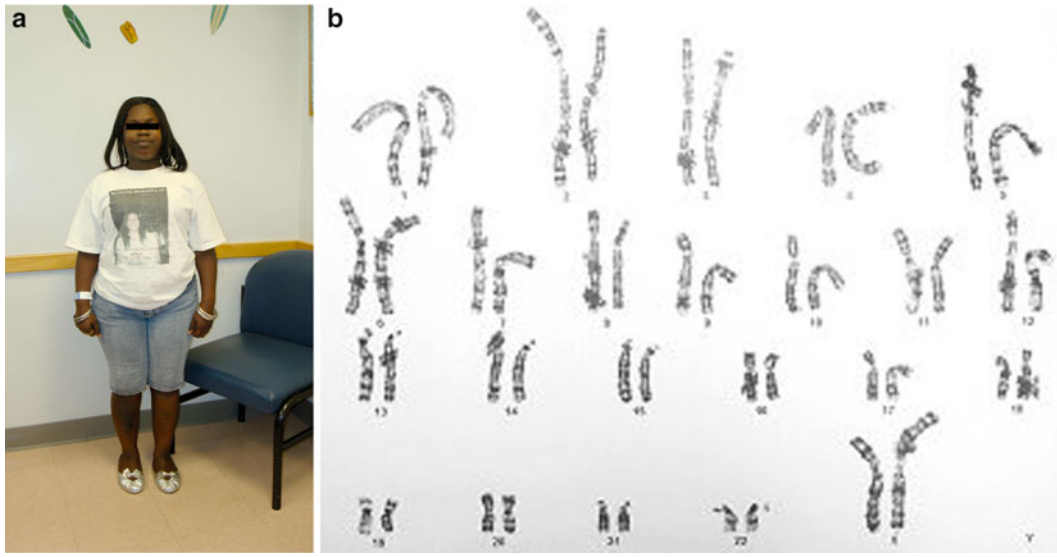

Fig. 14 (a, b) This 18-year-old adolescent girl (a) was evaluated for absence of menarche. She was noted to have Turner stage II breasts, absence of axillary hair, and scanty pubic hair. However, she has average stature for her age. The karyotype (b) shows 46,X,i(X)(q10) confirming the diagnosis of isochromosome Xq syndrome

Twin-Twin Transfusion Syndrome

Contents

Twin-twin transfusion syndrome results from imbalance in the net flow of blood leading to intrauterine blood transfusion from one twin to another twin as a serious complication in 10–30% of monochorionic diamniotic twin pregnancies (Banek et al. 2003; Weber and Sebire 2010).

Genetics/Basic Defects

1. Cause: a serious complication of monozygotic, monochorionic twin pregnancy through placental vascular anastomoses (unilateral arteriovenous anastomoses), resulting in transfusion of blood from one fetal twin to another twin (Banek et al. 2003).
2. Pathogenesis.
    1. Imbalance in net blood flow through transplacental fetofetal transfusion, resulting in a discrepancy in blood volume distribution in two twins
    2. The donor twin
        1. Becoming hypovolemic, hypotensive, and oliguric
        2. Leading to oligo-/anhydramnios and growth restriction
    3. The recipient twin
        1. Becoming hypervolemic, hypertensive, and polyuric
        2. Leading to polyhydramnios and congestive heart failure
3. Fetal cardiovascular hemodynamics in twin-twin transfusion syndrome (Wohlmuth et al. 2016).
    1. Twin-twin transfusion syndrome (TTTS) complicates 10–15% of monochorionic-diamniotic pregnancies.
    2. It originates from unbalanced transfer of fluid and vasoactive mediators from one twin to its co-twin via placental anastomoses.
    3. This results in hypovolemia in the donor and hypervolemia and vasoconstriction in the recipient twin.
    4. Consequently, the recipient demonstrates the following cardiovascular alterations:
        1. Atrioventricular valve regurgitation
        2. Diastolic dysfunction
        3. Pulmonary stenosis/atresia that do not necessarily correlate with Quintero stages
    5. Selective fetoscopic laser photocoagulation of placental vascular anastomoses disrupts the underlying pathophysiology and usually

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improves cardiovascular function in the recipient with normalization of systolic and diastolic function within weeks after treatment.
6. Postnatal studies have demonstrated early decreased arterial distensibility in ex-donor twins, but 10-year follow-up is encouraging with survivors showing normal cardiovascular function after TTTS.

4. Early prediction of twin-to-twin transfusion syndrome: A correlation exists between the subsequent development of TTTS and intertwines nuchal translucency (NT) discrepancy, (NT > 95th centile), crown-rump length discrepancy, or ductus venosus reverse flow at the first trimester scan (Stagnati et al. 2016).

Clinical Features

1. Donor twin
   1. Birth weight: small for gestational age
   2. Pallor and anemic
   3. Poor peripheral perfusion
   4. Oligohydramnios in the amniotic sac secondary to hypovolemia and decreased urine output
   5. Stuck twin phenomenon (the twin appears in a fixed position against the uterine wall) resulting from severe oligohydramnios
   6. Hydrops fetalis secondary to anemia and high-output heart failure
2. Recipient twin
   1. Birth weight: larger at birth
   2. Plethoric and ruddy
   3. Jaundice
   4. Polyhydramnios in the amniotic sac secondary to hypervolemia and increased fetal urine output
   5. Hydrops fetalis secondary to hypervolemia
   6. Hypertension
   7. Hypertrophic cardiomegaly
   8. Right-sided heart failure with tricuspid regurgitation and right ventricular outflow tract obstruction
   9. Increased risk of cardiac malformations
   10. Intravascular coagulation
   11. Rate and outcomes of pulmonary stenosis (PS) and functional pulmonary atresia (PA) in recipient twins with twin-twin transfusion syndrome (Ortiz et al. 2016):
      1. PS and PA were observed in 10.8% of recipients.
      2. Among these, about one third showed persistence of pulmonary valve pathology after delivery, which stresses the need for strict follow-up.
3. Staging of twin-twin transfusion syndrome: Quintero staging system (Quintero et al. 1999; Taylor et al. 2002; Bebbington 2010; Kontopoulos et al. 2016)
   1. Stage 1
      1. Bladder in the donor twin still visible
      2. Polyhydramnios in recipient sac (MVP >8 cm) and oligohydramnios in the donor sac (MVP <2 cm)
   2. Stage 2
      1. No longer visible bladder in the donor twin.
      2. No critically abnormal Doppler studies (CADs). CADs was defined as absent/reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein.
   3. Stage 3: Doppler abnormality consisting of absent or reverse flow in the umbilical artery, reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein
   4. Stage 4: Ascites or hydrops in either fetus
   5. Stage 5: Demise of one or both fetus
4. Prognosis
   1. Premature delivery in case of mild to moderate twin-twin transfusion syndrome
   2. Guarded with possible serious maternal and fetal complications
   3. Antenatal death as well as neonatal death secondary to preterm delivery
   4. Survival rate for those diagnosed before 28 weeks: 20–45%
5. Antenatal factors that predict poor outcome:
   1. Early gestational age at diagnosis with delivery before 28 weeks of gestation

2. Fetal polyhydramnios requiring multiple therapeutic amniocenteses
3. Fetal hydrops
4. Absent or reversed diastolic flow in umbilical artery Doppler studies

6. Neonatal complications (Blickstein 1990)
   1. Neurologic sequelae in 25% of surviving twin in case of fetal demise in other twin
   2. Divergent intrauterine growth in association with subsequent physical and mental deficiencies in the smaller twins
   3. Thrombocytopenia suggested as the cause of cataracts, impaired hearing, and growth retardation of the donor twin
   4. Intrauterine growth deficiency of the brain and profound neonatal hypoglycemia implicated as reasons for cerebral impairment of the donor twin, resulting in subsequent lower intelligence compared with its co-twin
   5. Circulatory overload with heart failure if severe hypervolemia occurs
   6. Occlusive thrombosis due to hyperviscosity
   7. Polycythemia that may lead to severe hyperbilirubinemia and kernicterus
   8. Brain damage with cerebral palsy, microcephaly, or encephalomalacia
   9. Clinical consequences of twin-to-twin transfusion (Chiang et al. 2003)
      1. Newborn infants with twin-to-twin transfusion were at risk for development of renal insufficiency, periventricular leukomalacia, and necrotizing enterocolitis.
      2. Intrauterine fetal demise of one twin and severe anemia (hemoglobin <10 g/dl) at birth were poor prognostic factors.
7. Maternal complications
   1. Secondary to multiple gestations
      1. Preeclampsia
      2. Preterm labor
      3. Hemorrhage
      4. Diabetes
   2. Maternal mirror syndrome
      1. A rare complication associated with fetal hydrops
      2. Also known as "Ballantyne syndrome" or "triple edema syndrome"
      3. A syndrome of severe water retention that "mirrors" fetal hydropic changes
      4. Frequent occurrence in the mid-trimester

Diagnostic Investigations

1. Difference in birth weight: intertwin difference $>20\%$ (heavier twin $= 100\%$) (Quintero 2003)
2. CBC to demonstrate intertwin differences of hemoglobin level (difference ≥ 5 g/dL) (Quintero 2003)
   1. Anemia: frequently in donor twin at birth
   2. Polycythemia: frequently in recipient twin at birth
3. Blood chemistry
   1. Hypoglycemia in either twins
   2. Hypocalcemia, hypoproteinemia in donor twin
   3. High creatinine in either twins with renal dysfunction
4. Thrombocytopenia in either twins
5. Hyperbilirubinemia in polycythemic recipient twin
6. Imagings
   1. Cranial ultrasound: intraventricular hemorrhage and periventricular leukomalacia in premature twins
   2. Chest radiography: pleural effusions and cardiomegaly in hydrops fetalis
   3. Echocardiography
      1. Myocardial dysfunction/hypertrophy
      2. Valvular insufficiency
      3. Pericardial effusion
   4. Renal ultrasound: abnormal renal echogenicity indicating hypoxic-ischemic cortical necrosis
   5. Abdominal ultrasound: ascites in hydrops fetalis
7. Demonstration of transplacental vascular connections: an important criterion for the diagnosis of the twin-twin transfusion syndrome (Blickstein 1990)
   1. Donor twin
      1. Placenta
         1. Pale

2. Swollen
3. Atrophied

2. Amniotic membrane showing amnion nodosum in the presence of oligohydramnios

2. Placenta of the recipient twin
1. Red
2. Congested
3. Hypertrophied

8. Surgical pathologic assessment of vascular anastomoses in monochorionic placentas with strong clinical correlation of placental types and occurrence of twin-twin transfusion (Bermúdez et al. 2002; Taylor et al. 2003)
1. Type A (placenta without vascular anastomoses): 0%
2. Type B (placenta with only deep arteriovenous anastomoses): 81%
3. Type C (placenta with only superficial anastomoses): 1%
4. Type D (placenta with combined deep arteriovenous and superficial anastomoses): 18%

9. Sonographic criteria for determining chorionicity (Barss et al. 1985)
1. Dichorionic
1. Separate placentas
2. Well-visualized septum

2. Monochorionic diamniotic
1. One placenta
2. A paper-thin, reflective hair-like septum (only small parts visible)

3. Dichorionic diamniotic: septum readily seen with a thickness similar to one wall of the umbilical cord

Genetic Counseling

1. Recurrence risk
1. Patient's sib: not increased unless in another pregnancy with monochorionic twinning (twin-twin transfusion syndrome affects 10–15% of monochorionic twins)
2. Patient's offspring: not increased unless in pregnancy with monochorionic twinning

2. Prenatal diagnosis (Blickstein 1990)
1. Changes in carbohydrate and fatty acid metabolic profiles in the amniotic fluid are noted in recipient sacs of TTTS pregnancies with cardiac dysfunction, and further changes are noted after treatment (Dunn et al. 2016).
2. Ultrasonography.
1. The required ultrasound (US) criteria (Cincotta and Fisk 1997)
1. Monochorionicity: most accurately diagnosed in the first trimester by the lack of chorion between the two amniotic sacs of the two twins and/or the presence of only a single extra-embryonic coelom
2. A marked discordance in amniotic fluid volume between the twins (known as the oligo/polyhydramnios sequence)
3. A discordance in size with the larger twin in the polyhydramniotic sac

2. First-trimester ultrasound determination of chorionicity in twin gestations (Maruotti et al. 2016)
1. The lambda sign predicts chorionicity with a high degree of accuracy before 14 weeks of gestation.
2. Presence of the lambda sign indicates dichorionicity.
3. Absence of the lambda sign indicates monochorionicity.

3. Divergent fetal size: striking differences in the sizes of the twins
1. Disparity in size of intertwin abdominal circumference (difference >18 mm).
2. Disparity in size or in the number of vessels in the umbilical cords: The donor twin may have a single umbilical artery. The size of the umbilical cord of the recipient twin may be much larger than that of its co-twin.

4. Divergent size of amniotic sacs (Quintero 2003)
1. Presence of polyhydramnios (largest pocket >8 cm) in one sac (the

recipient twin persistently has a distended bladder and produces a large amount of urine)
2. Presence of oligohydramnios (largest pocket <2 cm or stuck twin) in other sac (the donor twin produces little urine)

5. "Stuck twin" sign: a growth-retarded fetus tightly enwrapped within its membrane and trapped or stuck against the uterine wall due to oligohydramnios
6. Determination of monozygosity
   1. Like-sex twins
   2. Monochorionic diamniotic placentation (absence of twin peak sign, thin separating membrane, and single placenta showing divergent echogenicity of the cotyledons supplying the two cords)
7. A hydropic placenta: a marker of anemia, even before the fetus itself becomes hydropic (de Laat et al. 2009)
8. Evidence of hydrops in either twin
9. Evidence of congestive cardiac failure in the recipient twin
10. A sonographic staging classification for twin-twin transfusion syndrome allowing for the grading of the severity of the disease by standardized criteria (Quintero 2003)
    1. Stage I: visible bladder of the donor twin, normal Doppler studies
    2. Stage II: not visible bladder of the donor twin (during the length of examination, usually 1 h), not critically abnormal Doppler studies
    3. Stage III: critically abnormal Doppler studies in either twin, characterized as absent or reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile umbilical venous flow
    4. Stage IV: ascites, pericardial or pleural effusion, scalp edema, or overt hydrops of one or both twins
    5. Stage V: presence of one or both demised twins

3. Fetal echocardiography (Moon-Grady 2014).
   1. Possible advantages.
      1. Assessment of cardiovascular adaptation to intertwin transfusion
      2. Early recognition of deterioration
      3. Evaluation of antenatal management
   2. Fetal heart rate monitoring: A silent, sinusoidal pattern in tracings of the fetal heart rate may indicate signs of fetal anemia.
   3. Doppler studies.
      1. Detection of arterio-arterial anastomoses in monochorionic twins
      2. Doppler velocimetry of the umbilical arteries: intertwin differences in systolic/diastolic ratio >0.4 predicting growth discordancy of at least 350 g
   4. 2D ventricular assessment.
      1. Cardiomegaly
      2. Systolic dysfunction
      3. Hypertrophy
   5. Color Doppler AV valve assessment.
      1. Tricuspid regurgitation
      2. Mitral regurgitation
   6. Spectral (PW) Doppler.
      1. Tricuspid inflow
      2. Mitral inflow
      3. Ductus venosus "a" wave
      4. Umbilical venous pulsations
   7. Great vessel assessment.
      1. 2D outflow tracts
      2. Color dropper
4. Ultrasound-guided fetal blood sampling.
   1. Establishing the diagnosis of monozygosity when blood group studies are performed on both twins.
   2. Allowing an accurate antenatal assessment of the intertwin hemoglobin difference and consequently establishing the diagnosis of twin-twin transfusion.
   3. Revealing the degree of fetal anemia in the donor twin.
   4. Intrauterine death of one monochorionic twin in twin-twin transfusion syndrome puts the survivor at high risk of intrauterine death or of developing ischemic/hypoxic lesions. The fetal blood sampling is

a useful diagnostic tool to identify those fetuses that are not anemic and hence unlikely to be at risk of developing a cerebral lesion (Senat et al. 2002).

5. Fetoscopy: demonstration of perimortem fetofetal hemorrhage in twin-twin transfusion syndrome (Quintero et al. 2002).
    1. Plethora donor twin
    2. Pale recipient twin: consistent with perimortem fetofetal hemorrhage from recipient to donor twin

3. Management (Cincotta and Fisk 1997; Crombleholme 2003)
    1. General approach
        1. Monochorionic twining at high risk for twin-twin transfusion syndrome
        2. Requiring close obstetrical monitoring
        3. Requiring specialized care in neonatal intensive care unit
    2. Postpartum therapies
        1. Directed towards the problems of each twin, such as prematurity, anemia, polycythemia, and hydrops fetalis
        2. Severely anemic donor twin: requires packed red blood cell transfusions or partial exchange transfusions
        3. Polycythemic recipient twin: requires partial exchange transfusion to lower serum hematocrit
    3. Prenatal therapies (van Gemert et al. 2001; Ropacka et al. 2002; Gardiner et al. 2003; Walker et al. 2007)
        1. Treating the mother with digoxin with favorable results when the recipient twin is showing signs of cardiac failure (edema, ascites, and hydramnios) (De Lia et al. 1985).
        2. Treatment options.
            1. Prevent preterm labor and preterm premature rupture of the membranes from polyhydramnios (amniodrainage and septostomy)
            2. Isolate the twin circulations (cord ligation and selective laser photocoagulation)
        3. Serial amniodrainage (amnioreduction): currently the most widely used therapy because it is simple and requires commonly available skills and equipment.
            1. Removing large volumes of amniotic fluid from the recipient twin's sac.
            2. Reducing the amniotic fluid volume, thereby reducing the risk of preterm labor or ruptured membranes.
            3. Early, rapid, and radical amniodrainage is an effective and low-cost therapy for severe twin-twin transfusion syndrome (Jauniaux et al. 2001).
            4. The use of therapeutic amnioreduction was associated with a satisfactory perinatal survival rate for early stage disease (Duncombe et al. 2003).
            5. Overall perinatal survival with serial aggressive amnioreduction: about 60% in uncontrolled published series.
            6. Double survival rate (50%) and single survival rate (20%) in severe twin-twin transfusion syndrome presenting before 28 weeks of gestation.
            7. Fail to address the underlying cause of twin-twin transfusion syndrome.
            8. Complications: uterine contractions, premature rupture of membranes, chorioamnionitis, abruptio placenta, and inadvertent septostomy resulting in iatrogenic monoamniotic twins.
        4. Amniotic septostomy: intentionally puncturing the intertwine septum.
            1. To create a hole in the intertwine membrane between the anhydramniotic donor's sac and the hydramniotic recipient's sac
            2. Restoring normal amniotic fluid pressure gradient, allowing fluid to move along a hydrostatic gradient from the hydramnios sac into the oligohydramnios sac
            3. Also an inadvertent occurrence during amnioreduction procedure

4. Limited experience
5. Endoscopic laser coagulation of all placental vascular anastomosis (Wee and Fisk 2002).
    1. Fetoscopic laser coagulation of placental vascular anastomoses: the treatment of choice for severe twin-twin transfusion syndrome, interrupting blood flow between the twins and relieving uterine overdistension related to severe polyhydramnios (Diehl et al. 2014).
    2. Reduces and abolishes intertwine transfusion by ablating chorionic plate anastomoses, producing functionally dichorionic pregnancies.
    3. Proponents arguing that the procedure reduces the risk of neurological injury in survivors.
    4. Overall survival rate (58%) with single survival of 32% and double survival of 42% for cases presenting prior to 18 weeks.
    5. Fetoscopic laser photocoagulation for fetofetal transfusion syndrome in monochorionic triamniotic as well as dichorionic triamniotic triplets seems a valuable treatment (Ishii et al. 2014).
    6. Rare fetal complications (relationship to the procedure not established): aplasia cutis, limb necrosis, amniotic bands, and microphthalmia/anophthalmia.
    7. The incidence of prenatal brain damage is low following fetoscopic laser selective coagulation and is strongly associated with incomplete surgery (Stirnemann et al. 2016).
    8. Fetoscopic laser surgery for twin-twin transfusion syndrome is associated with an increased risk of funisitis (Zhao et al. 2016).
6. Selective feticide by cord occlusion (umbilical cord ligation) (Deprest et al. 2000): used as a last resort in cases in which both twins are at risk because of the serious condition of one twin.
    1. Considered in case of monochorionic twin pregnancy in which one twin is a nonviable fetus, especially the condition is compromising the nonaffected fetus.
    2. A typical example in twin reversed arterial perfusion sequence. The relatively normal twin risks high-output cardiac failure, complications of polyhydramnios, and death in utero.
    3. Another example of twin-twin transfusion syndrome, in which one fetus has major congenital anomalies or in utero-acquired abnormality, such as demonstrable cerebral lesions, terminal cardiac failure, or other conditions with a poor prognosis.
    4. Benefits of selective termination of the affected twin: Arrest the fetofetal transfusion process and protect the survivor.
7. In general, twin-twin transfusion syndrome diagnosed before 26 weeks of gestation has significantly better survival rates and fewer neurological sequelae after laser ablation therapy than amnioreduction. Twin-twin transfusion syndrome diagnosed after 26 weeks can best be treated by amnioreduction or delivery.
8. The perinatal survival of twin-twin transfusion syndrome pregnancies managed without in utero procedures is approximately 30% overall and 63% in the four most recent series when diagnosed at $<$ or $=$ 28 weeks (Berghella and Kaufmann 2001).
9. Outcomes of patients with twin-twin transfusion syndrome who were treated with either serial amniocentesis or selective laser photocoagulation of communicating vessels according to disease severity (stage): a relationship between perinatal morbidity and

mortality rates and stage in serial amniocentesis but not in selective laser photocoagulation of communicating vessel-treated twin-twin transfusion syndrome patients (Quintero 2003; Quintero et al. 2003).

10. Prompt recognition and management of the hemodynamic and hematological problems of infants with the acute types of twin-twin transfusion syndrome will result in optimal neurodevelopmental outcome (Seng and Rajadurai 2000).
11. In 42 twin gestations with stuck twin associated with acute hydramnios, targeted ultrasound cordocentesis in each fetus and therapeutic amniocentesis were performed (Weiner and Ludomirski 1994).
    1. The diagnosis of chronic twin-to-twin transfusion syndrome required: sonographic evidence of monochorionicity; rapid reaccumulation of fluid after amniocentesis; discordant fetal size, and divergent fetal hematocrit measurements with at least one above or below the 95% confidence interval for gestational age.
    2. These criteria were met in 20 of 42 (48%) pregnancies. The mean gestation was 23.8 +/− 2 weeks (range 21–27 weeks).
    3. In four pregnancies, the transfer of adult RBCs from the donor to the recipient was documented.
    4. Monochorionicity was confirmed in all postnatally.
    5. All recipients had polycythemia and hyperproteinemia. Hydrops developed only in the recipient twin (6 of 20) and was associated with an elevated umbilical venous pressure.
    6. All pregnancies were treated with aggressive serial therapeutic amniocenteses.
12. Antenatal management of twin-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS) (Slaghekke et al. 2016).
    1. Fetoscopic laser photocoagulation: a feasible treatment for twin-to-twin transfusion syndrome (Nakata et al. 2016; Thia et al. 2016) and clearly the only therapy that halts the disease process and allows both fetuses an opportunity to survive and protects a surviving co-twin in the event of the demise of one twin (Behrendt and Galan 2016).
    2. The optimal management for TTTS is fetoscopic laser coagulation of the vascular anastomoses, preferably using the Solomon technique in which the whole vascular equator is coagulated. The Solomon technique is associated with a reduction of residual anastomosis and a reduction in postoperative complications (Behrendt and Galan 2016).
    3. The optimal management for TAPS is not clear and includes expectant management, intrauterine transfusion with or without partial exchange transfusion, and fetoscopic laser surgery.

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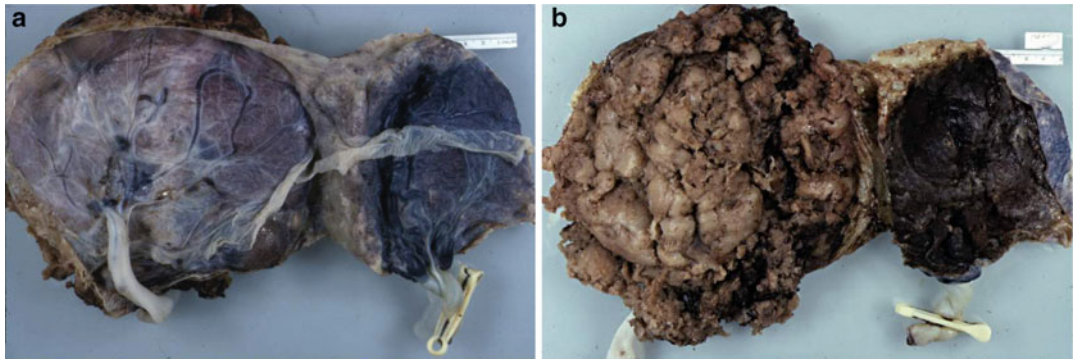

Fig. 1 (**a**, **b**) Diamniotic monochorionic twin placenta with features of twin-twin transfusion (the placental disks are not fused in this case): The placenta corresponding to the recipient twin (*right*) is small but plethoric and dark in color (**b**). The placenta of the donor twin (*left*) is large but anemic, pale, and edematous (**a**). The amniotic sacs were removed at the margins of the placental disks. The root of the thin monochorionic septum between the two sacs is shown on the fetal surface (first picture). The color difference between the two placentas is better shown on the maternal surface (second picture)

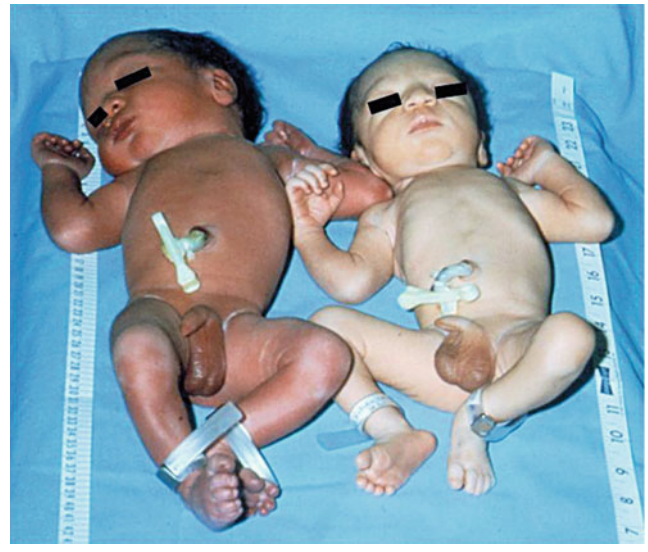

Fig. 2 The donor twin (*right*) showing smaller and pallor and the recipient twin (*left*) showing larger and plethoric at birth

Tyrosinemias

Contents

The genetic tyrosinemias, autosomal recessive disorders, are characterized by the accumulation of tyrosine in body fluids and tissues. There are three types of tyrosinemias: Types I, II, and III. Type I has a prevalence of about 1 in 100,000 newborns in the general population. Type III is extremely rare (Fig. 1).

Synonyms and Related Disorders

Congenital tyrosinosis; Fumarylacetoacetate hydrolase deficiency; Hawkinsinuria; Hepatorenal tyrosinemia; Hereditary tyrosinemia; Tyrosinemia, Type I; Tyrosinemia, Type II (oculocutaneous tyrosinemia, keratosis palmoplantaris with corneal dystrophy, Richner-Hanhart syndrome); Tyrosinemia, Type III

Genetics/Basic Defects

1. Tyrosinemia, Type I (Scott 2006)
    1. Caused by a deficiency of fumarylacetoacetate hydrolase (FAH) (Lindblad et al. 1977)
    2. Coded by the gene localized at 15q23-q25
2. Tyrosinemia, Type II
    1. Caused by a deficiency of tyrosine aminotransferase (TAT) (Goldsmith et al. 1973)
    2. Coded by the gene localized at 16q22
    3. More common in Italy where a common mutation (R57X) has been identified (Huhn et al. 1998)
3. Tyrosinemia, Type III
    1. Caused by a deficiency of 4-hydroxyphenylpyruvic dioxygenase (4-HPPD).
    2. Coded by the gene localized at 12q24-qter.
    3. A single mutation, A33T, is common in each of the families in which Hawkinsinuria has been identified (Tomoeda et al. 2000). Hawkinsinuria is somewhat unique in that it is inherited as an autosomal dominant, while other mutations of 4-HPPD cause the autosomal recessive tyrosinemia, Type III.

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Clinical Features

1. Tyrosinemia, Type I (Scott 2006; de Laet et al. 2013)
    1. Onset of disease
        1. Onset before 6 months of age: acute severe liver involvement
        2. Onset after 6 months of age (van Spronsen et al. 1994):
            1. Mild liver dysfunction
            2. Renal involvement
            3. Growth failure
            4. Rickets
    2. Hepatic disease
        1. Acute severe liver involvement: common with clotting abnormalities, ascites, and edema secondary to hypoalbuminemia
        2. Frequent hemorrhage
        3. Usually mild jaundice
        4. Firm and hard liver on physical examination
        5. Go on to develop cirrhosis, liver nodules, and hepatocellular carcinoma
    3. Renal disease
        1. Characteristic finding: tubular disorder with a Fanconi syndrome, the severity of which is variable.
        2. Typical features: aminoaciduria, glycosuria, phosphaturia, and renal tubular acidosis.
        3. Hypophosphataemic rickets.
        4. May progress to nephrocalcinosis, glomerulosclerosis, and chronic renal failure.
        5. Although renal disease may be the predominant feature, there is always some coexisting liver disease of varying severity.
    4. Neurologic disease
        1. Porphyria-like syndrome: most characteristic, usually precipitated by intercurrent infection
        2. Crises
            1. Pain can be severe including abdominal pain mimicking an acute surgical emergency.
            2. Weakness.
            3. Autonomic changes such as hypertension.
            4. Acute progressive ascending motor neuropathy, often with respiratory distress requiring assisted ventilation.
2. Tyrosinemia, Type II
    1. Ocular symptoms
        1. Onset: during first year of life.
        2. Recalcitrant pseudodendritic keratitis with photophobia, scleral inflammation, and pain (Macsai et al. 2001).
        3. Some degree of corneal ulceration and occasional birefringent crystals of tyrosine may be observed by slit lamp examinations.
    2. Skin lesions
        1. Hyperkeratotic plaques on the soles of the feet and palms of the hands.
        2. Dramatic yellowish thickening associated with the hyperkeratosis may be seen in the plantar surface of the digits (Rehak et al. 1981).
        3. Hyperkeratosis of the elbows, knees, and ankles has been reported in older individuals.
    3. Developmental delay: common
    4. No liver involvement
3. Tyrosinemia, Type III
    1. The rarest of the disorders of tyrosine metabolism
    2. Ambiguous clinical phenotype (Mitchell et al. 2001)
        1. Intellectual disability
        2. Ataxia
        3. Detected on routine screening (Mitchell et al. 2001)
        4. No liver involvement but has skin and ocular changes similar to tyrosinemia, Type II
    3. Hawkinsinuria (a variant of 4-HPPD deficiency)
        1. Affected children may demonstrate chronic acidosis and failure to thrive if fed standard infant formulas or if fed cow's milk as primary nutritional source (Danks et al. 1975).

2. Infants nourished with breast milk: escape symptoms during infancy.

Diagnostic Investigations

1. Clinical laboratory tests (Scott 2006; King et al. 2014)
    1. Tyrosinemia, Type I
        1. Acute early phase: may progress to acute liver necrosis, ascites, jaundice, and gastrointestinal bleeding
            1. Prothrombin and partial thromboplastin times: markedly prolonged.
            2. Other clotting factors: preservation of Factor V and Factor VIII, but decrease in Factors II, VII, XI, XI, and XII.
            3. Liver function tests: modestly elevated transaminase and normal or only slightly elevated serum bilirubin (Mitchell et al. 2001).
            4. Striking biochemical feature: a markedly elevated α-fetoprotein averaging approximately 160,000 ng/ml at the time of diagnosis.
            5. Presence of a characteristic odor of "boiled cabbage" or "rotten mushrooms" and elevation of α-fetoprotein often lead to the clinical recognition of tyrosinemia, Type I, from other causes of acute liver failure; documentation of elevations of plasma tyrosine, methionine, and phenylalanine and succinylacetone in the urine or plasma confirms the diagnosis.
            6. Marked elevation of succinylacetone in the urine or plasma can be considered pathognomonic for tyrosinemia, Type I.
        2. More chronic form of the disorder: renal involvement (major manifestations)
            1. Renal tubular dysfunction involves a generalized aminoaciduria, phosphate loss, and, for many, renal tubular acidosis (Roth et al. 1991).
            2. Renal loss of phosphate is believed to be the mechanism for the development of rickets.
            3. Growth failure is ascribed to the chronic illness from poor nutrition, liver involvement, and/or chronic renal disease.
    2. Tyrosinemia, Type II
        1. Plasma tyrosine levels: typically >500 μM/L, may exceed 1,000 μM/L
        2. Other amino acids: normal including methionine and phenylalanine
        3. Urine organic acids: an increased excretion of *p*-hydroxyphenylpyruvate, *p*-hydroxyphenyllactate, *p*-hydroxyphenylacetate, and small quantities of *N*-acetyltyrosine and 4-tyramine.
    3. Tyrosinemia, Type III
        1. Plasma concentration of tyrosine: from 350 to 650 μM/L.
        2. Increased excretion of 4-hydroxyphenylpyruvic acid, 4-hydroxyphenyllactate, and 4-hydroxyphenylacetate.
        3. The precise quantities vary with protein intake.
2. Imaging (de Laet et al. 2013)
    1. Bone X-ray of the wrist and chest: to define tubulopathy
    2. Ultrasound: to identify echogenicity of the parenchyma and nodular lesions of the liver and monitor kidney growth and changes in renal parenchyma
    3. CT scan with contrast: to identify malignant change of the liver (need a risk-benefit analysis to avoid extra radiation in children)
    4. MRI: best technique to differentiate nodules and carcinomas
3. Molecular genetic analysis for tyrosinemia, Type I
    a. Targeted mutation analysis for the four common FAH pathogenic variants.
    b. Sequence analysis of the entire coding region can detect pathogenic variants in >95% of affected individuals.

Genetic Counseling

1. Recurrence risk
   1. Autosomal recessive inheritance
      1. Patient's sib: each sibling of an affected patient has a 25% chance of being affected, a 50% risk of being an asymptomatic carrier, and a 25% chance of being unaffected and not carrier.
      2. Patient's offspring: not increased unless the spouse is a carrier.
   2. Autosomal dominant inheritance
      1. Patient's sib: each child of an affected individual has a 50% chance of inheriting the mutation.
      2. Patient's offspring: 50%.
2. Prenatal diagnosis (King et al. 2014)
   1. Molecular genetic analysis for tyrosinemia, Type I: If the *FAH* pathogenic variants have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing. Prenatal diagnosis of tyrosinemia type 1 using next generation sequencing (Rafati et al. 2016)
   2. Preimplantation genetic diagnosis: an option for some families in which the FAH pathogenic variants have been identified.
3. Management (Scott 2006)
   1. Tyrosinemia, Type I
      1. Artificial formula low in phenylalanine and tyrosine (utilization of a nutritionist skilled in metabolic disorders)
         1. Moderately useful in reducing succinylacetone
         2. Some benefit in the more chronic forms of the disease
         3. Not very effective in acute stage of the disorder in young children
      2. Nitisinone, [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC)], which blocks p-hydroxyphenylpyruvic acid dioxygenase (*p*-HPPD) and prevents the accumulation of fumarylacetoacetate and its conversion to succinylacetone
         1. Should begin as soon as the diagnosis is confirmed.
         2. At least 90% of patients with acute form will respond to nitisinone therapy.
         3. Major complications: tyrosine crystal deposition in the cornea, causing photophobia and an ocular inflammatory response. To prevent this, tyrosine concentrations should be monitored and the children utilize a phenylalanine- and tyrosine-restricted diet.
         4. Require long-term monitoring for possible development of hepatocarcinoma (MRI or CT scans of the liver annually).
      3. Prevention/treatment of secondary complications: carnitine deficiency, osteoporosis, and rickets that are secondary to renal tubular Fanconi syndrome
      4. Liver transplantation
         1. Reserved for children who have severe liver failure at presentation and fail to respond to nitisinone therapy
         2. For children who have documented evidence of malignant changes in hepatic tissue
   2. Tyrosinemia, Type II
      1. A low-protein diet and use of a special formula free of phenylalanine and tyrosine: effective in lowering the plasma level of tyrosine to <600 μM
      2. Resolution of both eye and skin symptoms within days to several weeks after institution of the diet and special formula
   3. Tyrosinemia, Type III: a diet low in phenylalanine and tyrosine can lower plasma tyrosine.

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Fig. 1 This 2.5-year-old Palestine girl was seen because of an abnormal newborn screen which showed an abnormal amino acid profile with a succinylacetone level of 3.6 umol/L with a normal being less than 0.40 umol/L. Her alpha-fetoprotein level was greater than 20,000. Her plasma tyrosine was 524 uM with a normal of 28–134. Her urinary organic acid, succinylacetone, was 15 millimoles per mole creatinine which is significantly elevated as normal is zero (0). These results confirmed the diagnosis of tyrosinemia, Type I. Family history showed that the mother's sister has a son and a daughter with tyrosinemia, Type I

Fig. 2 Previous patient at 5 years of age. She had a G-tube placement and gallbladder removed when she was 4. Her Gallbladder was only working 27%, the G-tube was placed to help give her the nutrition she was missing from her diet restriction when her body started to become very weak and ill all the time due to her not drinking her formula. At the age of 3, she was diagnosed with kidney stones and had a stent placed to help remove the stones.

Ulnar-Mammary Syndrome

Contents

Ulnar-mammary syndrome (UMS) was originally described by Gilly (1882) in 1882 in a woman with mammary hypoplasia, inability to lactate, and absence of the third to fifth digits and ulna. Later in 1978, Pallister et al. (1976) reported a complex malformation syndrome in a young woman with abnormal development of ulnar rays, forearms, mammary gland tissue, axillary apocrine glands, teeth, palate, vertebral column, and urogenital system. Ulnar-mammary syndrome is a pleiotropic disorder affecting limb, apocrine gland, teeth, hair, and genital development.

The incidence of UMS is unknown. Ulnar longitudinal deficiencies in general are rare, occurring 1 in 25000 births (Koskimies et al. 2011). The largest series of UMS contains three patients from a single family (Bamshad et al. 1995). Further case reports primarily in the genetics literature, bring the total to 117 reported cases (Ramirez and Kozin 2014).

Synonyms and Related Disorders

Pallister ulnar-mammary syndrome (Gonzalez et al. 1976; Pallister et al. 1976); Schinzel syndrome (Hecht and Scott 1984; Schinzel 1987)

Genetics/Basic Defects

1. Inheritance: autosomal dominant with variable expression (Schinzel et al. 1987; Sherman et al. 1986; Linden et al. 2009; Wollnik et al. 2002)
2. A gene for UMS mapped to chromosome 12q23-q24.1 (Bamshad et al. 1995)
3. Caused by mutations that disrupt the DNA-binding domain of the T-box gene, *TBX3* (Coll et al. 2002)
4. Mutations in human *TBX3* alter limb, apocrine, and genital development (Sasaki et al. 2002) in UMS (Bamshad et al. 1997).
5. No obvious phenotypic differences between those who have missense mutations and those who have deletions or (Bamshad et al. 1999)
6. The UMS gene, *Tbx3*, is required for development of posterior forelimb bones, muscles, and their attachment sites (Colasanto et al. 2016): Although descriptions of UMS limb phenotypes have entirely focused on bone phenotypes, the abnormal surface anatomy of UMS individuals (indicative of underlying soft tissue defects; Bamshad et al. 1999) and aberrant locomotion of Tbx3 mutant mice (Emechebe

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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et al. 2016) suggests that *TBX3* may play a broader role in musculoskeletal development than previously thought.

Clinical Features

1. The clinical expression of UMS is highly variable (Bamshad et al. 1996; Ramirez and Kozin 2014): Limb deficiencies in most patients
2. Posterior limb defects
    1. Widely variable
    2. Ulnar ray defects in most patients
        1. Hypoplasia of the terminal phalanx of the fifth digit
        2. Complete absence of the ulna and third, fourth, and fifth digits
    3. Postaxial digital duplications with or without contralateral limb deficiencies
    4. Camptodactyly
    5. Digital fusion
3. Apocrine gland abnormalities
    1. Mammary gland abnormalities: variable
        1. Hypoplasia to aplasia of the mammary glands and hypoplasia of the nipples
        2. Accessory nipples
        3. Inability to nipple feed
        4. Normal breast development and lactation
    2. Decreased ability to sweat
    3. Reduced body odor
    4. Absent axillary perspiration
    5. Sparse axillary hair
4. Genital abnormalities: hypogenitalism
    1. Affected males
        1. Delayed puberty
        2. Diminished to absent axillary hair
        3. Micropenis
        4. Cryptorchidism
        5. Small testes
        6. Shawl scrotum
        7. Reduced fertility
    2. Affected females
        1. Diminished to absent axillary hair
        2. Imperforate hymen in some affected females
5. Facial features (Joss et al. 2011)
    1. Upslanting PFs
    2. Wide nasal base
    3. Full cheek/wide midface
    4. Broad nasal tip
    5. Small nostrils
    6. Downturned mouth
    7. Pointed/prominent chin
6. Oral abnormalities (Joss et al. 2011)
    1. Misplaced/crowded teeth
    2. Absent teeth (canines)
    3. Hypodontia
    4. Bifid/broad uvula
    5. Tongue ties
7. Other abnormalities
    1. Delay puberty
    2. Short stature
    3. Obesity
    4. Scanty lateral eyebrows
    5. Subglottic stenosis
    6. Pyloric stenosis
    7. Renal agenesis/malformation
    8. Pulmonary hypoplasia
    9. Inguinal hernia
    10. Anal atresia/stenosis
    11. Musculoskeletal abnormalities
        1. Short forearms
        2. Hypoplastic humeri, scapulae, and clavicles
        3. Hypoplastic pectoralis major muscles
        4. Short, stiff, and crooked terminal phalanges of fourth to fifth toes
8. Differential diagnosis
    1. Hand-foot-uterus syndrome (Rogers and Anderson 1995)
        1. Autosomal dominant disorder
        2. Allelic to UMS speculated
        3. Manifestations similar to UMS include the following:
            1. Digital hypoplasia
            2. Carpal fusion
            3. Supernumerary nipples
            4. Genital anomalies
    2. Split hand/split foot syndrome: a causal relationship to UMS suggested (Franceschini et al. 1992)
        1. A three-generation family in which mother, maternal grandfather, and two

(male and female) children have variable manifestations of the UMS, including ulnar ray defects, obesity, hypogenitalism, delayed puberty, hypoplasia of nipples and apocrine glands, and a previously undescribed ectopia of upper canines.
2. The index patient also had split-hand appearance on the right due to complete absence of the 4th ray.

3. Scalp-ear-nipple syndrome (Edwards et al. 1994)
   1. Overlapping manifestations with UMS
      1. Mammary hypoplasia
      2. Diminished axillary perspiration
      3. Dental abnormalities: widely spaced or missing secondary teeth
      4. Digital syndactyly: characteristic limb anomaly found in this syndrome (vs limb deficiency or duplications in UMS)
   2. Aplasia cutis congenita of the scalp
   3. Alteration of the shape of the external ear: cupped or folded and stood out from the head
   4. Reduced axillary apocrine secretion and axillary hair growth
   5. Brittle finger nails
4. Limb-mammary syndrome: a new genetic disorder with mammary hypoplasia, ectrodactyly, and other Hand/Foot anomalies maps to human chromosome 3q27 (van Bokhoven et al. 1999)
   1. A report on a large Dutch family with a syndrome characterized by severe hand and/or foot anomalies, and hypoplasia/aplasia of the mammary gland and nipple.
   2. Less frequent findings include lacrimal-duct atresia, nail dysplasia, hypohydrosis, hypodontia, and cleft palate with or without bifid uvula.
   3. This combination of symptoms has not been reported previously, although there is overlap with the UMS and with ectrodactyly, ectodermal dysplasia, and clefting syndrome.
   4. Allelism with UMS and other related syndromes was excluded by linkage studies with markers from the relevant chromosomal regions.
   5. A genome-wide screening with polymorphic markers allowed the localization of the genetic defect to the subtelomeric region of chromosome 3q.
   6. Haplotype analysis reduced the critical region to a 3-cM interval of chromosome 3q27.
5. Patients with contiguous gene deletion of *TBX5* and *TBX3* with features of both Holt-Oram syndrome and UMS (Alby et al. 2013; Bogarapu et al. 2014)
   1. Bilateral symmetric limb malformations
   2. Congenital cardiac defects
   3. Rapidly progressive cardiac conduction disease
   4. This contiguous gene syndrome is reminiscent of Okihiro syndrome (congenital cardiac defects, anal atresia, and radial ray defects) and emphasizes the importance of array-CGH as a diagnostic tool in atypical syndromic presentations (a wide range of clinical consequences) with high intrafamilial variability.

Diagnostic Investigations

1. Radiography
   1. Short and stiff fifth finger
   2. Absent fifth finger ray
   3. Absent fourth finger ray
   4. Absent fourth to fifth finger rays
   5. Absent third to fifth finger rays
   6. Camptodactyly
   7. Hypoplastic/absent/deformed ulna
   8. Hypoplastic/absent/deformed radius
   9. Hypoplastic humerus, scapula, clavicle, and pectoralis major muscle
   10. Absent xiphisternum
   11. Postaxial polydactyly
   12. Short, stiff fourth and fifth toes
2. Endocrine investigations for hypogenitalism
3. Mutation analysis

1. Missense mutations (L143P and Y149S)
2. Nonsense mutation (Q360TER, S343TER)
3. Splice-site mutations (IVS2 + 1G → C, IVS6 + 2T → A) producing a truncated protein product
4. Frameshift mutations of small duplications

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased unless a parent is affected
   2. Patient's offspring: 50%
2. Prenatal diagnosis
   1. Ultrasonography and fetoscopy: possible to pregnancy at risk with presence of obvious fetal skeletal anomalies
   2. Mutation analysis of amniocytes and CVS: possible to families with identified mutation causing UMS
3. Management
   1. Orthopedic management of limb defects
   2. Orchiopexy for cryptorchidism
   3. Testosterone management for hyogonadism in male patients
   4. Bottle feeding of infants born to mothers who has hypoplastic or absent nipples

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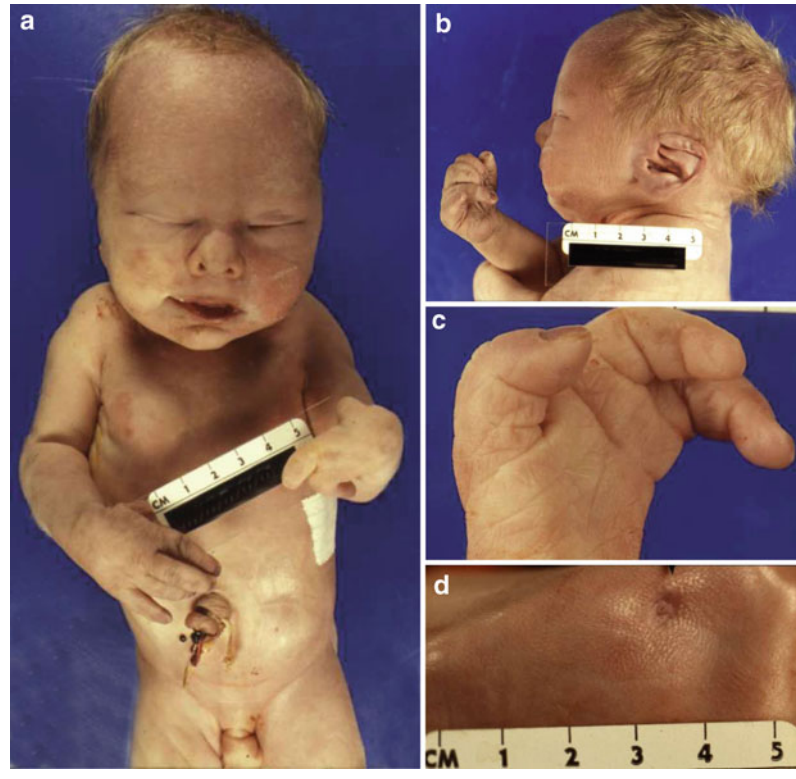

Fig. 1 A newborn (**a**, **b**) with UMS showing ulnar hypoplasia (missing fourth and fifth fingers) (**c**), ectrodactyly, syndactyly, and hypoplasia of the breast and nipples (**d**). The infant also had cryptorchidism, anal atresia, pulmonary hypoplasia, pyloric stenosis, and bilateral renal hypoplasia

Urofacial Syndrome

Contents

Urofacial syndrome (UFS), also known as Ochoa syndrome, is characterized by severe voiding dysfunction and peculiar facies, i.e., inversion of facial expression with grimacing while smiling (Ochoa and Gorlin 1987; Ochoa 1992, 2004). UFS may be more common than was previously thought, and it is likely that cases are missed because of failure to recognize the characteristic grimacing (Garcia-Minaur et al. 2001).

Synonyms and Related Disorders

Ochoa syndrome (Elejalde 1979)

Genetics/Basic Defects

1. Autosomal recessive inheritance (Al-Qahtani 2003) based on:
   1. Affected siblings (Bertolotti et al. 2007)
   2. Normal parents
   3. Presence of consanguinity
2. Mutations with a loss of function in the *Heparanase 2* (*HPSE2*) gene were identified in all urofacial syndrome patients originating from Colombia, the United States, and France (Pang et al. 2010).
   1. HPSE2 encodes a 592 aa protein that contains a domain showing sequence homology to the glycosyl hydrolase motif in the heparanase (*HPSE*) gene, but its exact biological function has not yet been characterized.
   2. Complete loss of HPSE2 function in urofacial syndrome patients suggests that HPSE2 may be important for the synergic action of muscles implicated in facial expression and urine voiding.
3. Whole-genome SNP mapping in one affected individual defined an autozygous region of 16 Mb on chromosome 10q23-q24, within which a 10 kb deletion encompassing exons 8 and 9 of *HPSE2* was identified (Daly et al. 2010). Homozygous exonic deletions, nonsense mutations, and frameshift mutations in five further unrelated families confirmed *HPSE2* as the causative gene for UFS.
4. Genetic homogeneity of the urofacial (Ochoa) syndrome confirmed in a new French family (Chauve et al. 2000).
5. Homozygosity and linkage-disequilibrium mapping of the urofacial (Ochoa) syndrome gene to a 1-cM interval on the chromosome 10q23-q24 (Wang et al. 1997).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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6. Most individuals with urofacial syndrome genetically studied to date carry biallelic, postulated functionally null mutations of *HPSE2* or, less commonly, of *LRIG2* (Woolf et al. 2014).
7. Biallelic mutations in *HPSE2* gene on chromosome 10q23-q24, predicted to abolish activity of heparanase 2, cause urofacial syndrome in families from different ethnic groups (Daly et al. 2010).
8. *LRIG2* mutations cause urofacial syndrome (Sturart et al. 2013).
    1. A subset of UFS-affected individuals have biallelic mutations in *LRIG2*, encoding leucine-rich repeats and immunoglobulin-like domains 2, a protein implicated in neural cell signaling and tumorigenesis.
    2. Importantly, rare variants in *LRIG2* might be relevant to nonsyndromic bladder disease.
    3. Previously, UFS was also shown to be caused by mutations in *HPSE2*, encoding heparanase-2.
    4. LRIG2 and heparanase-2 were immunodetected in nerve fascicles growing between muscle bundles within the human fetal bladder, directly implicating both molecules in neural development in the lower urinary tract.
9. Report of a family of three siblings, with an emphasis on the abnormalities in facial expression (Ganesan and Thomas 2011).
    1. Careful examination shows an unusual co-contraction of the orbicularis oculi and orbicularis oris muscles only when full facial expressions are exhibited, across a range of emotional or voluntary situations.
    2. This suggests a peripheral disorder in facial muscle control.
    3. Two thirds of patients have anal sphincter abnormalities.
    4. Aberrant organization of the facial motor and urinary-anal sphincter nuclei may explain these symptoms.

Clinical Features

1. Characteristic facial expression.
    1. Inversion of the facial expression when attempting to smile or laugh
    2. Facial grimace while smiling
    3. Smile looking like weeping
    4. Peculiar facial expression on smiling
2. Urinary manifestations: The urofacial syndrome (Ochoa syndrome) is considered to represent a subgroup of the nonneurogenic bladder dysfunction, characterized by nonneuropathic bladder-sphincter dysfunction, along with a characteristic inversion of the facial expression with laughing (Stamatiou et al. 2011).
    1. Bladder dysfunction
        1. Intermittent urinary flow
        2. Residual urine after voiding
        3. Enuresis
        4. Polyuria
    2. Urinary tract infection
    3. Hydronephrosis
3. Twelve out of 15 patients had nocturnal lagophthalmos (a novel sign). Lagophthalmos (inability to close the eyelids completely) may lead to keratitis, corneal abrasion, infection, vascularization, and in extreme cases, ocular perforation, endophthalmitis, and loss of the eye (Mermerkaya et al. 2014).
4. Constipation.
5. The urinary abnormalities may lead to renal deterioration and ultimate failure if untreated.

Diagnostic Investigations

1. Renal ultrasonography.
2. Radionuclide renogram and renal scan for a boy with incontinence, frequent infections of the urinary tract, and gene mutations consistent with Ochoa syndrome (Infante et al. 2013).
    1. Nuclear medicine images showed extensive bilateral renal scarring.
    2. Diuretic renogram showed obstructive pattern.

3. Voiding cystourethrogram (VCUG).
4. Urodynamic studies.
5. Abdominal sonograms (Al-Qahtani 2003): gall bladder stones, septated gall bladder.
6. Exome capture and massively parallel sequencing identifies a novel *HPSE2* mutation (Al Badr et al. 2011).
9. Early diagnosis of the urofacial syndrome is essential to prevent irreversible renal failure (Nicanor et al. 2005)
10. Kidney transplantation for a case of deteriorating renal function (Muños Fernández et al. 2001)

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis (Newman et al. 2013)
   1. Molecular genetic testing. If the disease-causing mutations have been identified in an affected family member, prenatal testing for pregnancies at increased risk is possible either through a clinical laboratory or a laboratory offering custom prenatal testing.
   2. Fetal ultrasonography. In families at risk of having an affected child, prenatal ultrasound of the urinary tract may show megacystis, hydroureteronephrosis, or renal pelvis dilatation in an affected pregnancy. These features are not specific for UFS.
   3. Preimplantation genetic diagnosis may be an option for some families in which the disease-causing mutations have been identified.
3. Management (Aydogdu et al. 2010)
   1. Intermittent urinary catheterization
   2. Appendicovesicostomy may be required for continent urinary diversion
   3. Nocturnal bladder emptying with an indwelling nighttime catheter for polyuria
   4. Antibiotic prophylaxis
   5. Anticholinergic therapy
   6. Intravesical botulinum toxin injection
   7. Bowel management
   8. Augumentation cystoplasty

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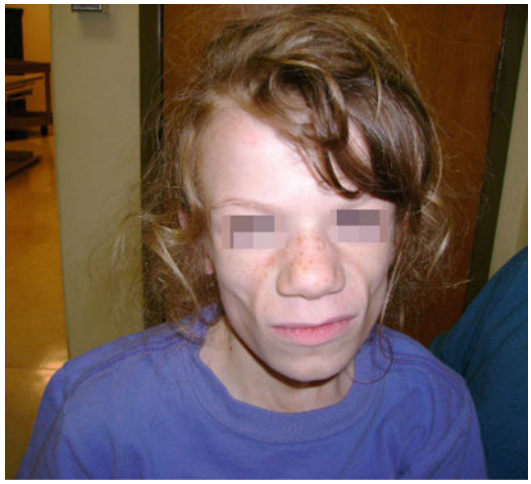

Fig. 1 This 7-year-old girl presented with vague abdominal discomfort associated with nausea, nonbilious vomiting, and weight loss for past 8–10 weeks duration. Abdominal CT revealed bilateral hydronephrosis. Note the "grimace" facial appearance after smiling

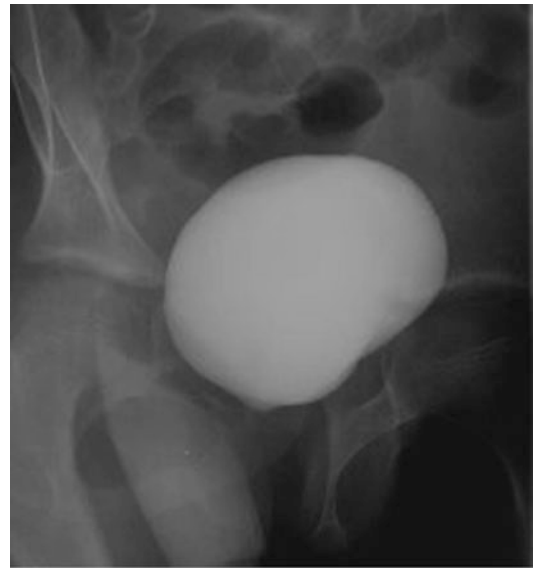

Fig. 3 Patient's VCUG showed smooth bladder wall

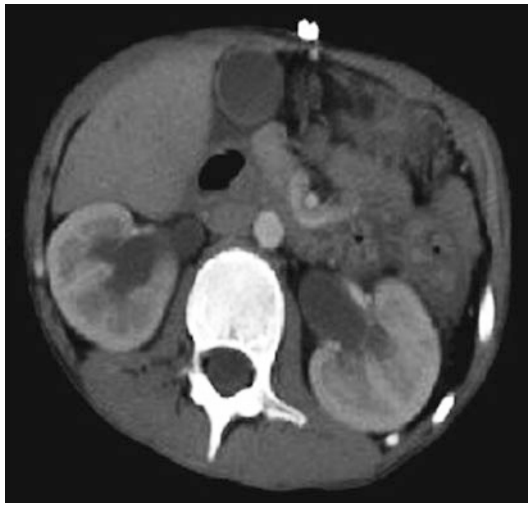

Fig. 2 Patient's CT scan of the abdomen showed bilateral hydronephrosis

VATER (VACTERL) Association

Contents

VATER association is an acronym for the following nonrandom association of defects: *V*ertebral defects, *A*nal atresia, *T*racheoesophageal fistula with *E*sophageal atresia, and *R*enal or *R*adial defects (Quan and Smith 1973; Smith 1974; Temtamy and Miller 1974). VACTERL association is an expanded acronym to include *C*ardiac defects and *L*imb defects. Diagnosis of VACTERL association is made if three out of the seven above defects are present in an infant. The incidence is estimated to be 1.6 cases in 10,000 live births.

Genetics/Basic Defects

1. Etiologic heterogeneity
    1. Isolated cases in most cases
    2. Reports of rare familial cases (single gene disorders)
    3. Reports of chromosome abnormality cases
    4. Recognized syndromes or phenotypes
    5. Observed more frequently in infants of diabetic mothers
2. Pathogenesis: suggestion of a defective mesodermal development during embryogenesis due to a variety of causes, leading to overlapping manifestations (Khoury et al. 1983)
3. Molecular basis of VACTERL association
    1. Report of a family in which a female infant was born and died at age 1 month due to renal failure. The mother and sister later developed classic mitochondrial cytopathy, associated with the A-to-G point mutation at nucleotide position 3243 of mitochondrial DNA (Damian et al. 1996; Stone and Biesecker 1997).
    2. Mitochondrial NP 3243 point mutation considered not a common cause of VACTERL association (Damian et al. 1996).
    3. Sonic hedgehog in the human: a possible explanation for the VATER association (Arsic et al. 2002).
    4. In addition to core Hedgehog pathway components, several Sonic hedgehog target genes, *Forkhead* and *5′Hoxd* genes (*Hoxd12* and *Hoxd13*), have also been implicated in VACTERL (Ngan et al. 2013).
    5. VACTERL: (polytopic) developmental field defect, instead of VACTERL association or VACTERL syndrome (Martinez-Frias and Frias 1999; Martinez-Frias et al. 2001).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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6. Recently, microdeletions of the FOX gene cluster at 16q24.1, comprising four genes, *FOXF1*, *MTHFSD*, *FOXC2*, and *FOXL1*, were reported to cause a phenotype resembling VACTERL association, with vertebral anomalies, gastrointestinal atresias (esophageal, duodenal, and anal), congenital heart malformations, and urinary tract malformations, as well as a rare lethal developmental anomaly of the lung, alveolar capillary dysplasia (Shaw-Smith 2010).
7. Targeted resequencing of 29 candidate genes and mouse expression studies implicate *ZIC3* and *FOXF1* in human VATER/VACTERL association (Hilger et al. 2015).
8. According to epidemiological studies, the majority of patients with VATER/VACTERL association present with a "renal" phenotype comprising a large spectrum of congenital renal anomalies. This finding is supported by evidence linking all of the human disease genes for the VATER/VACTERL association identified to date, namely, *FGF8*, *FOXF1*, *HOXD13*, *LPP*, *TRAP1*, and *ZIC3*, with renal malformations (Reutter et al. 2016).
9. So far, the *ZIC3* gene has been demonstrated to cause X-linked VACTERL association (Chen et al. 2016a). Different types of *ZIC3* mutations, including point mutations, deletions, and polyalanine expansion, have been reported to be responsible for both VACTERL or VACTERL-like association (Wessels et al. 2010; Chung et al. 2011; Hilger et al. 2015).

Clinical Features

1. VACTERL association: clinical variability (Weaver et al. 1986; Corsello et al. 1992; Oral et al. 2012)
   1. *V*ertebral anomalies
      1. Transitional vertebrae
      2. Hemivertebrae
      3. Fused vertebrae
      4. Block vertebrae
      5. Hypersegmentation of the vertebrae
      6. Hypersegmentation of the ribs
      7. Scoliosis
      8. Spina bifida
      9. Sacral anomalies
      10. Incomplete pedicle
      11. Sternal anomalies
   2. *A*nal and urachal anomalies
      1. Anal atresia with or without fistula
      2. Persistent urachus (cloacas)
      3. Rectrourethral prostatic fistula
      4. Rectrourethral bulbar fistula
      5. Cutaneous (perineal) fistula
      6. Vestibular fistula
      7. Ectopic anus
   3. *C*ardiac anomalies (Cunningham et al. 2013)
      1. Ventricular septal defect
      2. Atrial septal defect
      3. Patent ductus arteriosus
      4. Tetralogy of Fallot
      5. Transposition of the great arteries
      6. Other cardiovascular anomalies: right aortic arch, double aortic arch, coarctation of the aorta, dextrocardia, total anomalous pulmonary venous drainage, persistent left superior vena cava, congenital mitral stenosis, right anomalous coronary artery, single umbilical artery
   4. *T*racheoesophageal fistula
   5. *E*sophageal atresia
   6. *R*enal anomalies
      1. Renal agenesis/dysgenesis
      2. Ectopic kidney
      3. Horseshoe kidney
      4. Dysplastic kidney
      5. Duplex kidney
      6. Cystic dysplastic kidney
      7. Ureteral/urethral anomalies
      8. Hydronephrosis
      9. Renal ectopia
      10. Vesicoureteral reflux
      11. Posterior urethral valves
      12. Ureteropelvic junction obstruction
      13. The most common renal manifestation (RM) was vesicoureteral reflux in addition to a structural defect (present in 27%), followed by unilateral renal

agenesis (24%), and then dysplastic/multicystic kidneys or duplicated collected system (18% for each) (Cunningham et al. 2014). Twenty-two (88%) of the 25 patients with a structural RM had an associated anorectal malformation.

7. *L*imb defects
    1. Radial aplasia/dysplasia
    2. Hypoplastic thumbs
    3. Triphalangeal thumb
    4. Preaxial polydactyly
    5. Syndactyly
    6. Radioulnar synostosis
    7. Tibial developmental field defect (the dyad of tibial hypoplasia and homolateral hallucal deficiency/polydactyly) is the most common lower limb malformation pattern in VACTERL association (Castori et al. 2008)

2. Other associated abnormalities
    1. Failure to thrive
    2. Short stature
    3. Wide cranial suture
    4. Large fontanel
    5. Potter facies
    6. Ophthalmological abnormalities (Say et al. 1977)
    7. Ear anomalies
    8. Cleft palate
    9. Laryngeal stenosis
    10. Gastrointestinal anomalies
        1. Malrotation
        2. Meckel diverticulum
        3. Duodenal atresia
        4. Pyloric atresia
        5. Ileal atresia
        6. Pancreatic heterotopia
        7. Vermiform appendix agenesis
        8. Omphalocele
        9. Inguinal hernia
    11. Genital anomalies
        1. Hypospadias
        2. Cryptorchidism
        3. Bifid scrotum
        4. Micropenis
    12. Neurological anomalies
        1. Tethered cord
        2. Spinal dysraphia
        3. Occipital encephalocele
    13. Anomalies more commonly associated with CHARGE association

3. The spectrum of congenital anomalies of the VATER association (Botto et al. 1997)
    1. Of infants with VATER association, 74.8% had additional defects: Genital defects, cardiovascular anomalies, and small intestinal atresias were positively associated with VATER association.
    2. Infants with VATER association that included both renal anomalies and anorectal atresia were significantly more likely to have genital defects.
    3. A subset of infants with VATER association also had defects described in other associations, including diaphragmatic defects (Chen et al. 2016b), oral clefts, bladder exstrophy, omphalocele, and neural tube defects.

4. Morbidity and mortality in patients with VACTERL associations (Iuchtman et al. 1992)
    1. Morbidity
        1. During the first year of life, there was considerable morbidity resulting from the tracheoesophageal abnormalities.
        2. Anorectal, renal, or skeletal anomalies rarely caused death, but, when severe, were associated with a poor quality of life.
    2. Mortality rate (24%)
        1. Most deaths: caused by cardiovascular abnormalities.
        2. Infants weighing less than 2,050 g had a mortality rate of 26%, double that of heavier infants.

5. Differential diagnosis: conditions with multiple features in common with VACTERL association (Solomon 2011)
    1. Alagille syndrome (please see the chapter on "► Alagille Syndrome")
        1. Common features: vertebral anomalies, cardiac anomalies; may have renal anomalies
        2. Distinct features: bile duct paucity and cholestasis, ophthalmologic anomalies (especially posterior embryotoxon),

neurological anomalies, characteristic facial appearance; heterozygous mutations in *JAG1*, *NOTCH2*

2. Baller-Gerold syndrome
    1. Common features: radial anomalies, may also include anal anomalies
    2. Distinct features: craniosynostosis, skin anomalies, heterozygous mutations in *RECQL4*
3. CHARGE syndrome (please see the chapter on "▶ CHARGE Syndrome")
    1. Common features: cardiac malformations, genitourinary anomalies; may also include tracheoesophageal fistula
    2. Distinct features: colobomata, choanal atresia, neurocognitive and growth impairment, ear anomalies, cranial nerve dysfunction, characteristic facial features, heterozygous mutations in *CHD7*
4. Currarino syndrome
    1. Common features: sacral malformations, anorectal malformations
    2. Distinct features: presacral mass, heterozygous mutations/deletions of *HLXB9*
5. 22q11.2 deletion syndrome (also known by other names, such as DiGeorge syndrome or velocardiofacial syndrome) (please see the chapter on "▶ Del (22q11.2) Syndrome")
    1. Common features: cardiac malformations, renal anomalies, other VACTERL-type anomalies also reported
    2. Distinct features: hypocalcemia, palatal anomalies, learning difficulties, immune dysfunction, neuropsychiatric disturbances, characteristic facial features, deletion of one copy of chromosome 22q11.2
6. Fanconi anemia
    1. Common features: virtually all features of VACTERL association may occur; radial anomalies are considered an especially key feature
    2. Distinct features: hematologic anomalies, pigmentation anomalies, recessive or X-linked mutations in multiple genes (typically detected by chromosomal breakage studies)
7. Feingold syndrome (please see the chapter on "▶ Feingold Syndrome")
    1. Common features: GI atresia, cardiac defects, renal anomalies
    2. Distinct features: brachymesophalangy, toe syndactyly, microcephaly, cognitive impairment, characteristic facial appearance, heterozygous mutations in *MYCN*
8. Fryns syndrome
    1. Common features: GI malformations, cardiac defects, GU anomalies
    2. Distinct features: diaphragmatic defects, neurocognitive impairment, characteristic facial appearance, no well-characterized unifying causes
9. Holt-Oram syndrome (please see the chapter on "▶ Holt-Oram Syndrome")
    1. Common features: cardiac malformations, limb malformations
    2. Distinct features: cardiac conduction disease (also reported in VACTERL association), heterozygous mutations in *TBX5*
10. Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia (MURCS association); also known as Mayer-Rokitansky-Küster-Hauser syndrome type II
    1. Common features: vertebral anomalies, renal anomalies, GU anomalies, and anorectal malformations; may also have cardiac and limb anomalies
    2. Distinct features: syndactyly and hearing loss have been described, causes unknown; likely heterogeneous
11. Oculo-auriculo-vertebral syndrome (please see the chapter on "▶ Goldenhar Syndrome")
    1. Common features: vertebral anomalies, cardiac abnormalities, limb abnormalities, urogenital anomalies

2. Distinct features: ear anomalies (microtia), hemifacial microsomia, neurocognitive impairment, facial clefts (also described in patients with VACTERL association), causes unknown (likely heterogeneous)

12. Opitz G/BBB syndrome
    1. Common features: anal anomalies, heart defects, TEF, hypospadias
    2. Distinct features: hypertelorism, syndactyly; X-linked form (heterozygous/hemizygous mutations in *MID1*); autosomal dominant form (some cases due to deletion 22q11.2
13. Pallister-Hall syndrome
    1. Common features: imperforate anus, renal anomalies, limb anomalies (postaxial polydactyly should serve as a clue for the Pallister-Hall syndrome)
    2. Distinct features: hypothalamic hamartoma, bifid epiglottis (ranging to more severe types of clefts), nail hypoplasia, heterozygous mutations in *GLI3*
14. Townes-Brocks syndrome
    1. Common features: imperforate anus, thumb anomalies, renal anomalies, cardiac anomalies
    2. Distinct features: dysplastic ears, hearing loss, heterozygous mutations in *SALL1*
15. VACTERL with hydrocephalus (Lomas et al. 1998)
    1. Common features: all core component features of VACTERL
    2. Distinct features: hydrocephalus, heterozygous mutations in *PTEN*, heterozygous/hemizygous mutations in *ZIC3*; X-linked and recessive forms have been described

Diagnostic Investigations

1. Radiography (Barnes and Smith 1978; Fernbach and Glass 1988) for vertebral and limb defects and other malformations
2. Echocardiography for congenital heart defects
3. GI investigation for TE fistula or esophageal atresia
4. Renal ultrasonography for renal dysplasia
5. Urological evaluation of urogenital defects
6. Chromosome analysis

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: low recurrence risk unless in a single gene disorder (Auchterlonie and White 1982; Bartels et al. 2012)
    2. Patient's offspring: low recurrence risk unless in a single gene disorder
2. Prenatal diagnosis by ultrasonography (McGahan et al. 1988; Miller and Kolon 2001; Santos et al. 2013) revealing multiple congenital anomalies compatible to VATER/VACTERL association
    1. Vertebral anomalies
    2. Anorectal anomalies
    3. Congenital heart defects
    4. TE fistula or esophageal atresia
    5. Renal anomalies
    6. Limb defects
    7. Important clues (Tongsong et al. 1999)
        1. Radial atresia
        2. Absent or collapsed stomach
        3. Polyhydramnios
    8. Prenatal diagnosis of radial ray defects in fetuses conceived by assisted reproductive technology should include a differential diagnosis of VACTERL association with anorectal malformation. VACTERL association with hydrocephalus may occur in pregnancy after in vitro fertilization and embryo transfer (Chen et al. 2013).
3. Management
    1. Medical care
    2. Surgical care (Weber et al. 1980)
        1. TE fistula and/or esophageal atresia
        2. Major cardiac defects
        3. Urogenital anomalies
        4. Skeletal and limb defects
        5. Infants with the VATER association can lead reasonably normal lives following aggressive operative treatment and supportive care (Figs. 1–5).

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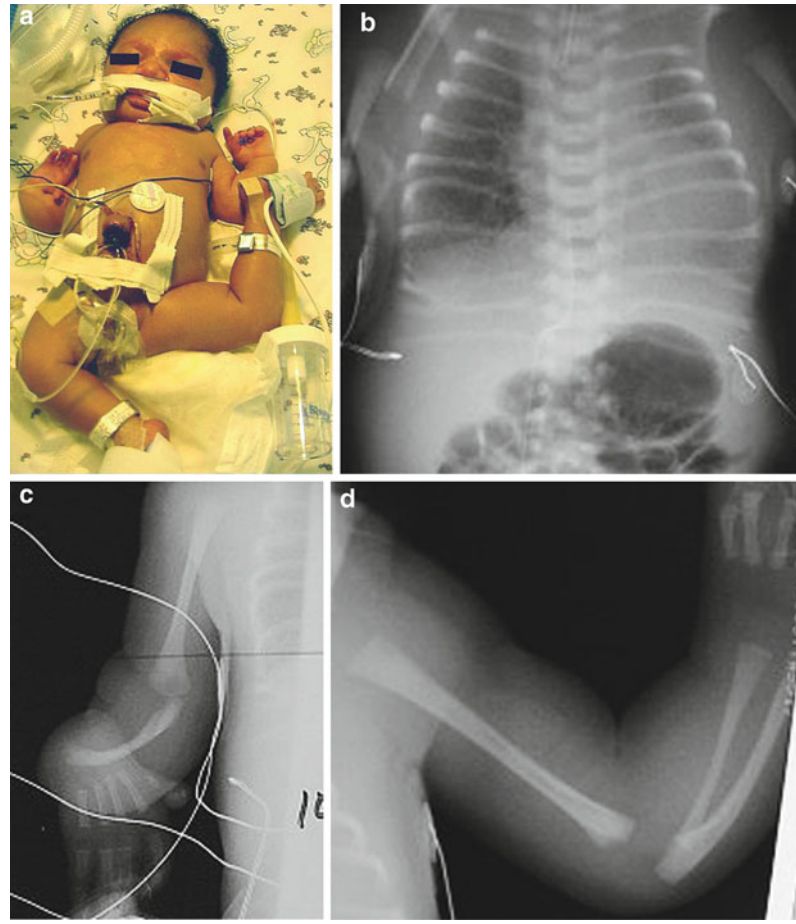

Fig. 1 (**a**–**d**) An infant (**a**) with VATER association showing club hands, abnormally rotated left lower limb, fused/split ribs, hemivertebrae (**b**), radial aplasia on the right (**c**), and radioulnar fusion on the left elbow (**d**)

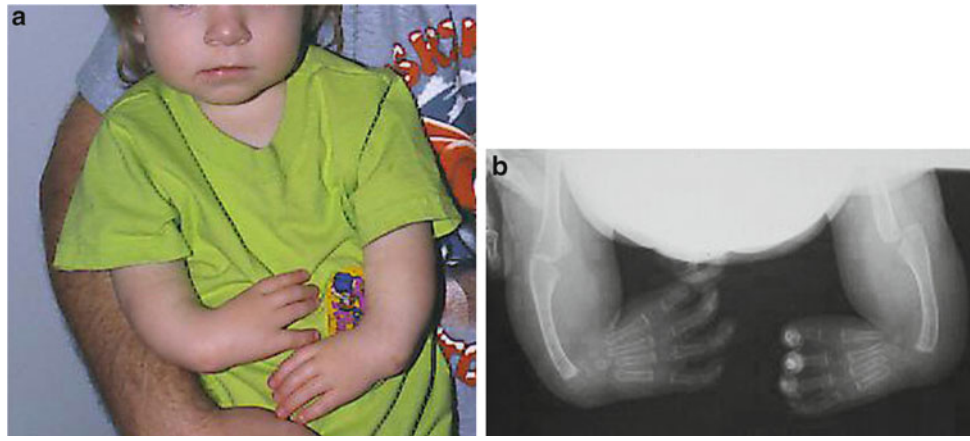

Fig. 2 (**a**, **b**) A child (**a**) with VATER association showing club hands and missing thumbs. Radiograph showed absence of the first phalanges and metacarpals and radial aplasia (**b**)

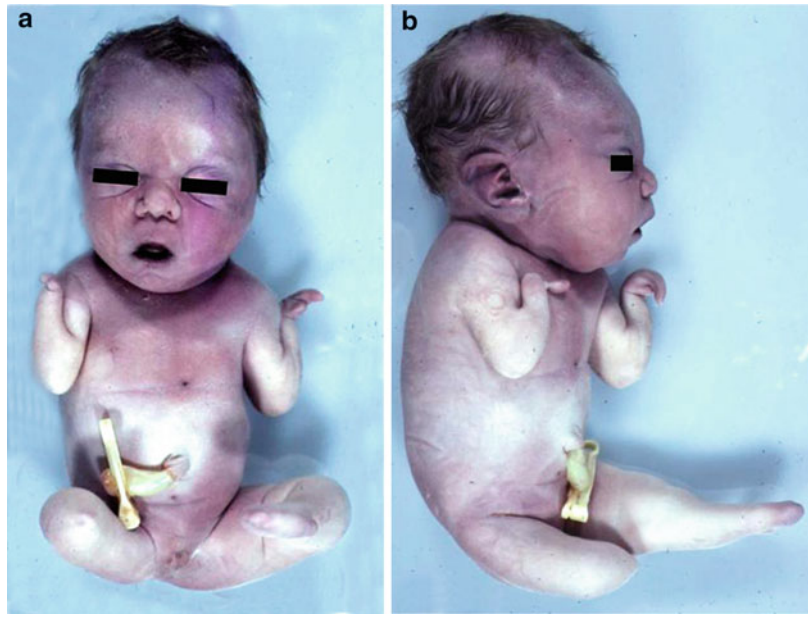

Fig. 3 (**a**, **b**) A male neonate with VATER association showing phocomelia, rudimentary external genitalia, and anal atresia, congenital heart anomalies (type 2 truncus arteriosus, tricuspid valve atresia, ventricular septal defect, large atrial septal defect), type 1 tracheoesophageal fistula, nonlobated lungs, agenesis of kidneys and ureters, malrotation of bowel, and vesicocolonic fistula were demonstrated in the necropsy

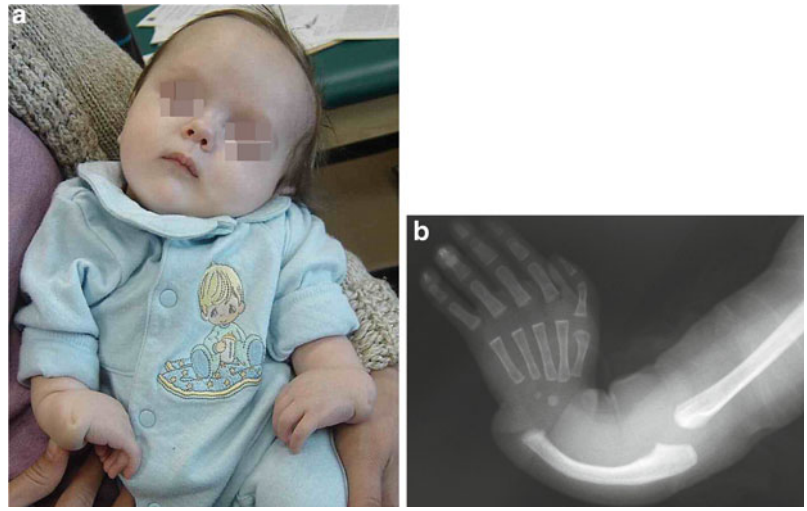

Fig. 4 (**a**, **b**) An infant with club hands (**a**) and radial aplasia, illustrated by a radiograph (**b**)

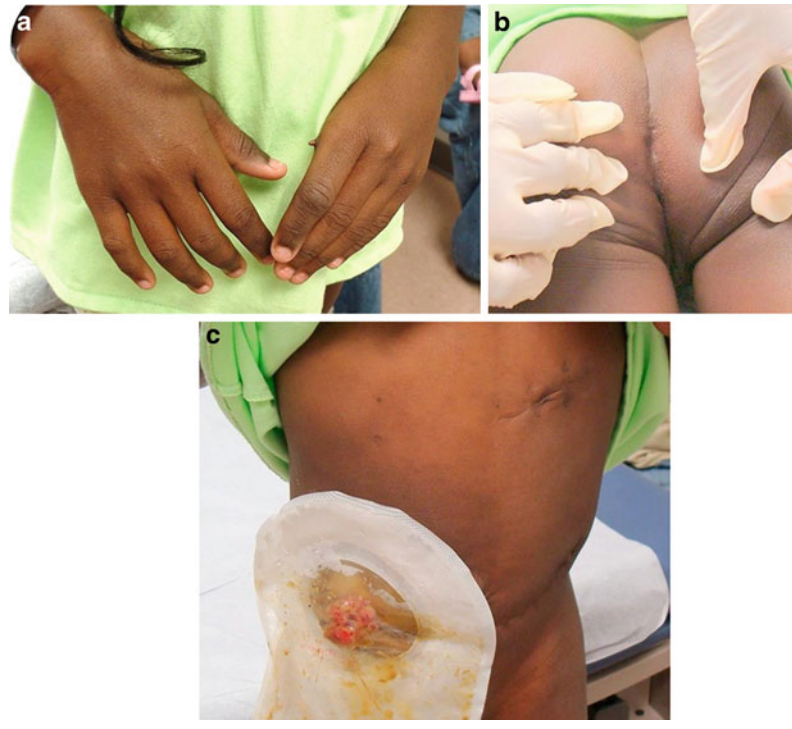

Fig. 5 (**a**–**c**) A girl with VATER association showing a remnant left thumb (**a**), anal atresia (**b**), and colostomy (**c**)

Von Hippel-Lindau Disease

Contents

Von Hippel-Lindau disease (VHL) is a rare hereditary cancer syndrome. The prevalence is estimated at 1 in 85,000 with an incidence of 1 in 45,500 live births (Friedrich 2001).

Synonyms and Related Disorders

Angiomatosis retinae; Von Hippel-Lindau syndrome

Genetics/Basic Defects

1. Inheritance (Schimke et al. 2009)
    1. Autosomal dominant
    2. Reduced penetrance (95% penetrance at age 60)
    3. Positive family history in up to 80% of cases
    4. Sporadic new mutation in about 20% of cases
    5. Parental mosaicism described
2. Molecular pathogenesis of VHL disease
    1. VHL disease.
        1. Caused by deletions or mutations in a tumor suppressor gene (Latif et al. 1993), the *VHL* gene, located on chromosome 3p25–26, which encodes an ubiquitin ligase that is involved in the cellular response to hypoxia
        2. Two-hit theory of Knudson in a familial cancer syndrome such as VHL disease (Lubensky et al. 1998)
            1. Although sporadic cases require a "2-hit" model of gene inactivation, familial cases require only a single "hit" because one allele is already affected at the time of conception (Wizigmann-Voos and Plat 1996).
            2. Prediction of the genotype of each neoplasm which consists of an allele with an inherited germ line mutation and loss of the second wild-type allele through allelic deletion.
            3. Loss of heterozygosity at chromosome 3p at the *VHL* gene region has been demonstrated in different VHL disease-associated tumors.
        3. A germ line mutation in the *VHL* gene (Hes et al. 2003)
            1. Predisposes carriers to tumors in multiple organs
            2. Consistently detected in 100% of classic families with more than one

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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affected family member or classic sporadic patients with multiple VHL-related tumors
3. Missense mutations leading to an amino acid substitution in *VHL* gene product pVHL, observed in 40% of the families with an identified *VHL* gene germ line mutation
4. Microdeletions, insertions, splice site, and nonsense mutations, all predicted to lead to a truncated protein: observed in 30% of the families
5. Large deletions including deletions encompassing the entire gene: account for the remaining 30% of the *VHL* gene germ line mutations

4. Somatic mutations
   1. Report of a case of somatic mosaicism in the asymptomatic mother of a VHL patient who was subsequently diagnosed with pheochromocytoma (Murgia et al. 2000). This is the first report providing molecular evidence of somatic mosaicism in von Hippel-Lindau disease. Mosaicism could provide some genetic explanation for the clinical heterogeneity and variable severity of the VHL phenotype, and should be considered, as a possible event when evaluating sporadic cases of VHL or patients with isolated VHL-related tumors.
   2. Independent somatic alteration of both alleles of the VHL tumor suppressor gene leading to tumorigenesis in nonfamilial (VHL-related) tumors. Somatic VHL gene mutations and allele loss: frequent events in sporadic clear cell renal cell carcinomas and sporadic central nervous system hemangioblastoma, uncommon in sporadic (i.e., nontumor syndrome associated) pheochromocytoma (Hes et al. 2003).

2. *VHL* gene.
   1. Mapped on chromosome 3p25
   2. Involved in blood vessel formation by regulation of the activity of hypoxia-inducible factor (HIF)-1α

3. Patients with VHL disease.
   1. With a positive family history: have inherited an inactive *VHL* allele from an affected parent
   2. Without a positive family history: have a parent who is mosaic for a *VHL* mutation, presumably as the result of a de novo mutation during early development
4. Angiogenesis of VHL tumors: critical role of inactivation of *VHL* gene.
   1. Overexpression of vascular endothelial growth factor (VEGF) resulting in hypervascularization
   2. Negative regulation of hypoxia-inducible mRNAs including VEGF mRNA by VHL protein
5. Tumor development in VHL disease.
   1. Inactivation of the VHL tumor suppressor gene is an early, causal event in the development of clear cell renal cell carcinomas and hemangioblastomas. Its protein product, pVHL, is part of an E3 ubiquitin ligase complex that targets HIFα subunits for destruction in the presence of oxygen (Kaelin 2003). Accordingly, pVHL-defective tumor cells overproduce a variety of HIF target genes, which have been implicated in metabolism, mitogenesis, and angiogenesis.
   2. Linked to inactivation or loss of the remaining wild-type *VHL* allele in a susceptible cell, leading to loss of the *VHL* gene product pVHL.
   3. Inactivation of *VHL* gene contributing to tumorigenesis of the VHL tumor since VHL protein is required for the downregulation of transcription activity of certain genes.
6. *VHL* gene alterations in sporadic benign and malignant pheochromocytomas (Dannenberg et al. 2003).
   1. No distinction in the nature of *VHL* alterations between benign and malignant pheochromocytomas and no correlation with histopathologic or clinical features.

2. Novel VHL mutations in sporadic pheochromocytomas: slightly correlated with malignancy.
3. *VHL* mutations may have some impact on the malignant transformation of pheochromocytomas.

7. Clinical and laboratory studies of VHL disease have provided a paradigm for demonstrating the importance of familial cancer syndromes in elucidating mechanisms of tumorigenesis in familial and sporadic cancer (Clifford and Maher 2001).

3. Cytogenetic abnormalities in tumors of patients with von Hippel-Lindau disease (Jordan et al. 1989)
   1. A deletion of 3p may be a primary cytogenetic change in renal cell carcinomas (RCCs) associated with VHL disease in addition to playing a role in sporadic RCC.
   2. Duplications of 5q and deletions of 14q may be important secondary changes in the progression of the malignant phenotype.
4. Genotype-phenotype correlations (Neumann and Bender 1998; Couch et al. 2000)
   1. Families with pheochromocytoma have in >90% missense mutations, whereas families with renal cell carcinoma show the entire spectrum of the mutations in the *VHL* gene (Neumann et al. 1995).
   2. The mutations associated with VHL type 1 (without pheochromocytoma) are deletions and protein-truncating mutations such as nonsense mutations and microdeletions-insertions in most families.
   3. In VHL type 2 (with pheochromocytoma), 96% of families have missense mutations. However, not all missense mutations are associated with a high risk of pheochromocytoma.
   4. A substantial proportion of patients with familial pheochromocytoma have VHL gene mutations. but in contrast, most familial clusters of clear cell renal cell carcinoma (RCC) without evidence of VHL do not have germline VHL mutations (Richards et al. 1998).
   5. Visual morbidity secondary to retinal hemangioblastoma was not related to the type of extraocular manifestation but appeared to be related to the type of germline mutation (Dollfus et al. 2002).
   6. HIF-α binding site missense mutations elevate age-specific risk for CNS hemangioblastoma (Lee et al. 2016).

Clinical Features

1. Great variation in the clinical presentation with variable age of onset (Schimke et al. 2009)
2. Several characteristic features of VHL but no single unique pathognomonic findings (Couch et al. 2000)
3. Classification of VHL disease: The classic VHL phenotypes (Schimke et al. 2009; Sano and Horiguchi 2003; Bausch et al. 2013)
   1. VHL type 1
      1. Typical VHL manifestations such as hemangioblastomas of the CNS and/or retina and clear cell renal cell carcinomas, pancreatic cysts, and neuroendocrine tumors
      2. Without pheochromocytoma
      3. Truncating or null mutations in the VHL gene (deletions or frameshift, nonsense, or splice site mutations) observed in approximately 96–97% of patients with type 1 VHL
   2. Subtypes of type 1 VHL
      1. VHL type 1 A
         1. Frequency of pheochromocytoma: low
         2. Frequency of renal cell carcinoma: low
      2. VJL type 1B
         1. Frequency of pheochromocytoma: low
         2. Frequency of renal cell carcinoma: high
   3. VHL type 2
      1. With pheochromocytomas
      2. Missense mutations observed in 92–98% of patients with type 2 VHL

4. Subtypes of type 2 VHL
    1. VHL type 2 A
        1. Frequency of pheochromocytoma: high
        2. Frequency of renal cell carcinoma: low
        3. VHL without predisposition to renal cell carcinoma and pancreatic neuroendocrine tumor
        4. Specific mutations (Y98H, Y112H, V116F, L188 V) in the *VHL* gene conferring an increased risk for VHL disease
    2. VHL type 2B
        1. Frequency of pheochromocytoma: high
        2. Frequency of renal cell carcinoma: low
        3. VHL with predisposition to renal cell carcinoma and pancreatic neuroendocrine tumor
        4. Specific mutations (R167Q, R167W) in the *VHL* gene conferring an increased risk for VHL disease
    3. VHL type 2C
        1. No associated tumors
        2. VHL with only pheochromocytoma manifestation (no other manifestations)
        3. Specific mutations (V155 L, R238W) in the *VHL* gene conferring an increased risk for VHL disease
4. Tumors/cysts linked to VHL disease, typically develop in the second, third, and fourth decades of life (Findeis-Hosey et al. 2016)
    1. Retinal angioma/hemangioblastoma
        1. Responsible for the first manifestation of VHL in 50% of the patients
        2. Retinal lesions
            1. Formerly called retinal angiomas
            2. Histologically identical to hemangioblastomas
            3. Identified in about 70% of the patients
            4. Bilateral in about 50% of the patients
            5. Multiple in about 66% of the patients
        3. Complications when the condition is unrecognized and untreated at early stage
            1. Majority of retinal angiomas eventually hemorrhage
            2. Resulting in massive exudation and retinal detachment
            3. Ultimate development of neovascular glaucoma and blindness
    2. Cerebellar hemangioblastomas (80% of CNS hemangioblastoma) (Friedrich 2001)
        1. The most common initial manifestation (34.9%)
        2. Cumulative occurrence: 60.2%
        3. The most common cause of death (47.7%)
        4. Symptoms and signs
            1. Headache
            2. Slurred speech
            3. Nystagmus
            4. Positional vertigo
            5. Labile hypertension (without pheochromocytoma)
            6. Vomiting
            7. Wide-based gait
            8. Dysmetria
    3. Spinal hemangioblastoma (20% of CNS hemangioblastoma) (Friedrich 2001)
        1. More specific for VHL disease
        2. About 80% of cases are caused by VHL.
        3. Cumulative occurrence (14.5%)
        4. Symptoms and signs
            1. Pain
            2. Sensory and motor loss secondary to cord compression
    4. Renal lesions
        1. Clear cell renal cell carcinoma (ccRCC) accounts for ~80% of all RCC, and biallelic *VHL* gene defects occur in ~75% of sporadic ccRCC (Shenoy and Pagliaro 2016).
        2. Renal cysts: precursor lesions to clear cell renal cell carcinomas (75% of patients with VHL) which is a frequent cause of death.
    3. Hemangioblastoma.

4. Renal cell adenoma.
5. Renal cell carcinoma (20–40%).

5. Endocrine manifestations of von Hippel–Lindau disease (Cassol and Mete 2015)
   1. Pancreatic neuroendocrine proliferations
      1. Ductuloinsular complexes
      2. Islet dysplasia
      3. Endocrine microadenoma
      4. Neuroendocrine tumors
   2. Pheochromocytomas
   3. Extra-adrenal paragangliomas
6. Pheochromocytomas (tumor of adrenal medulla)
   1. Type 1 families
      1. Absence of pheochromocytomas.
      2. Most type 1 families are affected by deletions or premature termination mutations.
   2. Type 2 families (7–20% of families)
      1. Presence of pheochromocytomas.
      2. Most type 2 families are affected by missense mutations.
   3. Arg238trp and arg238gln mutations: associated with a 62% risk for pheochromocytoma
   4. Location of tumors
      1. Usually located in one or both adrenal glands
      2. May present anywhere along the sympathetic axis in the abdomen or thorax (paragangliomas) or head and neck (chemodectomas)
   5. Symptoms and signs
      1. Sustained or episodic hypertension
      2. Asymptomatic
7. Pancreatic lesions
   1. Type of lesions
      1. Simple pancreatic cysts
      2. Serous cystadenomas
      3. Pancreatic neuroendocrine tumors
   2. Rarely causing endocrine or exocrine insufficiency unless the lesion is extensive
   3. Occasionally causing biliary obstruction secondary to cysts in the head of the pancreas
8. Liver lesions
   1. Hemangiomas
   2. Cyst
   3. Adenoma
   4. Carcinoid of the common bile duct
9. Splenic lesions
   1. Hemangiomas
   2. Cyst
10. Pulmonary lesions
    1. Hemangiomas
    2. Cyst
11. Bladder hemangioblastoma
12. Endolymphatic sac tumors of the inner ears (labyrinth)
    1. Tinnitus or vertigo
    2. Deafness
13. Papillary cystadenomas of the epididymis in males
    1. Relatively common in males
    2. Unilateral: rarely causing problem
    3. Bilateral: infertility
14. Papillary cystadenomas of the broad ligament in females: much less common
15. Skin lesions
    1. Nevus
    2. Café au lait spot
16. Bone lesions
    1. Hemangioma
    2. Cyst

5. Diagnosis of VHL disease usually made on clinical grounds (Sanfilippo et al. 2003)
   1. A positive family history of VHL disease plus one of the following lesions (hemangioblastoma or visceral lesion):
      1. Retinal hemangioblastoma
      2. Cerebellar hemangioblastoma
      3. Pheochromocytoma
      4. Renal cell carcinoma
      5. Multiple pancreatic cysts
   2. A negative family history of VHL disease needs one of the following (Friedrich 2001):
      1. Two or more retinal or cerebellar hemangioblastomas, or
      2. One hemangioblastoma plus one visceral tumor
6. Prognosis (Maher et al. 1990)
   1. Life expectancy: $<$50 years

2. Major causes of death (Shanbhogue et al. 2016)
    1. Renal cell carcinoma: the leading cause of death
    2. Cerebellar hemangioblastoma
3. Improved prognosis in patients with:
    1. Earlier diagnosis
    2. Regular monitoring for predictable complications
    3. Followed by early interventions
    4. Even though the risk of VHL related death has decreased significantly, the main cause of death is still CNS hemangioblastomas (Binderup et al. 2016)

Diagnostic Investigations

1. Biochemical test: elevated urinary catecholamines (VMA, metanephrine, and total catecholamine) suggesting pheochromocytoma even in the absence of hypertension
2. Eye examinations (Sanfilippo et al. 2003)
    1. Ophthalmoscopy.
    2. Fluorescein angiography, a valuable tool useful in detecting subclinical fundus lesions.
    3. Annual audiometry as a first-line endolymphatic sac tumor screening tool, and in countries where periodic surveillance magnetic resonance imaging of the central nervous system is performed, specific images of the inner ear should be included (Paulsen et al. 2011).
        1. Audiometric abnormalities in patients with von Hippel-Lindau disease without magnetic resonance imaging-visible endolymphatic sac tumors could be due to microscopic endolymphatic sac tumors.
        2. Determination of audiometric endolymphatic sac tumor characteristics could further target screening and improve endolymphatic sac tumor diagnosis.
3. Imaging features (Choyke et al. 1995; Khan 2015)
    1. Radiography for rare associated bone cysts and osseous hemangiomas (Leung et al. 2008)
    2. Ultrasound examinations
        1. Evaluation of the epididymis and broad ligament
        2. Screening of the kidneys
    3. CAT scan (Torreggiani et al. 2002; Taouli et al. 2003)
        1. CNS hemangioblastomas
            1. Cystic lesions (75%)
            2. An enhancing lesion with multiple cystic areas (15%)
            3. An enhancing solid mass (10%)
        2. Retinal hemangiomas too small to be depicted on CT scans, the diagnosis mainly dependent on the results of an ophthalmoscopic examination
        3. CNS hemangioblastomas and retinal angiomas: the commonest and usually the earliest features of the disease
        4. Papillary endolymphatic sac tumors presenting as a thin peripheral rim of calcification, representing the expanded cortex of petrous bone
        5. Low sensitivity in the detection of renal cell carcinoma associated with VHL
            1. Not reliable in differentiating cystic renal cell carcinomas, cancers within a cyst, and atypical cysts
            2. Impossible to differentiate a renal cell adenoma from a renal cell carcinoma
        6. Pheochromocytoma
            1. Most tumors are localized in the adrenal glands, but 15–18% of the lesions are found in an extraadrenal location (paragangliomas).
            2. The diagnosis is based on biochemical tests (serum and urinary catecholamines) and imaging.
            3. On CT (Neumann et al. 1998), pheochromocytoma typically appears as a solid or complex cystic mass with some areas of necrosis and hemorrhage, possible calcifications, and marked enhancement.

7. Pancreatic masses (Charlesworth et al. 2012)
    1. Simple pancreatic cysts: benign
    2. Serous cystadenomas: benign
    3. Pancreatic neuroendocrine tumors: typically nonsecretory islet cell tumors and may occasionally be malignant (Hammel et al. 2000)
8. Other abdominal lesions
    1. Liver cysts
    2. Cystadenomas of the epididymis and of the broad ligament

4. ^{68}Ga DOTATATE PET/CT
    1. Endolymphatic sac tumor showing increased activity (Papadakis et al. 2016a)
    2. Epididymal cystadenomas in VHL showing increased activity (Papadakis et al. 2016b)
5. MRI to document the presence of CNS and visceral tumors
    1. MRI appearances of a CNS hemangioblastoma: a well-demarcated cystic lesion with a highly vascular mural nodule that always abuts on the pia mater
    2. Spinal hemangioblastomas: intramedullary tumors in most patients (75%) but may be radicular (20%) or intradural extramedullary (5%)
    3. Pheochromocytoma: high signal intensity on T2-weighted MRI, differentiating it from adrenal cortical nodules
    4. Endolymphatic sac tumors: high signal intensity with T1 imaging on MRI as a mass on the posterior wall of the petrous part of the temporal bone
6. Radionuclide studies
    1. To provide an indication of metabolic activity of CNS tumors by positron emission tomography (PET) with 2-[fluorine 18]-fluoro-2-deoxy-D-glucose (FDG)
    2. To detect bone metastases resulting from primary malignant tumor of bone of VHL
    3. To assess renal function prior to resection of renal tumors
    4. To detect pheochromocytoma using iodine-131 metaiodobenzylguanidine (^{131}I MIBG)
7. Angiography
    1. Hemangioblastoma: a hypervascular lesion with intense and prolonged early enhancement of the mural nodule associated with dilated feeding vessels
    2. Endolymphatic sac tumors
        1. Hypervascular on angiography and the blood supply is derived from the external carotid artery
        2. Large tumors with an additional blood supply from the internal carotid artery and posterior circulation

4. Cytogenetic and fluorescence in situ hybridization studies on sporadic and hereditary tumors associated with VHL (Decker et al. 1994)
    1. FISH with single copy probes for interphase cytogenetics detected four subclones with deletions in the VHL region in 8/22 tumors, including four tumors which appeared cytogenetically normal.
    2. FISH proved to be a powerful tool in tumor genetic studies, especially helpful in detecting tumor subclones in benign and slowly growing tumors.
    3. FISH: a simple and reliable method to detect VHL germline deletions and practically useful in cases where other methods of screening have failed to detect a VHL gene abnormality (Pack et al. 1999).
5. Histologic features of VHL tumors (Sano and Horiguchi 2003)
    1. High degree of vascularization
    2. Presence of a clear cell component
6. NIH group recommendation for monitoring VHL patients and family members (Friedrich 2001)
    1. Birth to 2 years
        1. Annual physical examination
        2. Annual ophthalmologic examination
    2. 2–10 years: urinary catecholamines every 1–2 years
    3. 11–19 years
        1. Biannual MRI of the brain and spine

2. Annual ultrasound examination of abdomen
3. CT scans of abdomen every 6 months if renal cysts or tumor present

4. 20–59 years: annual CT scan of abdomen
5. 60 years and above without VHL
   1. MRI of the brain and spine every 3–5 years
   2. CT scan of the abdomen every other year
6. Not necessary to monitor the family members identified previously with an empiric risk of 50% of being affected but are found not to have inherited the mutation

7. Molecular genetic analysis
   1. Considered standard for the evaluation of patients and families with suspected VHL disease: detects mutations in nearly 100% of affected individuals.
   2. Clinical testing.
      1. Sequence analysis
      2. Deletion/duplication analysis
   3. Identification of *VHL* gene germ line mutations.
      1. Identification of constitutional *VHL* gene deletions by FISH using probes from the *VHL* gene critical region in 3p25.3
         1. Offers a comprehensive way to screen for the presence of germ line deletions because it enables visualization of individual cells
         2. May identify mosaicism or cryptic translocation events that cannot be readily detected by other molecular strategies in patients with submicroscopic germ line deletions and a normal karyotype
         3. Enable to identify a de novo mosaic for the *VHL* gene deletion
      2. Molecular diagnosis accomplished in virtually all families with classic VHL disease (families with multiple tumors) and in the majority of isolated patients with multiple VHL-associated tumors
         1. Qualitative and quantitative Southern blotting to detect partial or complete gene deletions responsible for 28% of all cases
         2. FISH to confirm deletions
         3. DNA-sequence analysis of the protein-encoding region (all three exons) to detect point mutations in the remainder (72%) of the cases
         4. It is now possible to identify germline mutations in virtually all families with VHL (Stolle et al. 1998)
   4. Mosaicism.
      1. A potential cause for failure of molecular diagnosis in VHL.
      2. Individuals with mosaicism:
         1. Asymptomatic
         2. Manifesting as a single-system disease
         3. Manifesting as a multisystem disease
      3. Kindreds with germline mutations identified in offspring with mosaic parents: Mosaicism in VHL is important to search for and recognize when an individual without a family history of VHL has VHL (Sgambati et al. 2000).
   5. Identification of a mutation in a proband allows the identification of mutation carriers among family members who do not yet exhibit any clinical manifestation of VHL.
   6. DNA polymorphism analysis as a method for identifying VHL disease gene carriers among asymptomatic members of disease families (Glenn et al. 1992).

Genetic Counseling

1. Recurrence risk
   1. Patient's sib
      1. A small risk of having a sib with VHL since parental mosaicism accounts for some apparently sporadic or new cases of VHL.
      2. A 50% risk of having a sib with VHL disease if one of the parent is clinically affected or has a disease-causing *VHL* gene mutation.
   2. Patient's offspring
      1. A 50% risk of inheriting the VHL disease-causing mutation.

    2. An individual mosaic for a disease mutation is at increased risk of having affected offspring, despite negative testing for the mutation by routine DNA diagnostic tests.
2. Prenatal Testing and Preimplantation Genetic Diagnosis (PGD) (Frantzen et al. 2015)
    1. Once the VHL pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis (PGD) for a pregnancy at increased risk for VHL syndrome are possible options.
    2. PGD has been successfully used in pregnancies at risk for VHL syndrome (Rechitsky et al. 2002, Simpson et al. 2005).
3. Management
    1. All patients with pheochromocytomas should be screened for MEN-2 and von Hippel-Lindau disease to avert further morbidity and mortality in the patients and their families (Neumann et al. 1993). All patients in families with MEN-2 or von Hippel-Lindau disease should be screened for pheochromocytoma, even if they are asymptomatic.
    2. Ocular management (Sanfilippo et al. 2003).
        1. Laser photocoagulation therapy or cryotherapy of retinal lesions
        2. Several treatment strategies on the horizon that show promise for the ocular management of VHL disease
            1. Vascular endothelial growth factor (VEGF) inhibitors
            2. Use of radiotherapy, such as brachytherapy or linear accelerator-based radiosurgery
    3. In general, pancreatic NET with or without VHL disease shows a slow-growth phenotype and patients have a good prognosis. VHL patients at lower metastatic risk from pancreatic neuroendocrine tumor should be spared the risks of surgical resection (Tamura et al. 2010).
    4. Surgery: the mainstay of treatment for the tumors arising in patients with VHL disease (Sanfilippo et al. 2003).
        1. Renal cell carcinomas
            1. Partial nephrectomy or radiofrequency ablation to spare renal function if tumor involvement is not extensive.
            2. Total nephrectomy often necessary for extensive tumor involvement.
        2. Resection of symptomatic brain stem hemangioblastomas, in general, is a safe and effective management strategy in patients with VHL disease. Most patients maintain their preoperative functional status, although long-term decline in functional status may occur due to VHL disease-associated progression (Wind et al. 2011).
        3. Pregnant patients with spinal hemangiomas and VHL must be closely monitored for neurological compromise, as pregnancy can exacerbate both symptomatic and previously asymptomatic lesions. Patients must be evaluated on a case-by-case basis for surgical intervention, which should be carefully considered if clinical function begins to decline (Hayden et al. 2009).
        4. Stereotactic radiosurgery has been proposed as an alternative treatment strategy for CNS hemangioblastomas (Richard et al. 2000; Wind et al. 2011).
        5. Possibility of proliferative changes and tractional retinal detachment can arise following photocoagulation for retinal capillary hemangiomas in patients with VHL (Suzuki et al. 2016).
        6. In the future, antiangiogenic drugs could represent a potential medical treatment of CNS hemangioblastomas in view of their highly vascular structure (Richard et al. 2000).
    5. Somatic inactivation of the *VHL* gene is the main molecular event in most sporadic RCC, and the treatment of advanced RCC has been revolutionized by targeted therapy with drugs that block angiogenesis. These drugs are now in first line in metastatic sporadic RCC and have shown promising results for RCC, pancreatic neuroendocrine

tumors, and malignant pheochromocytomas in VHL patients (Richard et al. 2013).

6. Therapeutic management of central nervous system hemangioblastomas: ranging from neurosurgical resection, radiation therapy, and systemic therapies (Hodgson et al. 2016).
7. VHL appears to be a pivotal gene in the oxygen-sensing pathway, mainly involved in targeting the hypoxia-inducible factors for ubiquitination. This discovery is opening the way for the development of new specific drugs inhibiting hypoxia-inducible factors and/or their downstream targets, possibly representing an attractive treatment not only for von Hippel-Lindau disease but also for sporadic renal cell carcinomas and others cancers (Richard 2003).
8. Missense mutations can result in the translation of functional VHL protein (pVHL) that is rapidly degraded resulting in functional loss of the pVHL, and inhibitors of pVHL degradation may slow protein degradation and restore pVHL function (Schunemann et al. 2016).

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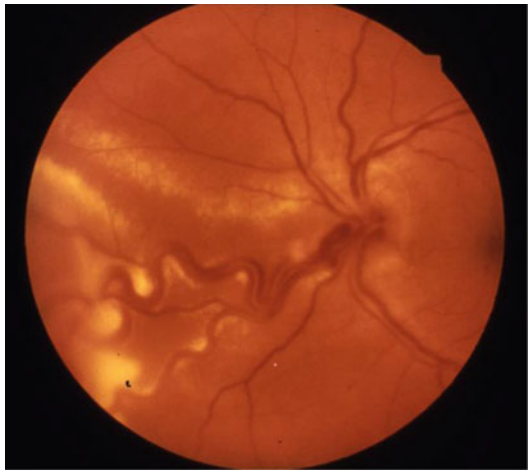

Fig. 1 Retinal malformation secondary to von Hippel-Lindau disease

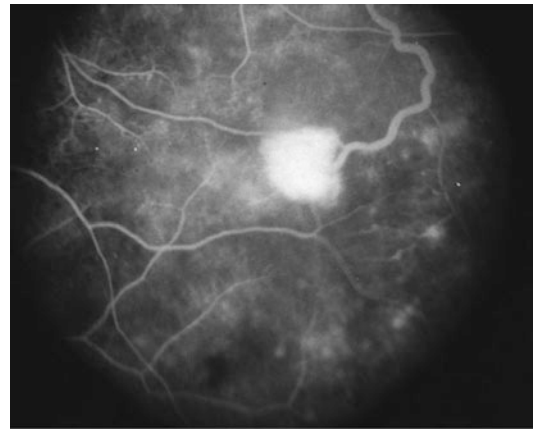

Fig. 3 A giant macroaneurysm of retinal vessels in a patient with von Hippel-Lindau disease

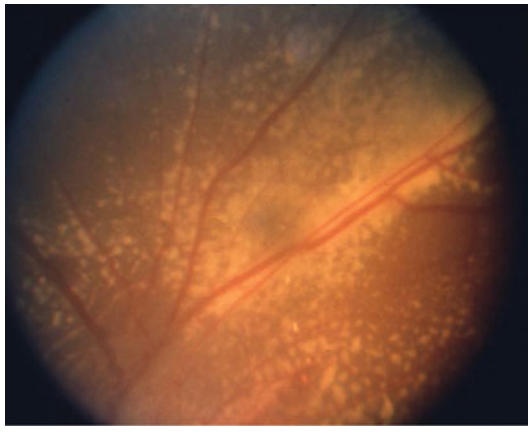

Fig. 2 Retinal exudates from vascular leakage in a patient with von Hippel-Lindau disease

Waardenburg Syndrome

Contents

Waardenburg syndrome (WS) is a rare autosomal dominant disorder characterized by patchy depigmentation, sensorineural hearing loss, and other developmental defects. There are four types of this syndrome. Types I and II are more common than types III and IV. The overall syndrome affects about 1 in 42,000 people (Waardenburg 1951).

Synonyms and Related Disorders

Klein-Waardenburg syndrome (Waardenburg syndrome with upper limb anomalies); Tietz/Waardenburg type 2A syndrome; Waardenburg syndrome with dystopia canthorum; Waardenburg syndrome with or without neurologic involvement; Waardenburg syndrome without dystopia canthorum; Waardenburg-Shah syndrome (Waardenburg syndrome with Hirschsprung disease)

Genetics/Basic Defects

1. Inheritance: genetic heterogeneity (Hageman and Delleman 1977)
    1. Autosomal dominant
        1. Type I (Waardenburg syndrome): presence of dystopia canthorum (lateral displacement of the inner canthi of the eyes in the presence of normal interpupillary distance)
        2. Type II (Waardenburg syndrome with ocular albinism; absence of dystopia canthorum)
        3. Type III (Klein-Waardenburg syndrome; presence of musculoskeletal abnormalities) (Klein 1983)
    2. Autosomal recessive: Type IV (Shah-Waardenburg syndrome or Waardenburg-Hirschsprung disease) (Bonnet et al. 1996)
2. Cause (Read and Newton 1997; Pingault et al. 2010)
    1. Type I and Type III (Hoth et al. 1993):
        1. Mutations in *PAX3* (paired box) gene on chromosome 2q35.
        2. Two similar mutations in close proximity can result in significantly different phenotypes, WS type I in one family and WS type III in another.
    2. Type II:
        1. Some patients are associated with mutations in *MITF* (microphthalmia associated transcription factor) gene

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(Tassabehji et al. 1994; Yang et al. 2013) on chromosome 3p12-p14.1 (Hughes et al. 1994)
2. Mutations in *SOX10* gene (encoding the Sry BOX10 transcription factor) on chromosome 22q13 (Bondurand et al. 2007; Iso et al. 2008)
3. Homozygous deletions of snail homolog 2 (*SNAI2*) in two patients (Sanchez-Martin et al. 2002)

3. Tietz syndrome and Waardenburg syndrome type 2A are allelic conditions caused by MITF mutations (Cortés-González et al. 2016):
   1. Tietz syndrome is inherited in an autosomal dominant pattern and is characterized by congenital deafness and generalized skin, hair, and eye hypopigmentation.
   2. Waardenburg syndrome type 2A typically includes variable degrees of sensorineural hearing loss and patches of de-pigmented skin, hair, and irides.
   3. Posterior microphthalmos might be part of the clinical characteristics of Tietz/Waardenburg syndrome type 2A and expand both the clinical and molecular spectrum of the disease.
4. Type IV (Fernández et al. 2014) :
   1. Mutations in the genes for endothelin-3 (*EDN3*) (Hofstra et al. 1996) on chromosome 20q13.2-q13.3 or endothelin B receptor (*EDNRB*) on chromosome 13q22.
   2. Mutations in *SOX10* gene (Touraine et al. 2000).
   3. Shah-Waardenburg syndrome or Waardenburg syndrome type 4 (WS4) is a neurocristopathy characterized by the association of deafness, depigmentation, and Hirschsprung disease. Three disease-causing genes have been identified so far for WS4: *EDNRB*, *EDN3*, and *SOX10*.
   4. *SOX10* mutations, found in 45–55% of WS4 patients, are inherited in autosomal dominant way.
   5. In addition, mutations in *SOX10* are also responsible for an extended syndrome involving peripheral and central neurological phenotypes, referred to as PCWH (peripheral demyelinating neuropathy, central dysmyelinating leucodystrophy, Waardenburg syndrome, Hirschsprung disease).
   6. Such mutations are mostly private, and a high intra- and interfamilial variability exists.
3. Pathogenesis: None of the following theories explains all the features of Waardenburg syndrome (Dourmishev et al. 1999).
   1. Deficient neural crest theory (Mallory et al. 1986)
      1. Developmental abnormality of the neural crest as a cause of the disease
      2. Supported by the association of Waardenburg syndrome with aganglionic megacolon
   2. As a part of the first arch syndrome theory
   3. A relationship of Waardenburg syndrome with status dysraphicus theory
   4. Intrauterine necrosis theory
4. Interaction among SOX10, PAX3, and MITF, three genes altered in Waardenburg syndrome: An interaction between three of the genes that are altered in WS, could explain the auditory-pigmentary symptoms of this disease (Bondurand et al. 2000)
5. Genotype-phenotype correlations (DeStefano et al. 1998)
   1. Specific mutations in the *PAX3* gene correlate with the expression of different features of Waardenburg syndrome.
   2. Odds for the presence of eye pigment abnormality, white forelock, and skin hypopigmentation were 2, 8, and 5 times greater, respectively, for individuals with deletions of the homeodomain and the Pro-Ser-Thr-rich region compared to individuals with an AA substitution in the homeodomain. Odds ratios that differ significantly from 1.0 for these traits may

indicate that the gene products resulting from different classes of mutations act differently in the expression of WS.

Clinical Features

1. Wide clinical spectrum.
2. Facial appearance:
    1. Dystopia canthorum (lateral displacement of the medial canthi)
    2. Bushy eyebrows with synophrys
    3. A narrow nose with prominent nasal root
    4. Marked hypoplasia of the nasal bone
    5. Short philtrum
    6. Short/retro positioned maxilla
3. Congenital sensorineural deafness (deafmutism) (Song et al. 2016):
    1. Waardenburg syndrome is the most common syndromal cause of deafness and is responsible for 2–3% of congenital deafness.
    2. Mutations in *SOX10* (96.5%), *MITF* (89.6%), and *SNAI2* (100%) are more frequently associated with hearing impairment than other mutations.
    3. The distinct disease-causing genes are able to better predict the auditory phenotype compared with different clinical types of WS.
    4. Consequently, it is important to confirm the clinical diagnosis of WS with molecular analysis in order to optimally inform patients about the risk of hearing loss.
4. Pigmentary abnormalities:
    1. Cutaneous pigmentary abnormalities
        1. Achromatic spots, with sharply defined irregular borders and containing scattered islands of hyperpigmentation, resemble those of piebaldism.
        2. Hyperpigmented macules on normally pigmented skin that have been described as a “patchy skin” and give the cases a “dappled appearance”
    2. Hair pigmentary abnormalities
        1. White forelock (may be evident at birth, soon afterwards, or develop later)
        2. Premature graying of the scalp hair and of the eyebrows, cilia, or body hair
    3. Fundus pigmentary abnormalities
        1. Albinotic fundi (generalized decrease in retinal pigment) (Delleman and Hageman 1978)
        2. Pigmentary mottling in the periphery
    4. Partial albinism
    5. Heterochromia (different color) of the iris
    6. Bilateral isohypochromia iridis (pale blue eyes)
    7. Ocular albinism (type II)
5. Musculoskeletal abnormalities (type III, Klein-Waardenburg syndrome) (Goodman et al. 1982):
    1. Ortho-osteomyo-dysplasia of the upper limbs
    2. Bilateral upper limb defects
    3. Flexion contractures
    4. Fusion of the carpal bones
    5. Syndactyly
6. Congenital aganglionic megacolon association (type IV, Shah-Waardenburg syndrome).
7. Occasional associated anomalies (da-Silva 1991).
    1. Cleft lip/palate
    2. Neural tube defects
    3. Facial asymmetry
    4. Facial palsy
    5. Hypokalemic periodic paralysis
    6. Preauricular pit
    7. Hypoplasia of the middle ear ossicles
    8. Blepharoptosis
    9. Microphthalmia
    10. Hypertelorism
    11. Iris coloboma
    12. Fixed dilated pupil, anterior lenticonus
    13. High-arched palate
    14. “Cupid bow” configuration of the upper lip
    15. Prognathism
    16. Microcephaly

17. Mental retardation
18. Esophageal atresia with tracheoesophageal fistula
19. Imperforate anus
20. Bifid spine
21. Vertebral agenesis
22. Absence of vagina and right adnexal uteri
23. Syndactyly
24. Cardiovascular anomalies
25. Polythelia
26. Urinary anomalies
27. Hyperkeratosis of palms and soles
28. Black forelock
29. Hyperpigmented skin lesions

8. Diagnostic criteria for Waardenburg type I and type II as proposed by the Waardenburg Consortium. To be affected with Waardenburg type I, an individual must have two major or one major plus two minor criteria. To be affected with Waardenburg type II, an individual should show two major features (with one major feature of an affected first-degree relative who should show two major features) (more stringent criteria by Liu et al. 1995) (Read and Newton 1997; Konno and Silm 2001).
    1. Major criteria
        1. Congenital sensorineural hearing loss
        2. Pigmentary disturbances of iris
            1. Complete heterochromia iridium (two eye of different color)
            2. Partial or segmental heterochromia (segments of blue or brown pigmentation in one or both eyes)
            3. Hypoplastic blue eyes (characteristically brilliant blue in both eyes)
        3. Hair hypopigmentation (white forelock)
        4. Dystopia canthorum, or
        5. Affected first-degree relatives
    2. Minor criteria
        1. Congenital leukoderma (several areas of hypopigmented skin)
        2. Synophrys or medial eyebrow flare
        3. Broad and high nasal root
        4. Hypoplasia of alae nasi
        5. Premature graying of hair (scalp hair predominantly white before age 30)

Diagnostic Investigations

1. Audiologic evaluation for hearing loss
2. Histochemical studies of achromic skin
    1. Absent melanocytes
    2. Presence of only a few dihydroxyphenylalanine (dopa)-positive cells
3. Ultrastructural findings of depigmented skin
    1. Absence or dramatically reduced melanocytes
    2. Dendritic cells containing poorly melanized melanosomes
    3. Absence of melanosomes in the keratinocytes
4. Chromosome abnormalities observed in type I Waardenburg syndrome (Konno and Silm 2001)
    1. Inversion 2q35-q36.1
    2. Deletion 2q35-q36.2
    3. Del(2)(q34;q36.2)
5. Molecular studies of mutations for different types of Waardenburg syndrome (Konno and Silm 2001; Milunsky 2014)
    1. Testing methods
        1. Sequence analysis for gene mutations
        2. Deletion/duplication analysis for gene deletions
        3. Diagnostic exome sequencing can be a useful tool for the identification of pathogenic gene variants in WS patients and for differentiation between WS and similar disorders (Jang et al. 2015)
    2. Different types of Waardenburg syndrome
        1. Waardenburg syndrome type I: *PAX3* gene mutation
        2. Waardenburg syndrome type II: 15–20% of cases have heterozygous mutation in the *MITF* gene.
        3. Waardenburg syndrome type III: interstitial deletion of chromosome 2 (2q35-q36.2) including the *PAX3* gene
        4. Waardenburg syndrome type IV:
            1. Mutations in the gene encoding endothelin-3 (Edn 3) or one of its receptors, the endothelin-B receptor (Ednrb)
            2. Mutations in *SOX10*

Genetic Counseling

1. Recurrence risk
   1. Autosomal dominant inheritance
      1. Patient's sibs: not increased unless one of the parent is also affected or has germinal mosaicism (Kapur and Karam 1991)
      2. Patient's offspring: 50%
   2. Autosomal recessive inheritance
      1. Patient's sibs: 25%
      2. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis (Milunsky 2014)
   1. Possible when a mutation has been defined in the family
   2. Impossible to predict how severe the fetus will be affected
3. Preimplantation genetic diagnosis: available for families in which disease-causing mutation has been identified (Milunsky 2014)
4. Management (Konno and Silm 2001)
   1. No effective treatment available.
   2. Photoprotection to protect the amelanotic areas from burning with sun exposure:
      1. Sunscreens
      2. Camouflage
         1. Hair dye
         2. Dermablend
   3. Autologous grafts or transplants of autologous cultured melanocytes used to repigment the areas of hypomelanosis (piebaldism).
   4. Important to diagnose and improve hearing loss: auditory habilitation with a cochlear implant with excellent prognosis (Cullen et al. 2006).
   5. Folate supplementation during pregnancy advisable for a fetus at risk for Waardenburg type I, although the risk for neural tube defect is low.
   6. WS has features that can be important for anaesthetic management, including laryngomalacia, multiple muscle contractures, limited neck movements, cyanotic cardiomyopathy and electrolyte imbalance (Peker et al. 2015).
   7. Cochlear implantation could be a good treatment option for hearing loss in Waardenburg syndrome (Koyama et al. 2016).

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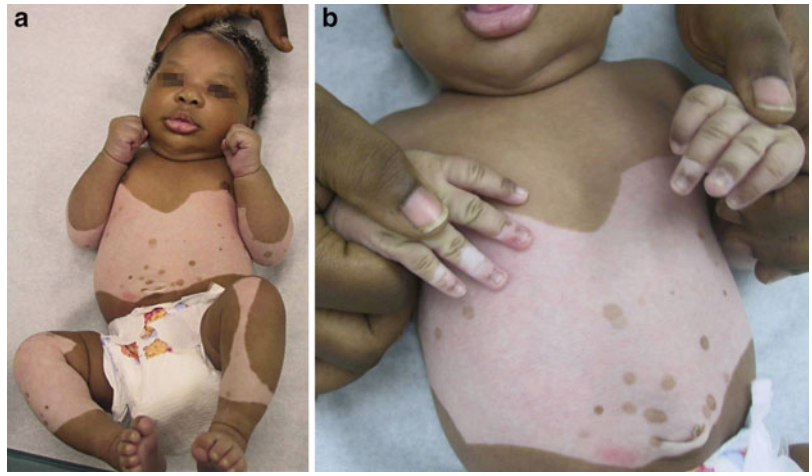

Fig. 1 (**a**, **b**) A 3-week-old infant with Waardenburg syndrome showing white forelock and vitiligo involving symmetrically anterior lower chest, anterior upper abdomen, lower legs, elbows, and fingers

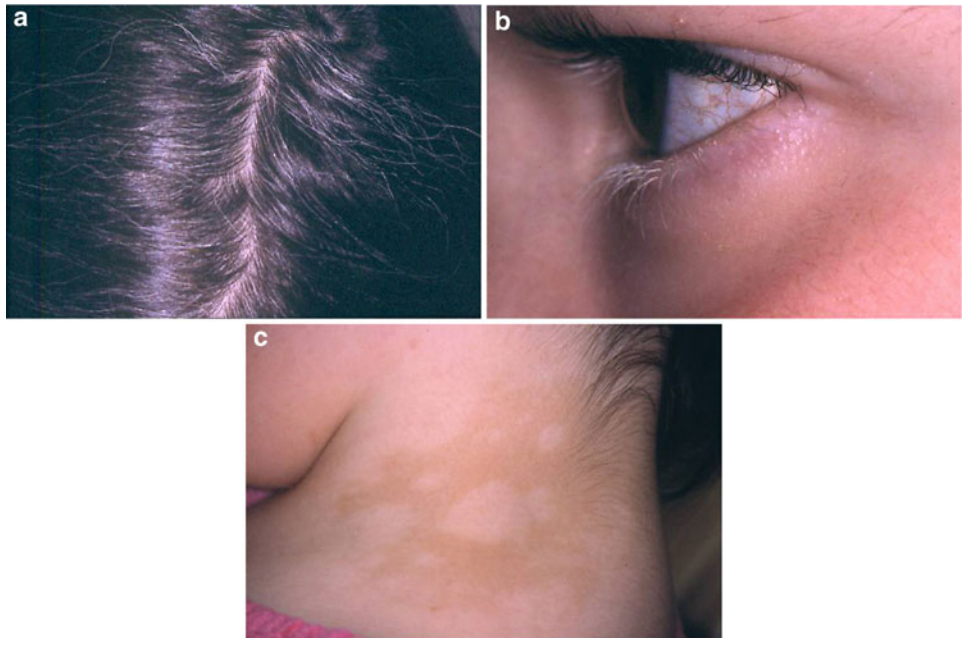

Fig. 2 (**a**–**c**) An adult patient with Waardenburg syndrome showing white forelock (**a**), white eyelashes (**b**), and patchy hyperpigmented macules on the neck (**c**)

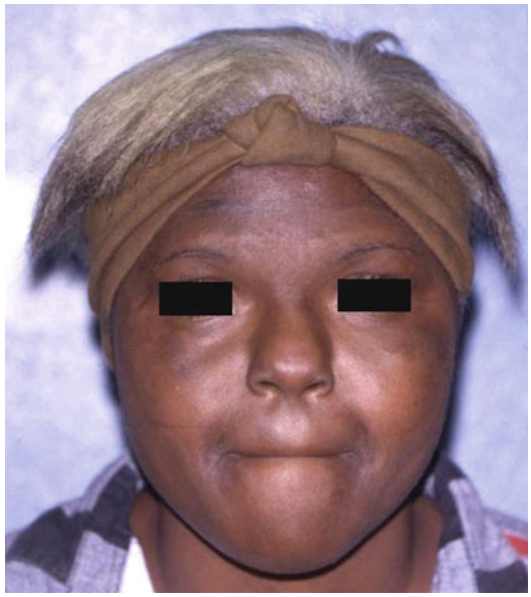

Fig. 3 A patient with Waardenburg syndrome. Notice grey forelock hair, broad-based brow, and increased interpalpebral space

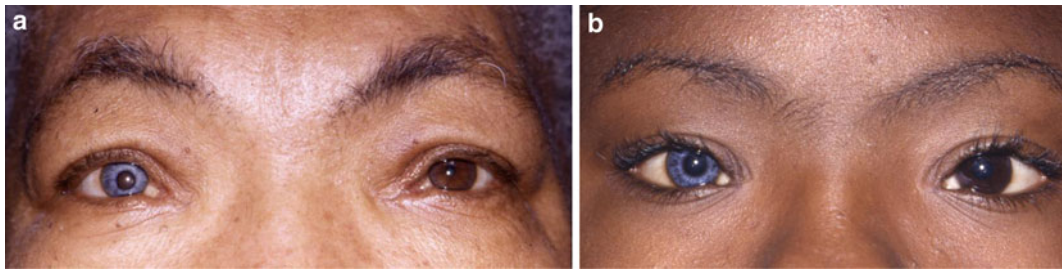

Fig. 4 (**a**, **b**) Two patients with Waardenburg syndrome showing iris heterochromia

Weill-Marchesani Syndrome

Contents

Weill-Marchesani syndrome (WMS), a rare connective tissue disorder, was first described by Weill in 1932 (Weill 1932) and further delineated by Marchesani in 1939 (Marchesani 1939). It is also known as spherophakia-brachymorphia syndrome or congenital mesodermal dysmorphodystrophy.

Synonyms and Related Disorders

Congenital mesodermal dysmorphodystrophy; Marchesani syndrome; Glaucoma-lens ectopia-microspherophakia-stiffness-shortness (GEMSS) syndrome; Spherophakia-brachymorphia syndrome

Genetics/Basic Defects

1. Autosomal dominant (AD) inheritance (Faivre et al. 2003b)
    1. Caused by heterozygous mutations within the fibrillin-1 gene which is mapped to chromosome 15q21.1 (Wirtz et al. 1996).
    2. Autosomal dominant WMS and Marfan syndrome appear to be allelic conditions at the fibrillin-1 locus.
    3. Coin the acronym GEMSS syndrome (Glaucoma, Ectopia, Microspherophakia, Stiff joints, Short stature) to distinguish this dominant Weill-Marchesani-like syndrome from the classic, recessively inherited syndrome (Verloes et al. 1992).
2. Autosomal recessive (AR) inheritance with occasional brachymorphism in heterozygotes
    1. Homozygosity mapping of an autosomal recessive WMS gene to chromosome 19p13.3-p13.2 (Faivre et al. 2002).
    2. *ADAMTS10* (a disintegrin-like and metalloprotease with thrombospondin motifs 10) mutation cause autosomal recessive Weill-Marchesani syndrome (Dagoneau et al. 2004; Shah et al. 2014; Steinkellner et al. 2014).
    3. ADAMTS10 is a member of the extracellular matrix protease family and is expressed in skin, fetal chondrocytes, and fetal and adult hearts.
3. Clinical homogeneity (fail to distinguish AR and AD inheritance in individual cases) and genetic heterogeneity (two modes of inheritance (AR and AD) have been reported) (Faivre et al. 2003a)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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4. Possible genetic carriers in the spherophakia-brachymorphia syndrome (Kloepfer and Rosenthal 1955)
    1. Criteria are presented which were found useful to distinguish 38 heterozygous carriers of the spherophakia-brachymorphia gene from 36 homozygous normals and 5 homozygous affected individuals.
    2. With the exception of 17 individuals (8 under 3 years old) information was sufficient to classify all persons observed.
    3. Four of these 17 could be placed in heterozygous or normal groups from pedigree relationship and subjective impressions.
    4. Anthropometric stigmata which were found most useful to distinguish the various genotypic groups were short stature, short fingers, and wide atd angles.

Clinical Features

1. Unable to distinguish autosomal recessive and autosomal dominant WMS by clinical features alone.
2. Proportionate short stature.
    1. Heights of adult males: 142–169 cm
    2. Heights of adult females: 130–157 cm
3. Ophthalmological features (Chu 2006).
    1. Microspherophakia (small spherical lens)
        1. The most important clinical feature of the syndrome
        2. Golden ring in the eyes due to reflection of light from 360° periphery of small crystalline globular lens (microspherophakia) with stretched zonules (Nayak et al. 2015)
    2. Ectopia lentis: usually results in downward displacement of the lens
    3. Lenticular myopia: usually the first ophthalmologic finding and is progressive
    4. Secondary glaucoma
        1. Resulting from pupillary block (Willi et al. 1973) in most cases due to forward movement of the lens or by dislocation of the lens into the anterior chamber
        2. The most serious complication because it can lead to blindness
4. Presenile vitreous liquefaction has been described in a large family with autosomal dominant WMS (Evereklioglu et al. 1999).
5. Skeletal features.
    1. Brachydactyly
    2. Enlarged interphalangeal joints
    3. Joints stiffness
    4. Pectus excavatum
    5. Scoliosis
6. Occasional cardiac features (Kojuri et al. 2007).
    1. Mitral valve prolapse
    2. Mitral valve insufficiency
    3. Mitral valve stenosis (van de Woestijne et al. 2004)
    4. Pulmonary hypertension
    5. Subvalvular fibromuscular aortic stenosis
    6. Congenital pulmonic valve stenosis
    7. Patent ductus arteriosus
    8. Ventricular septal defect
    9. Prolonged QT interval
7. Normal intelligence.
8. Similarity of geleophysic dysplasia and Weill-Marchesani syndrome (Kochhar et al. 2013).
    1. Although similar in phenotype, they can be distinguished clinically.
        1. Weill-Marchesani syndrome, on the basis of microspherophakia and ectopia lentis
        2. Geleophysic dysplasia by progressive cardiac valvular thickening, tracheal stenosis, and/or bronchopulmonary insufficiency, often leading to early death
    2. Mutations in *FBN1*, *ADAMTS10*, or *ADAMTS17* cause Weill-Marchesani syndrome by disrupting the microfibrillar environment, while geleophysic dysplasia is associated with enhanced TGF-β signaling mediated through mutations in *FBN1* or *ADAMTSL2*.
    3. A 35-year-old woman with geleophysic dysplasia, with short stature, small hands and feet, limitation of joint mobility, mild skin thickening, cardiac valvular disease, restrictive pulmonary disease, and microspherophakia was studied.

    1. Sequencing of *ADAMTSL2* demonstrated two changes: IVS8-2A>G consistent with a disease-causing mutation and IVS14-7G>A with potential to generate a new splice acceptor site and result in aberrant mRNA processing.
    2. The unaffected mother carries only the IVS8-2A>G transition providing evidence that the two changes are in trans-configuration in the patient.
9. The evolving phenotype of Weill-Marchesani syndrome – diagnostic confusion with geleophysic dysplasia (Pimienta et al. 2013).
    1. Clinical findings and evolving phenotype for a period of 18 years in a patient whose diagnosis, and distinguishing characteristics, transformed from geleophysic dysplasia to WMS.
    2. Molecular testing demonstrated novel mutations in the *ADAMTS10* gene confirming a diagnosis of autosomal recessive WMS in the proposita.

Diagnostic Investigations

1. Confirmation by molecular genetic testing in addition to clinical features.
    1. *ADAMTS10* sequence analysis available clinically to identified homozygous mutations in autosomal recessive WMS.
    2. Significance of mutations in *FBN1* in autosomal dominant WMS is unclear.
2. Carrier testing for relatives at risk requires prior identification of the disease-causing mutations in the family.
3. ECG and echocardiography (Kojuri et al. 2007).
    1. The most noteworthy ECG abnormality was prolonged QTc (QTc>0.46 sec) which was detected in three patients (50%).
    2. The most common echocardiographic abnormality was mitral valve prolapse (MVP) which was detected in three patients (50%), two of whom also had prolonged QTc.
    3. The criterion for the diagnosis of MVP was systolic displacement of the mitral valve leaflets by more than 2 mm above the plane of the annulus in the parasternal view.
    4. One patient had severe congenital valvular aortic stenosis (maximum gradient = 107 mmHg) and was scheduled for aortic valve replacement.
4. Ultrasound biomicroscopy: a useful technique to confirm the diagnosis of spherophakia (Macken et al. 1995).
5. The use of extended-depth spectral-domain optical coherence tomography supported the diagnosis of subclinical Weill-Marchesani syndrome in a patient without other commonly associated findings and provided a better understanding of the mechanism of angle closure in this patient (Cobot et al. 2014).
6. Electron microscopy and immunological studies of skin fibroblasts from WMS patients suggest that the syndrome is associated with impairment of the extracellular matrix.
7. Histology of the lens in the WMS (Fujiwara et al. 1990).
    1. Degeneration and necrosis of the epithelial cells of the lens are caused by various factors including aging, inflammation, trauma, and surgery.
    2. Destruction of the cortical fibers is a common histological change seen in lenses with senile cortical cataracts; in the present case of Weill-Marchesani syndrome it was considerable.
8. Histopathology of the lenses (Lim et al. 2016).
    1. The epithelial cell changes, hyaloid degeneration, and subcapsular cortical fiber changes.
    2. The authors attributed these changes to physical and mechanical factors, because the lens is highly mobile and often comes in contact with the iris.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib

1. Autosomal dominant inheritance
    1. Fifty percent risk if one parent is affected
    2. Recurrence risk: small if neither parent is affected
2. Autosomal recessive inheritance: 25% affected, 50% carriers

2. Patient's offspring
    1. Autosomal dominant inheritance: 50% risk
    2. Autosomal recessive inheritance: 100% obligatory carriers for a disease-causing mutation in the *ADAMTS10* gene

2. Prenatal diagnosis/preimplantation genetic diagnosis (Tsilou and MacDonald 2013)
    1. Prenatal diagnosis: If the disease-causing mutation(s) have been identified in the family, prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis (usually performed at ~15–18 weeks' gestation) or chorionic villus sampling (usually performed at ~10–12 weeks' gestation).
    2. Preimplantation genetic diagnosis: may be an option for some families in which the disease-causing mutation(s) have been identified.
3. Management
    1. Early detection and removal of an ectopic lens to decrease the possibility of pupillary block and glaucoma.
    2. A dislocated spherophakic lens may cause severe corneal endothelial dysfunction due to corneolenticular contact, and prompt lensectomy is important to prevent such complications (Chung et al. 2007).
    3. Medical treatment of glaucoma: difficult because of paradoxical response to miotics and mydriatics.
    4. Surgical management of glaucoma.
        1. Peripheral iridectomy to prevent or relieve pupillary block
        2. Trabeculectomy in advanced chronic angle closure glaucoma
    5. Airway management: difficult during anesthesia because of stiff joints, poorly aligned teeth, and maxillary hypoplasia.
    6. Periodic ophthalmic examinations for early detection and removal of an ectopic lens.
    7. Avoid ophthalmic miotics and mydriatics to prevent inducing pupillary block.
    8. Advanced chronic angle closure glaucoma in Weill-Marchesani syndrome may be treated with a combination of lensectomy, anterior vitrectomy, and sutured intraocular lens and Molteno tube shunt surgery (Harasymowycz and Wilson, 2004).
    9. Removal of the microspherophakia is recommended to control intraocular pressure and improve vision. Advanced glaucoma in Weill-Marchesani syndrome should be treated with combined glaucoma surgery and lens extraction (Guo et al. 2015).
    10. Anesthetic management (Dal et al. 2003; Karabiyik 2003).
        1. Airway control and intubation may be difficult in patients with WMS because of stiff joints, poorly aligned teeth, and maxillary hypoplasia with a narrow palate.
        2. Special consideration should be given to difficult intubation, cardiac abnormalities, and patient positioning (Riad et al. 2006).
        3. Secure the airway with a laryngeal mask airway (LMA) rather than an endotracheal tube.
        4. The LMA was inserted cautiously without hyperflexion or extension to the neck, with careful placement through the abnormal teeth structure.

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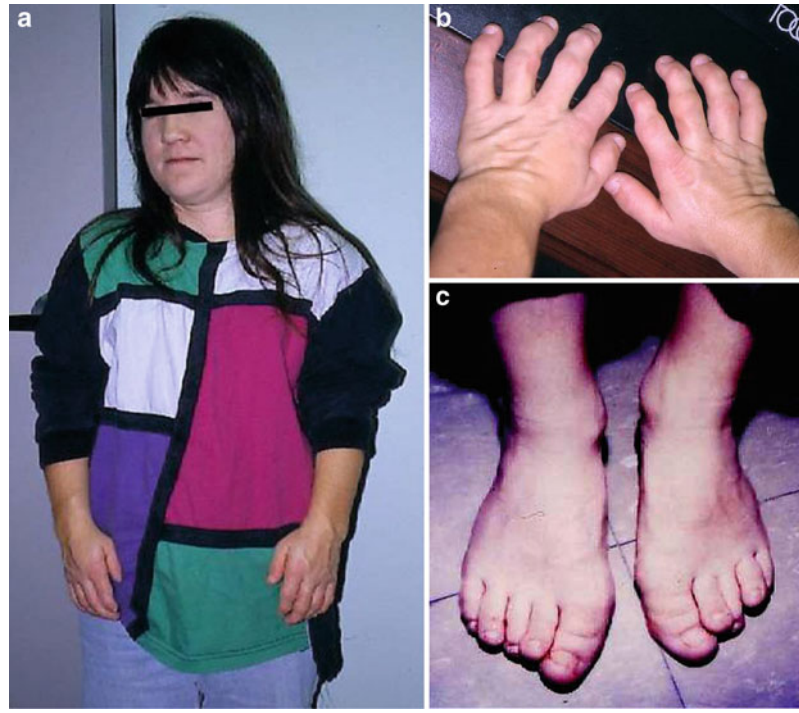

Fig. 1 (**a**–**c**) A 14-year-old female (**a**) with Weill-Marchesani syndrome. She had short stature, spherophakia, and brachydactyly. She was again followed at 30 years of age with findings of short stature, shallow orbits, small eyes, myopia, brachydactyly, and enlarged and stiff interphalangeal joints (**b**, **c**). Her daughter has small lens/cornea, short stature, and brachydactyly

Williams Syndrome

Contents

In 1961, Williams et al. (1961) described children with a constellation of abnormalities including "unusual" facial features, growth retardation, supravalvular aortic stenosis, and cognitive impairment. In 1962, Beuren et al. (1962) described a series of children with similar features, dental anomalies, peripheral pulmonary artery stenosis, and friendly personalities. Consequently, Williams syndrome (WS) is also known as Williams-Beuren syndrome (WBS). These characteristics are observed in virtually every patient with Williams syndrome, now known to be caused by a microdeletion of chromosome 7q11.23. The incidence of the syndrome is estimated to be between 1 in 20,000 and 1 in 50,000 live births.

Synonyms and Related Disorders

Chromosome 7q11.23 deletion syndrome; Williams-Beuren syndrome

Genetics/Basic Defects

1. Inheritance
   1. Sporadic new deletion in most cases
   2. Autosomal dominant inheritance with variable clinical expression within and between families (Morris et al. 1993; Õunap et al. 1998; Pankau et al. 2001)
   3. Rare autosomal dominant transmission of microdeletion involving the Williams syndrome critical region in a few cases
2. A disorder of microdeletion or contiguous gene deletion (Pober 2010)
3. Association of the elastin (*ELN*) gene disruption by chromosome translocation or partial deletion involving chromosome 7q11.23 and the supravalvular aortic stenosis (Curran et al. 1993): the first clue to the location of the Williams syndrome microdeletion
4. Caused by the haploinsufficiency of genes within a microdeletion of the long arm of chromosome 7 (7q11.23) involving the elastin locus (Lowery et al. 1995; Nickerson et al. 1995; Hirota et al. 1996)
5. Deletions in the *ELN* gene (Osborne 1999; Donnai and Karmiloff-Smith 2000)
   1. Pathogenesis (Ewart et al. 1993):
      1. Identification of hemizygosity at the elastin locus using genetic analyses in four familial and five sporadic cases of WS.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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   2. Fluorescent in situ hybridization and quantitative Southern analyses confirmed these findings, demonstrating inherited and de novo deletions of the elastin gene.
   3. These data indicate that deletions involving one elastin allele cause WS and implicate elastin hemizygosity in the pathogenesis of the disease.
2. Mechanism: deletions typically caused by unequal recombination during meiosis (Urban et al. 1996): The deletions are rather uniform in size as they arise spontaneously by inter- or intrachromosomal crossover events within misaligned duplicated regions of high sequence identity that flank the typical deletion (Francke 1999).
3. Deletion with equal frequency on the maternally or paternally inherited chromosome 7.
4. A total of at least 16 genes mapped within the commonly deleted interval.
5. *ELN* gene mutations:
   1. Responsible for supravalvular aortic stenosis and other vascular stenoses (Li et al. 1997)
   2. Possibly responsible for some of the connective tissue problems: lax joints, premature aging of the skin, joint contractures, a hoarse voice, bladder and bowel diverticula, hernias
   3. Majority of patients with Williams syndrome with large deletion spans (approximately 1.5 Mb of DNA), which contain many genes that contribute to the additional clinical symptoms not seen in patients with isolated supravalvular aortic stenosis
6. Genetic studies demonstrate that isolated nonsyndromic supravalvular aortic stenosis is associated with intragenic deletions within the *ELN* gene, while Williams syndrome involves deletions spanning the entire *ELN* gene (Lashkari et al. 1999).
7. Other genes identified in the commonly deleted region: e.g., *LIMK1*, *CLIP-115*, *CYLN2*, *GTF21RD1*, and *STX1A* (Jurado 2003; Hoogenraad et al. 2004). With the exception of elastin, no definite role in the Williams phenotype has been shown for these other genes to date, and indeed for many genes haploinsufficiency is unlikely to have an effect (Metcalfe 1999).
8. Neither LIMK1 hemizygosity (contrary to a previous report) nor STX1A hemizygosity is likely to contribute to any part of the WS phenotype, and they emphasize the importance of such patients for dissecting subtle but highly penetrant phenotypes (Tassabehji et al. 1999).

Clinical Features

1. Characteristic dysmorphic facies (Burn 1986), frequently referred to as elfin facies (100%). Effort must be made to curtail the use of "elfin facies" to denote a resemblance to a mythological creature since the term is not well received by family members (Lashkari et al. 1999; American Academy of Pediatrics Committee on Genetics 2001).
   1. Broad forehead
   2. Medial eyebrow flare
   3. Strabismus
   4. Periorbital fullness
   5. Stellate lacy iris pattern
   6. Short nose with bulbous nasal tip
   7. Flat nasal bridge
   8. Malar flattering
   9. Prominent full cheeks and lips
   10. Long smooth philtrum
   11. Wide mouth
   12. Pointed chin
   13. Mild micrognathia
   14. Long narrow face and long neck in older children and adults
2. Spectrum and significance of ocular features (Greenberg and Lewis 1988)
   1. A stellate pattern of the anterior iris stroma which was observed only in individuals with blue or hazel iris color (62%)
   2. Strabismus (29%), most commonly esotropia
   3. Hypermetropic discs (55%)

4. A simplex vertical branching of the central retinal vessels at the disc (70%)
5. Situs inversus vasorum (15%)

3. Cardiovascular diseases (Hallidie-Smith and Karas 1988; Eronen et al. 2002)
   1. Supravalvular aortic stenosis (80%), often a progressive condition that may require surgical repair
   2. Generalized arteriopathy (narrowing of arteries secondary to abnormal elastin protein, an important component of elastic fibers in the arterial wall)
      1. Arterial stenoses make up the large majority of cardiovascular issues in patients with WS (Collins 2013). Sudden death in patients with WS is significantly greater than in the general population. Prolongation of the QTc is common in patients with WS.
      2. Peripheral pulmonary artery stenosis often present in infancy and usually improves over time.
      3. Possible worsening over time of the coarctation of the aorta, renal artery stenosis, and systemic hypertension.
      4. Possible narrowing of any arterial wall since elastin protein is an important component of elastic fibers in the arterial wall.
   3. Other congenital cardiac defects
      1. Mitral valve prolapse (11.6%)
      2. Bicuspid aortic valve (15%)
      3. Aortic hypoplasia
      4. Septal defects
      5. Left ventricular hypertrophy
4. Variable mental retardation (75%)
5. Characteristic cognitive/behavioral profile (90%) (Pober and Dykens 1996)
   1. Characteristic behavioral pattern
      1. Relative preservation of linguistic abilities
      2. Gross deficiencies in visual-spatial processing and motor skills
   2. Motor disabilities affecting balance, strength, coordination, and motor planning
   3. Delayed speech acquisition, followed by excessive talking ("cocktail party" verbal abilities)
   4. Overfriendliness and an empathetic nature
   5. Uncontrollable loquacity
   6. Behavioral problems (Kaplan et al. 2001)
      1. Hypersensitivity to sound (hyperacusis)
      2. Sleep problems
      3. Attention deficit/hyperactivity disorder (ADHD)
      4. Anxiety
      5. Distractability
      6. Inflexibility
      7. Ritualism
   7. A cognitive and behavioral phenotype (Udwin and Yule 1991)
      1. Concentration difficulties.
      2. Excessive anxiety.
      3. Poor relationships with peers.
      4. Significantly poorer visuospatial and motor skills.
      5. However, the Williams syndrome children were not uniformly poor in all areas of nonverbal abilities.
6. Other features
   1. Growth
      1. Postterm birth (>41 weeks)
      2. Failure to thrive
      3. Short stature (50%)
      4. Hypothyroidism
      5. A premature and abbreviated pubertal growth spurt
   2. CNS/neurologic findings (Chapman et al. 1996)
      1. Tone abnormalities varied as a function of age, with younger children frequently exhibiting decreased tone and older subjects almost exclusively having increased tone (muscle hypotonia early, muscle tone increases with age, hypertonia in some cases)
      2. The gait (awkward gait) and coordination abnormalities (poor coordination) persisted among older subjects, indicating that they were not simply maturational problems.
      3. Chiari I malformation.
      4. Hyperreflexia of the lower extremities.
   3. EENT
      1. Ocular findings
         1. Strabismus

2. Hyperopia
3. Stellate iris
4. Retinal vessel tortuosity

2. Chronic otitis media
3. Sensorineural and/or conductive hearing loss: present in 22.6% of children and adults with WS (Barozzi et al. 2012)
4. Dental abnormalities
    1. Hypodontia/Microdontia
    2. Malocclusion
    3. Overbite
    4. Excessive interdental spacing
    5. Small roots
    6. High incidence of caries
5. A hoarse or brassy voice

4. GI
    1. Difficulty feeding
    2. Gastroesophageal reflux/vomiting
    3. Prolong colic
    4. Bowel diverticula
    5. Hernias
    6. Rectal prolapse
    7. Constipation
    8. Peptic ulcers
5. Renal findings (Pober et al. 1993)
    1. Bladder diverticula: the most common defects
    2. Renal artery stenosis
    3. Renal agenesis
    4. Marked asymmetry in kidney size
    5. Small kidneys
    6. Solitary kidney
    7. Pelvic kidney
    8. Duplicated kidneys
    9. Horseshoe kidney
    10. Renal cysts
    11. Nephrocalcinosis
    12. Vesicouriteral reflux
6. Orthopedic problems
    1. Low/hoarse voice
    2. Hernias
    3. Joint laxity mostly during infancy
    4. Joint contractures may develop by childhood and adolescence (50%).
    5. Radioulnar synostosis
    6. Kyphosis
    7. Lordosis
    8. Scoliosis
    9. Hallux valgus
    10. Hypoplastic nails
    11. Clinodactyly of fifth fingers
7. Social phenotype of Williams syndrome (Järvinen et al. 2013)
    1. A strong drive to approach strangers
    2. A gregarious personality
    3. Heightened social engagement yet difficult peer interactions
    4. High nonsocial anxiety
    5. Unusual bias toward positive affect
    6. Diminished sensitivity to fear
8. Idiopathic infantile hypercalcemia (15%)
    1. Symptoms and signs of hypercalcemia (usually resolves during childhood)
        1. Extreme irritability
        2. Vomiting
        3. Constipation
        4. Muscle cramps
    2. Possible lifelong persistence of abnormal calcium and vitamin D metabolism
    3. Hypercalcinuria predisposing to nephrocalcinosis
9. Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome (Bellugi et al. 1990)
    1. A dissociation between language and cognitive functions in Williams syndrome adolescents
    2. Exhibit an unusual fractionation of higher cortical functioning, with marked cognitive deficits, but selective sparing of syntax
    3. Peaks and valleys of abilities specific to Williams syndrome individuals
10. Three physical manifestations were noted which have not been emphasized in the previous reports of this condition (Morris and Carey 1990)
    1. Unusual sacral creases were found in 25/48 patients
    2. A linear array of hemangiomas (nevus flammeus) on the back in 3/48
    3. Limitation of supination in 5/48
11. Natural history of Williams syndrome: a progressive disorder with multisystem involvement (Morris et al. 1988)

12. Williams syndrome in adults (Morris et al. 1990)
    1. Variable in clinical presentation, ranging from severely affected patients with complicated medical histories to mildly affected patients who are generally in good health (Lopez-Rangel et al. 1992).
    2. Cardiovascular complications were common including hypertension, supravalvular aortic stenosis, aortic hypoplasia, pulmonic artery stenosis, peripheral stenoses, and mitral valve prolapse.
    3. Joint limitation was progressive, often accompanied by kyphoscoliosis and lordosis.
    4. Recurrent urinary tract infections led to radiologic studies showing urethral stenosis and bladder diverticula and vesicoureteral reflux.
    5. Gastrointestinal problems included obesity, chronic constipation, diverticulosis, and cholelithiasis.
    6. Hypercalcemia was documented, although others had hypercalcemic symptoms (abdominal pain, polyuria, and constipation).
    7. One 45-year-old man had parathyroid hyperplasia.

Diagnostic Investigations

1. Echocardiography for cardiac lesions.
2. Ultrasonography:
    1. Bladder and kidneys
    2. Intravascular ultrasound imaging: to detect vascular wall thickening with secondary lumen narrowing
3. Serum creatinine level.
4. Blood calcium levels to detect hypercalcemia during early infancy.
5. Thyroid function test.
6. Ophthalmologic evaluation for strabismus and retinal vessel tortuosity.
7. Urinalysis to detect hypercalcinuria.
8. Renal ultrasound for possible nephrocalcinosis if hypercalcinuria is noted.
9. Intravascular ultrasound imaging: to detect generalized arteriopathy (Rein et al. 1993).
10. Radiography: osteosclerosis of the metaphyses of long bones, the skull vault, or lamina dura of the alveolar bone in adolescence and adulthood, if overt hypercalcemia is present.
11. Multidetector row computed tomography (MDCT) (Das et al. 2014):
    1. Arterial stenosis is a matter of concern for the majority of patients with WBS. Most affected patients experience a mild course, but a small number, especially those with associated coronary artery disease and SVAS, require careful observation either with echocardiography or other noninvasive imaging.
    2. MDCT evaluation of complex cardiovascular abnormalities of WBS including coronary artery disease is feasible with modern MDCT scanners.
12. Several unreported biochemical alterations, related to haploinsufficiency for specific genes at 7q11.23, are relatively common in WBS (Palacios-Verdú et al. 2014):
    1. Triglyceride plasma levels were significantly decreased in individuals with WBS while cholesterol levels were slightly decreased compared with controls.
    2. Hyperbilirubinemia, mostly unconjugated, was found in 18.3% of WBS cases and correlated with subclinical hypothyroidism and hypotriglyceridemia, suggesting common pathogenic mechanisms.
13. Full cytogenetic studies:
    1. Larger deletions detectable by standard cytogenetic techniques, especially by high-resolution chromosome analysis
    2. To rule out possible chromosomal rearrangements involving the 7q11.23 locus as well as any other cytogenetic abnormalities
14. Fluorescence in situ hybridization (FISH) with a cosmid probe corresponding to *ELN* for diagnostic testing: remains the most

widely used laboratory test (Lowery et al. 1995)
1. Ninety-nine percent of the patients with a hemizygous submicroscopic deletion of 7q11.23 detectable by FISH
2. Cases undetectable by FISH
    1. Rare cases with a smaller deletion which does not fully encompass the FISH probe
    2. Cases with phenocopies of Williams syndrome with same clinical phenotype produced by mutation or deletion of other gene(s)
    3. Cases with a Williams syndrome-like phenotype associated with various cytogenetic rearrangements

15. Other diagnostic laboratory tests (Pober 2010):
    1. Microsatellite marker analysis.
    2. Intragenic restriction fragment length polymorphism (RFLP) and the gene dosage of ELN using FP4 probe (Mari et al. 1995).
    3. Multiplex ligation-dependent probe amplification.
    4. Quantitative polymerase-chain-reaction (qPCR) assay.
    5. Array comparative genomic hybridization (array-CGH).
    6. Array-CGH and qPCR are useful for detection of deletion sizes and prediction of the interrupted genes and their impact on the disease phenotype (Hussein et al. 2016).
16. Molecular genetic testing (to detect deletion of the WBSCR critical region) (Morris 2013):
    1. FISH
    2. Deletion/duplication testing

Genetic Counseling

1. Recurrence risk
    1. Patient's sib (Lashkari et al. 1999):
        1. Recurrence risk low (<1%) (most cases are sporadic and neither parent is affected).
        2. Presence of a small theoretical risk of germ line mosaicism in an unaffected parent (Kara-Mostefa et al. 1999).
        3. If a parent is affected, the risk is 50%.
    2. Patient's offspring: 50% recurrence risk of having an affected offspring in individuals who have the deletion of the Williams syndrome critical region (parent-to-child transmission observed occasionally)
2. Prenatal diagnosis
    1. Prenatal ultrasonography: a well-defined WBS prenatal phenotype cannot be delineated (Marcato et al. 2014)
    2. Amniocentesis or CVS
        1. Rarely utilized because most cases are sporadic and no prenatal indicators exist for low-risk pregnancies
        2. Utilized for pregnancies at 50% risk of having Williams syndrome
        3. FISH probe covering approximately 180 kb of the critical region deleted in the Williams syndrome including *ELN* gene, lim-kinase1 (*LIMK1*), and the D7S613 locus
3. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require molecular genetic testing that detects deletion of the WBSCR (Morris 2013)
4. Management
    1. Management of hypercalcemia (Lashkari et al. 1999)
        1. Limit high calcium food
        2. Avoid preparations containing vitamin D
    2. Supravalvular aortic stenosis (a life-threatening component of the phenotype): surgically correctable
    3. Early dental care
    4. Education and vocational concerns
        1. Early daily learning activities and strategies
            1. Auditory cues
            2. Music activities, singing/rhyming songs, and toys with soft sounds
            3. Teaching communication skills through daily routines
            4. Use of language expansions and parallel talk
        2. Special education for older children

3. Restrictive levels of care required for most adult patients
5. Social and emotional concerns
   1. At increased risk for exploitation and abuse
   2. Teaching of appropriate social skills
6. Psychotherapy
   1. Verbally oriented psychotherapy
   2. Group therapy

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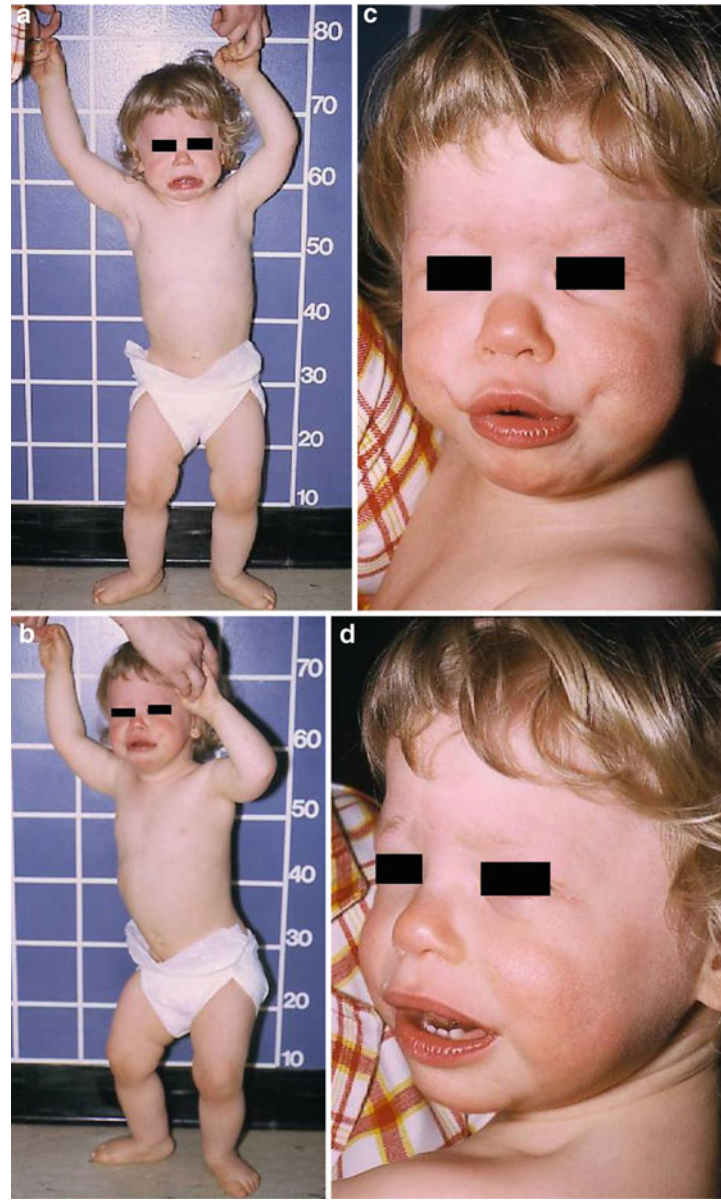

Fig. 1 (**a**–**d**) An infant with Williams syndrome showing periorbital fullness, stellate lacy iris pattern, flat nasal bridge, short nose with bulbous tip, wide mouth, and full cheeks and lips

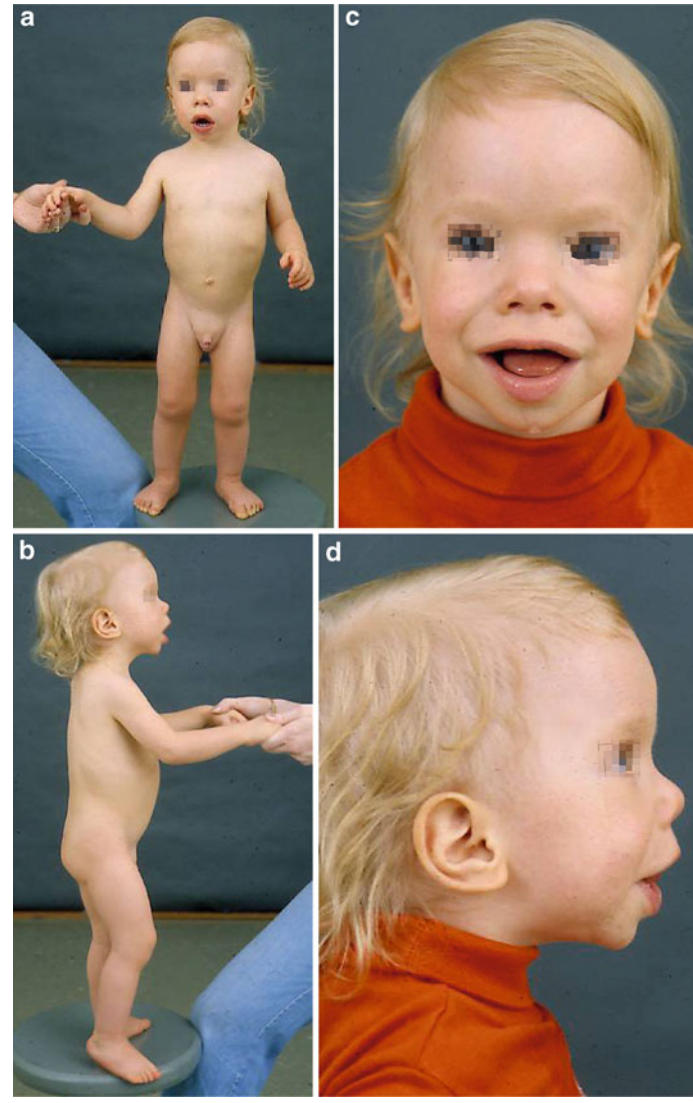

Fig. 2 (**a**–**d**) A child with Williams syndrome showing similar features

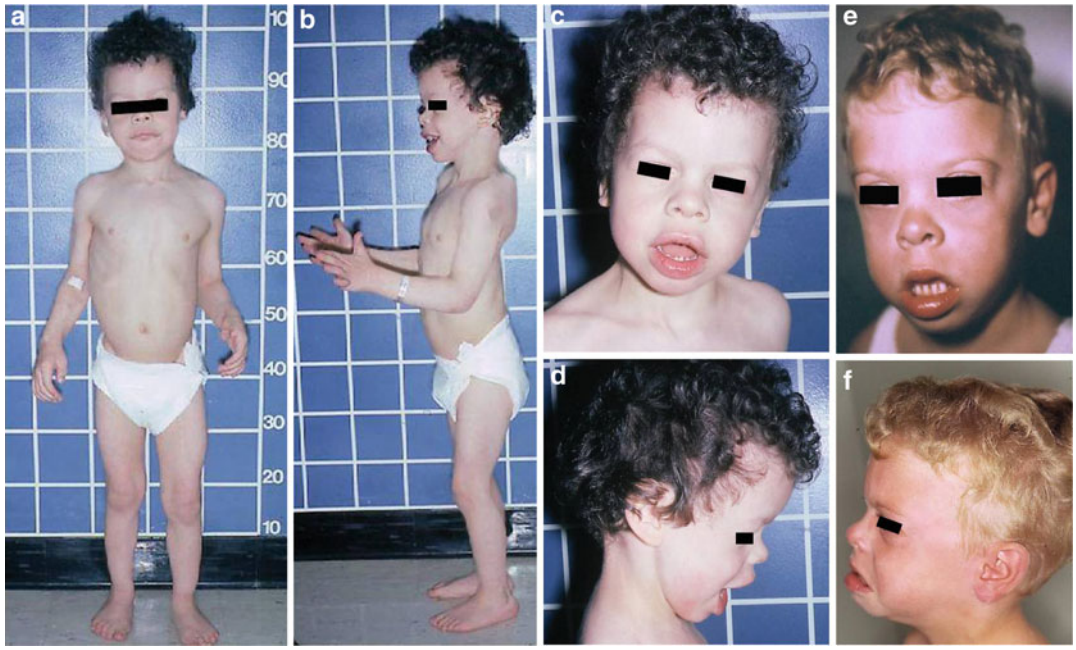

Fig. 3 (**a**–**f**) Two young children (**a**–**d**, **e**, **f**) with Williams syndrome showing characteristic facial appearance

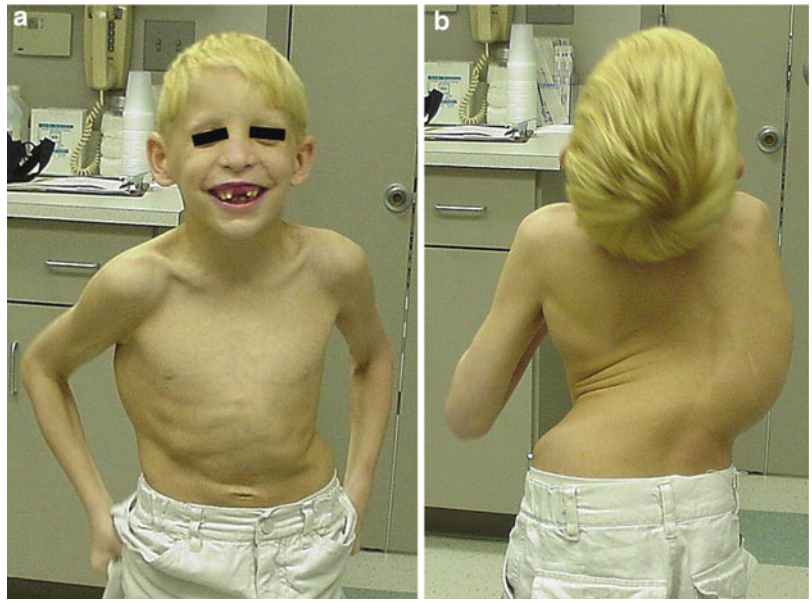

Fig. 4 (**a**, **b**) A child with Williams syndrome and severe scoliosis

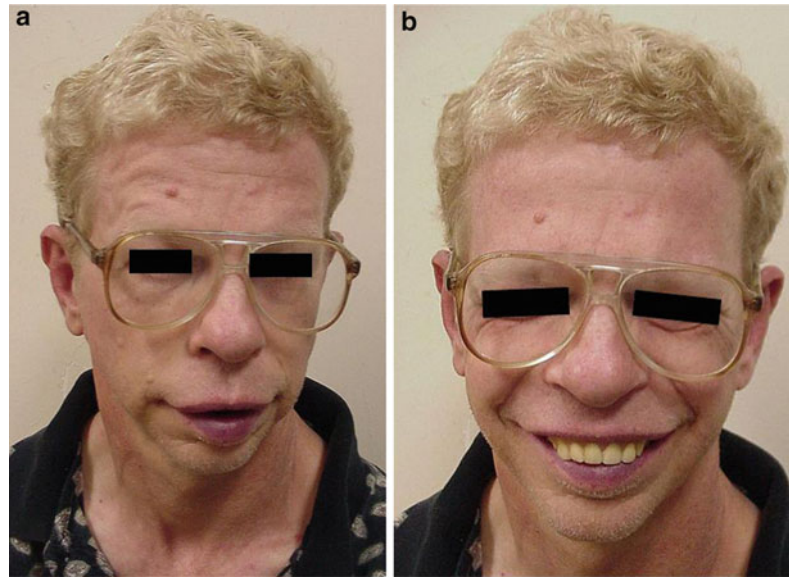

Fig. 5 (**a**, **b**) An adult with Williams syndrome confirmed by FISH studies

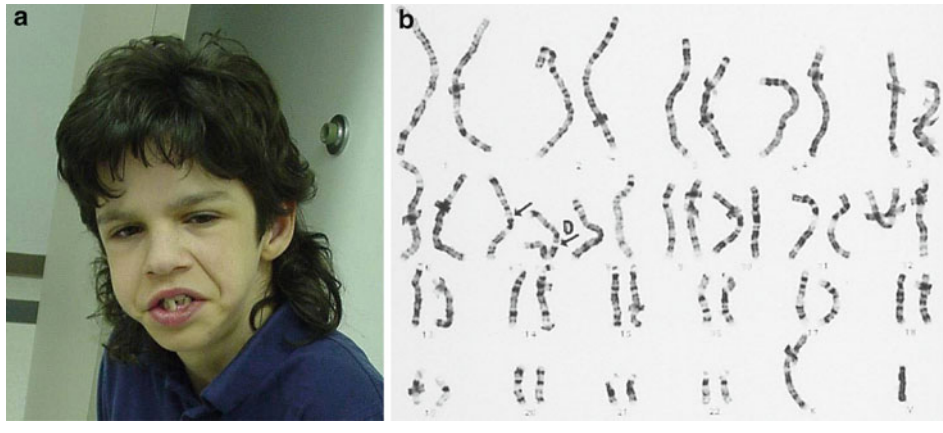

Fig. 6 (**a**, **b**) A child (**a**) with Williams syndrome. A G-banded karyotype showing del(7q11) (*arrow* with D) (**b**)

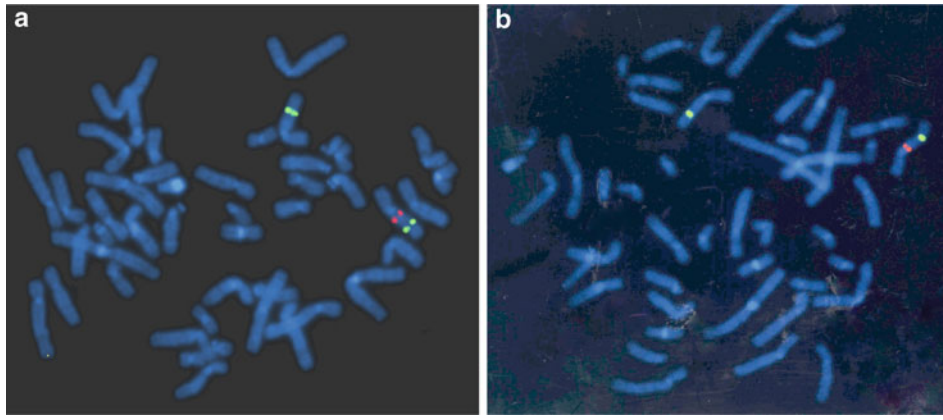

Fig. 7 (**a**, **b**) FISH showing the classic microdeletion seen in Williams syndrome (7p11.23) [LSI® Williams Syndrome (Elastin Gene) Region Probe, Vysis/Abbott]. The metaphase cells show only one chromosome 7 homologue with the orange signal (normal chromosome 7). The hemizygous deletion is shown on the chromosome with only the green loci [internal control probes for D7S486 and D7S522 (7q31)]

Winchester Syndrome

Contents

Winchester syndrome was one of the first recognized autosomal-recessive, multicentric forms of the disorder. It was originally described nearly 50 years ago in two sisters with severe skeletal and joint deformities. Their unaffected, healthy parents were first cousins (Winchester et al. 1969). The children suffered from progressive bilateral and symmetric osteolysis of the carpals and tarsals, interphalangeal joint erosions mimicking juvenile idiopathic arthritis, generalized osteoporosis, and eventual loss of function of the larger joints, including the shoulder, elbow, hip, and knee joints.

Synonyms and Related Disorders

Arthritis; Inherited osteolysis syndromes; Multicentric osteolysis; Multicentric osteolysis, nodulosis, and arthropathy (MONA); Nodulosis, arthropathy, and osteolysis (NAO); Torg syndrome; "Vanishing bone" syndromes

Genetics/Basic Defects

1. Winchester syndrome is caused by mutations of matrix metalloproteinase 2 gene (*MMP2*) located on chromosome 16q13-q21 (Martignetti et al. 2001; Rouzier et al. 2006).
2. Homozygous mutations in membrane type-1 metalloproteinase (MT1-MMP or MMP14): identified in the cultured fibroblasts from a patient with Winchester syndrome. The resulting hydrophobic-region signal-peptide substitution (p.Thr17Arg) decreases MT1-MMP membrane localization with consequent impairment of pro-MMP2 activation (Evans et al. 2012).
3. MONA (multicentric osteolysis, nodulosis, and arthropathy [MIM 259600]) and Winchester syndromes have been grouped together as allelic disorders on the basis of their phenotypic overlap and the discovery of *MMP2* mutations in two recently diagnosed Winchester families (Al Aqeel et al. 2000; Al-Aqeel 2005; Zankle et al. 2005, 2007; Mosig et al. 2008).

Clinical Features

1. Onset of the condition: toward the end of the first year of life with symmetrical painful swelling of the hands, fingers, wrists, and ankles (Al Kaissi et al. 2011).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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2. Intermittent polyarthralgia: resulting in progressive joint contractures.
3. Oval or linear raised areas of thickened skin may appear over the back, flanks, and lateral aspects of the arm. These lesions spread to cause leathery, thickened, hypertrichotic, and pigmented skin.
4. Other features:
    1. Corneal opacities appearing in mid-childhood
    2. Retarded growth
    3. Carpal and tarsal osteolysis
    4. Rheumatoid-like destruction of the small joints
    5. Gingival hypertrophy
5. Classification of osteolysis described by Hardegger et al. (1985):
    1. Type 1, hereditary multicentric osteolysis with dominant transmission
    2. Type 2, hereditary multicentric osteolysis with recessive transmission
    3. Type 3, nonhereditary multicentric osteolysis with nephropathy
    4. Type 4, Gorham–Stout syndrome
    5. Type 5, Winchester syndrome defined as a multicentric disease of autosomal-recessive inheritance
6. Classification of osteolysis as proposed by the 2001 Nosology of the International Skeletal Dysplasia Society (Spranger et al. 2002):
    1. Multicentric hands and feet
        1. Multicentric carpal–tarsal osteolysis with and without nephropathy: AD
        2. Winchester syndrome: AR
        3. Torg syndrome (includes NAO syndrome) (Torg et al. 1969): AR (*MMP2* mutations)
    2. Distal phalanges
        1. Hajdu–Cheney syndrome: AD
        2. Mandibuloacral syndrome: AR
    3. Diaphyses and metaphyses
        1. Familial expansile osteolysis: AD (*RANK* mutation)
        2. Juvenile hyaline fibromatosis including systemic juvenile hyalinosis: AR (*CMG2* mutations)
7. Zankl et al. (2005, 2007) defined a continuous clinical spectrum involving Torg syndrome, Winchester syndrome (OMIM 277950), and NAO syndrome.
    1. Torg syndrome
        1. Presence of multiple, painless, subcutaneous nodules and mild to moderate osteoporosis and osteolysis that is usually limited to the hands and feet.
        2. Radiographically, the osteolysis is accompanied by a characteristic widening of the metacarpal and metatarsal bones.
    2. NAO syndrome
        1. Only been described in patients from Saudi Arabia
        2. Generally more severe, with multiple prominent and painful subcutaneous nodules, massive osteolysis in the hands and feet, and generalized osteoporosis
        3. Additional features including coarse face and body hirsutism
    3. Winchester syndrome
        1. There are severe osteolysis in the hands and feet and generalized osteoporosis and bone thinning, similar to NAO, but subcutaneous nodules are characteristically absent.
        2. Various additional features including coarse face, corneal opacities, gum hypertrophy, and EKG changes.
8. Differential diagnosis (Vanatka et al. 2011):
    1. Juvenile idiopathic arthritis
        1. Positive rheumatoid factor test
        2. Presence of rheumatoid nodules
        3. Characteristic pattern of bone destruction
        4. Painful periarticular inflammation
        5. Increased erythrocyte sedimentation rate
    2. Other osteolytic and arthritis-like diseases and syndromes
        1. Idiopathic multicentric osteolysis: a uncommon disease presenting during childhood with resorption of the carpus and tarsus with nephropathy
        2. Inherited multicentric osteolysis (Lee et al. 2010)

1. A rare familial skeletal condition characterized by osteolysis leading to bone dysplasia.
2. Affected patients frequently experience pain, dysfunction, and disability.
3. The condition has been reported in literature with synonymous names such as "vanishing bone" syndrome; inherited osteolysis/arthritis syndromes; multicentric carpal–tarsal osteolysis; nodulosis, arthropathy, and osteolysis (NAO); and Torg–Winchester syndrome (Al Aqeel et al. 2000; Martignetti et al. 2001; Mosig et al. 2007).
4. Clinical symptoms or signs usually occur early in childhood (usually 2nd or 3rd year of life). Findings include multiple bone and joint pain and bony "dysplasia" with associated decreased range of movement and function.
5. Diagnosis is usually made with characteristic osteolytic changes on radiological investigations.
6. Serologic and histologic investigations are always negative for classical inflammatory or autoimmune causes.

Diagnostic Investigations

1. Radiology (Grover et al. 2009)
   1. Multifocal osteoporosis
   2. Progressive osteolysis
   3. Degenerative changes in the vertebral bodies and carpal and tarsal bones, including the metaphyses and epiphyses
2. Diagnostic criteria (Winter 1989): above skeletal radiologic characteristics combined with at least two of the following features:
   1. Short stature
   2. Progressive articular contractures
   3. Corneal opacities
   4. Thickened hyperpigmentation or hirsutism of the skin
   5. Hypertrophy of the gums
   6. Coarsened facial features
3. Molecular genetic analysis of *MMP2* gene (clinical research laboratories listed in www.GeneTests.org)
   1. Multicentric osteolysis, nodulosis, and arthropathy: sequence analysis of the entire coding region
   2. Winchester syndrome: sequence analysis of the entire coding region

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is also a carrier
2. Prenatal diagnosis: has not been accomplished
3. Management
   1. Anti-inflammatory therapy
   2. Surgical treatments, including soft tissue release with pinning or joint arthrodesis, may offer pain relief and improve alignment, but outcomes are inconsistent.
   3. Pamidronate treatment in multicentric osteolysis
      1. It was reported to show no improvement in peripheral osteolysis in multicentric osteolysis and nodular arthropathy caused by mutation in matrix (Phadke et al. 2007).
      2. Patients with inherited multicentric osteolysis may benefit from bisphosphonate therapy. These benefits may include pain relief, decreased analgesic requirements, improved BMD, and potentially reducing new fracture or osteolytic collapse risk (Lee et al. 2010).

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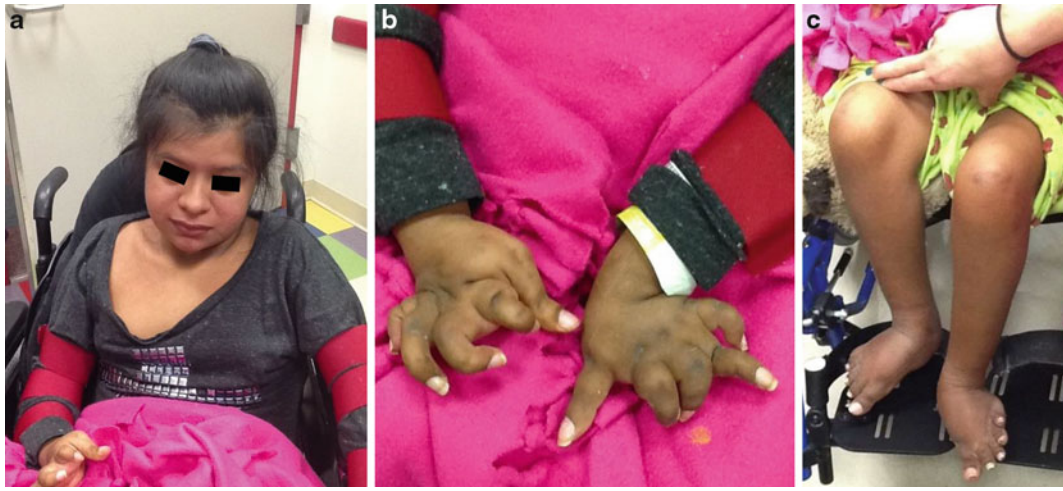

Fig. 1 (**a**–**c**) A 17-year-old Hispanic female was admitted for evaluation of severe joint contractures. Symptoms started at 2 years of age with fever, joint pain, and swelling. She was diagnosed with juvenile idiopathic arthritis (*JIA*) and treated with corticosteroids, methotrexate, and anti-inflammatory medications. Therapy was subsequently discontinued due to lack of response. Her symptoms progressed to joint contractures and inability to walk. Her brother had similar disease and died of respiratory complications at the age of 14 years. On examination, the patient was a small-built, wheelchair-bound teenager with severe flexion contractures in the wrists, fingers, knees, ankles, and toes without synovitis or joint effusions. Laboratory studies showed no signs of inflammation, and rheumatoid factor (RF) and anti-cyclic citrullinated peptide were negative (Velayuthan et al. 2014). Based on the clinical and following radiographic findings, the patient was diagnosed with Winchester syndrome

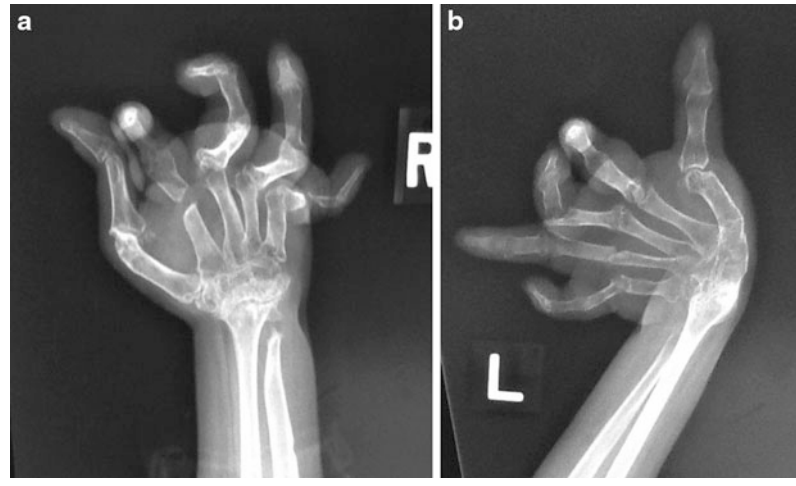

Fig. 2 (**a**, **b**) Fingers, hands, and wrists are markedly deformed with destructive arthritis in metacarpal, phalangeal, and interphalangeal joints. Distal ends of both ulnas and distal end of the second metacarpal/proximal end of the second proximal phalange of the right hand are markedly eroded. Generalized osteopenia of phalanges and metacarpals with thin cortices seen as thin (pencil) lines are noted

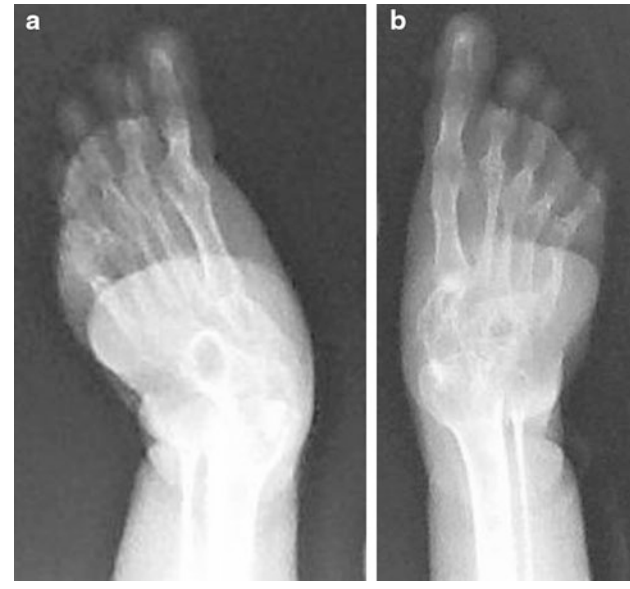

Fig. 3 (**a**, **b**) Destruction of tarsals and fusion of interphalangeal joints are seen on both foot

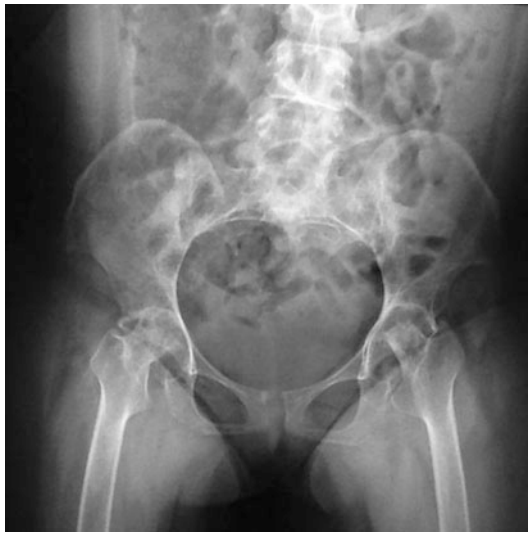

Fig. 4 Erosion of left femoral head is seen

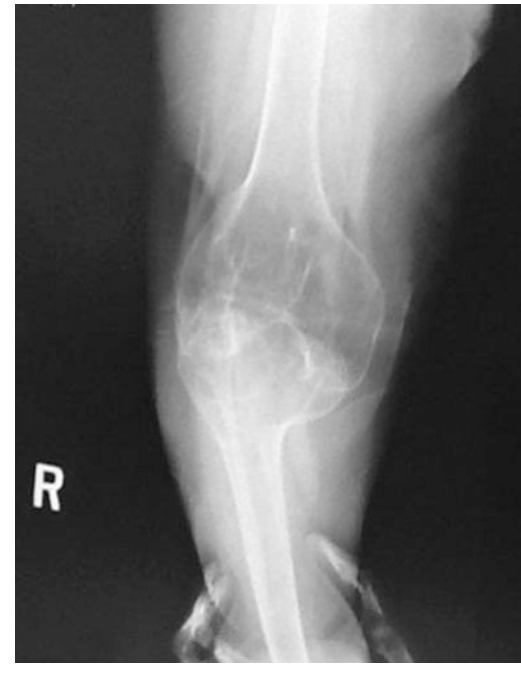

Fig. 5 The knees are ankylosed (only right knee is shown)

Wolf–Hirschhorn Syndrome

Contents

Wolf–Hirschhorn syndrome (WHS) is a chromosome 4p deletion syndrome, first described by Cooper and Hirschhorn in 1961, followed by the report of Wolf et al. in 1965. The incidence is estimated to be approximately 1 in 50,000 births.

Synonyms and Related Disorders

Chromosome 4p16.3 deletion syndrome; Pitt-Rogers-Danks syndrome

Genetics/Basic Defects

1. Caused by the deletion of the distal short arm of chromosome 4 (Altherr et al. 1997; Dufke et al. 2000; Battaglia et al. 2001)
    1. Variable size of the deletion
    2. Deletion of the terminal band (4p16.3): essential for full expression of the phenotype
    3. Identification of a 165 kb minimal critical region (WHSCR) within 4p16.3 (Wilson et al. 1981; Wright et al. 1997; Rauch et al. 2001)
    4. Mechanism of deletions
        1. De novo deletions (75%): interstitial deletion of preferential paternal origin (Dallapiccola et al. 1993) in 85–90%
        2. Deletions resulting from unusual cytogenetic abnormality (12%) such as ring chromosome 4
        3. Deletions resulting from unbalanced product of a parental chromosomal rearrangement (Ogle et al. 1996), usually of a reciprocal translocation (Lurie et al. 1980) (10–15%)
2. Types of chromosome abnormalities
    1. Detectable by conventional cytogenetic technique: large deletions
    2. Detectable only by molecular methods
        1. Terminal microdeletions
        2. Interstitial microdeletions
        3. Cryptic translocations
3. Genotype–phenotype correlation (Wieczorek et al. 2000; Zollino et al. 2000, 2003, 2008)
    1. Patients with a large 4p16.3 deletion, averaging between 5 and 18 Mb: causing the widely recognizable WHS phenotype.
        1. Severe mental and growth retardation
        2. Major malformations
        3. Seizures
        4. Characteristic facial appearance with wide forehead, large and protruding

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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eyes, hypertelorism, prominent glabella, down-turned mouth, and micrognathia
2. Patients with a 4p16.3 microdeletion not exceeding 3.5 Mb.
   1. Milder phenotype
   2. Lack major congenital malformations
3. Patients with a very large deletion exceeding 22–25 Mb, causing a severe phenotype that can hardly be defined as typical WHS.
4. Using genotype–phenotype correlation analysis in eight informative patients, Zollino et al. (2003) characterized the following distinctive WHS clinical signs that represent the minimal diagnostic criteria for this condition and mapped this basic phenotype outside the currently defined WHSCR and designated as a new critical region, WHSCR-2.
   1. Presence of typical facial appearance
   2. Mental retardation
   3. Growth delay
   4. Congenital hypotonia
   5. Seizures
5. Genotype–phenotype correlation study using microarray and FISH-based molecular cytogenetic investigations (Shimizu et al. 2014).
   1. Chromosomal rearrangements in all patients including previously unreported complex chromosomal mosaicism.
   2. Demonstrated the correlation of deletion size from 4pter with seizure severity and with occurrence of renal hypoplasia/dysplasia and structural ocular anomalies.
   3. Described additional clinical features including hypercholesterolemia.
   4. Moreover, a new susceptible region distal to the previously supposed candidate gene *LETM1* was suggested for the occurrence of seizures.

4. *LETM1* (Schlickum et al. 2004)
   1. A gene deleted in WHS encodes mitochondrial protein.
   2. Current evidence suggests that at least some (neuromuscular) features of WHS may be caused by mitochondrial dysfunction.

Clinical Features

1. Maternal gestational history (Battaglia et al. 2015)
   1. Intrauterine growth retardation
   2. Decreased fetal movements
   3. Small placenta
2. Developmental history
   1. Delayed psychomotor development
   2. Difficulty in ambulation, often with ataxic gait
   3. Seizures (>75% of cases)
3. Behavior history
   1. Stereotypes
      1. Holding the hands in front of the face
      2. Hand washing or flapping
      3. Patting self on chest
      4. Rocking
      5. Head shaking
      6. Stretching of legs
   2. Absence of speech
   3. Babbling or guttural sounds, occasionally modulated in a communicative way
   4. Comprehension limited to simple orders or to a specific context
   5. Affect disorder that improves over time
   6. Walking with or without support
   7. Self-feeding
   8. Helps in dressing and undressing self
   9. Improved abilities and adaptation to new situations
   10. Communicative abilities and verbal comprehension with extension of the gesture repertoire and decreased occurrence of withdrawal and anxiety behaviors
4. Growth: Severe growth retardation (short stature)

5. CNS
    1. Profound mental retardation
    2. Microcephaly
    3. Seizures (50–100%)
    4. Congenital hypotonia with muscle hypotrophy particularly of the lower limbs
    5. Malformation (33%)
        1. Hypoplasia of cerebellum
        2. Cavum or absent septum pellucidum
        3. Agenesis of corpus callosum
        4. Hypoplasia or absence of olfactory bulbs and tracts
        5. Microgyria
        6. Migration defects
        7. Hydrocephalus
6. Skull
    1. Frontal bossing
    2. High frontal hairline
    3. Hemangioma over forehead or glabella
    4. Scalp defect with or without underlying bony defect
7. Face: characteristic dysmorphic features collectively described as "Greek warrior helmet" facies (prominent glabella, hypertelorism, broad beaked nose, and frontal bossing)
8. Eyes
    1. Hypertelorism
    2. Down-slanting palpebral fissures
    3. Epicanthal folds
    4. Strabismus
    5. Coloboma
    6. Proptosis due to hypoplasia of orbital ridges
    7. Ectopic pupils
    8. Esotropia
    9. Ptosis
    10. Microphthalmia
    11. Megalocornea
    12. Sclerocornea
    13. Cataracts
    14. Hypoplastic anterior chamber and ciliary body of iris
    15. Persistence of lenticular membrane
    16. Hypoplastic retina with formation of rosettes
    17. Cup-shaped optic disks
    18. Congenital nystagmus
    19. Early-onset glaucoma
    20. Rieger anomaly
9. Nose
    1. Broad or beaked nose
    2. Nasolacrimal duct stenosis or atresia
10. Mouth
    1. Short upper lip
    2. Short philtrum
    3. Cleft lip or palate
    4. Bifid uvula
    5. Carplike mouth
    6. Micrognathia
    7. Retrognathia
11. Ears
    1. Low-set ears
    2. Large, floppy, or misshapen ears
    3. Microtia
    4. Preauricular dimples
    5. Chronic otitis media with effusion
    6. Sensorineural hearing loss
12. Cardiovascular
    1. Atrial septal defect
    2. Ventricular septal defect
    3. Persistent left superior vena cava
    4. Valve abnormalities
    5. Complex cardiac defects
13. Pulmonary
    1. Bilateral bilobed or trilobed lungs
    2. Lung hypoplasia secondary to diaphragmatic hernia
14. GI anomalies
    1. Diastasis recti
    2. Umbilical or inguinal hernias
    3. Accessory spleens
    4. Absent gallbladder
    5. Diaphragmatic hernia
    6. Intestinal malrotation
15. Genitourinary anomalies (25%)
    1. Hypoplastic kidneys
    2. Cystic dysplastic kidneys
    3. Unilateral renal agenesis
    4. Hydronephrosis
    5. Exstrophy of the bladder
    6. Hypoplastic external genitalia
    7. Cryptorchidism and hypospadias in males

8. Hypoplastic Mullerian derivatives (i.e., agenesis of vagina, cervix, or uterus; hypoplastic uterus; ovarian streaks) in females

16. Skeletal anomalies (60–70%)
    1. Long slender fingers with additional flexion creases
    2. Long narrow chest
    3. Hypoplastic widely spaced nipples
    4. Hypoplasia or duplication of thumbs and great toes
    5. Talipes equinovarus
    6. Hypoplasia of pubic bones
    7. Vertebral and rib anomalies
    8. Defective calvarium ossification
    9. Scoliosis
    10. Kyphosis
    11. Osteoporosis
    12. Delayed bone maturation
    13. Sacral dimple
17. Infection prone, immunodeficiency
18. Malignant hematological disorders (Sharathkumar et al. 2003)
    1. Myelodysplastic syndrome
    2. Leukemia
19. Dermatoglyphics
    1. Hypoplastic dermal ridges
    2. Transverse palmar creases (25%)
    3. Excess of digital arches
    4. t or t′
20. Pitt-Rogers-Danks syndrome (PRDS) (Pitt et al. 1984; Clemens et al. 1996; Wright et al. 1998)
    1. Phenotypic overlap with WHS.
        1. Prenatal and postnatal growth retardation
        2. Microcephaly
        3. Seizures
        4. Developmental delay
        5. Facial features
            1. A wide mouth
            2. Short upper lip
            3. Flat philtrum
            4. Beaked nose
            5. Prominent eyes
            6. Maxillary hypoplasia
    2. Microdeletion of 4p16.3 detected in most cases.
    3. Current evidence suggests that PRDS is not a separate clinical entity but may represent the milder end of the WHS spectrum (Battaglia and Carey 1998).
21. Fetal phenotype
    1. Major anomalies
        1. Intrauterine growth retardation
        2. Microcephaly
        3. Cleft palate
        4. Corpus callosum agenesis
        5. Ventricular septal defect
        6. Diaphragmatic hernia
        7. Renal hypoplasia
    2. Minor anomalies
        1. Scalp defect
        2. Hypertelorism usually with a prominent glabella
        3. Pulmonary isomerism
        4. Common mesentery
        5. Hypospadias
        6. Sacral dimple
22. Prognosis (Shannon et al. 2001)
    1. Crude infant mortality rate: 17%.
    2. Mortality rate in the first 2 years: 21%.
    3. Cases with large de novo deletions are more likely to die than those with smaller deletions.
    4. Follow-up of patients, spanning 23 years, showed a slow but constant evolution over time, in all areas (Battaglia et al. 2008).
        1. There was an improvement of the motor, and the communicative skills, and of the verbal comprehension with extension of the gesture repertoire and a reduction of isolation and anxiety.
        2. Forty-five percent of patients were able to walk, either independently or with support (range: 2–12 years); 18% could help dressing and undressing themselves and doing simple household tasks.
    5. Causes of death.
        1. Birth anoxia
        2. Withdrawal of treatment after premature delivery
        3. Lower respiratory tract infections

4. Sudden unexplained death
5. Congenital anomalies, such as congenital heart disease, dysplastic kidneys, renal hypoplasia, diaphragmatic hernia, and pulmonary hypoplasia

Diagnostic Investigations

1. Conventional cytogenetic studies: most common method to detect chromosome arm 4p deletions (60–70% of deletions) (Johnson et al. 1976; Chen 2015).
2. High-resolution cytogenetic studies: to detect smaller deletions of chromosome band 4p16.3 (Fang et al. 1997).
3. Fluorescence in situ hybridization (FISH) using Wolf–Hirschhorn critical region probe (Fryns et al. 1998; Roulston et al. 1991): detecting >95% of deletions. Molecular cytogenetic studies using FISH allow the diagnosis to be made in patients with very small deletions or cryptic translocations. FISH uses genetic markers that have been precisely localized to the area of interest. The absence of signal from either the maternal or the paternal allele for the marker is indicative of monosomy for that chromosomal region.
4. Array comparative genomic hybridization (aCGH).
    1. A new technology that can analyze the entire genome at a significantly higher resolution over conventional cytogenetics to characterize unbalanced rearrangements.
    2. Chromosome microarray can detect all currently known deletions of WHS critical region and can determine if the deletion is "pure" or part of a more complex imbalance (Ikonomou et al. 2013).
    3. Thirty-three patients with WHS were analyzed using aCGH (South et al. 2008).
        1. Observation of a much higher than expected frequency of unbalanced translocations (15/33, 45%).
        2. Seven of these 15 cases were cryptic translocations not detected by a previous karyotype combined with WHS-specific FISH.
5. Immune workup (Hanley-Lopez et al. 1998).
    1. Common variable immunodeficiency
    2. Immunoglobulin A (IgA) and immunoglobulin G2 (IgG2) subclass deficiency
    3. IgA deficiency
    4. Impaired polysaccharide responsiveness
    5. Normal T-cell immunity
6. Radiography.
    1. Delayed bone maturation
    2. Microcephaly
    3. Hypertelorism
    4. Micrognathia
    5. Anterior fusion of vertebrae
    6. Fused ribs
    7. Dislocated hips
    8. Proximal radioulnar synostosis
    9. Clubfeet
7. Echocardiography to detect heart defects.
8. Renal ultrasound to detect renal anomalies.
9. MRI and CT scans to demonstrate underlying brain pathology including agenesis of corpus callosum and ventriculomegaly.
10. EEG for seizure monitoring.
11. Swallowing study for feeding difficulty.
12. Comprehensive audiologic and otologic evaluation to rule out possible hearing impairment (Lesperance et al. 1998).
13. Ophthalmologic examination.
14. Developmental testing.
    1. Speech and motor evaluation
    2. Appropriate psychometric evaluation
15. Growth charts are available from 0 to 4 years of age, based on the study of 101 individuals (Anntonius et al. 2008). The use of these specific growth charts is recommended because standard growth charts are inapplicable for patients with WHS.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. De novo deletion cases: no significant increased risk

2. Deletion resulting from a parental chromosomal rearrangement: increased risk for unbalanced product in offspring
2. Patient's offspring: reproduction unlikely due to mental retardation

2. Prenatal diagnosis available to families in which one parent is known to be a carrier of a chromosome rearrangement by amniocentesis, CVS, or PUBS
   1. Ultrasonography to detect in utero manifestation of distinct phenotype (Tachdjian et al. 1992)
      1. Severe intrauterine growth retardation
      2. Increased nuchal fold thickness
      3. Microcephaly
      4. Typical facial appearance described as "Greek warrior helmet" facies (Ikonomou et al. 2013)
      5. Hypertelorism, usually with prominent glabella
      6. Micrognathia
      7. Cleft lip and palate
      8. Diaphragmatic hernia
      9. Anomalous urinary stream from the ventral surface of the penis (possible hypospadias by color flow map (Ikonomou et al. 2013))
   2. Chromosome analysis (Dietze et al. 2004; Ikonomou et al. 2013)
      1. Conventional karyotyping: 46,XY,del(4)(p16.3).
      2. FISH using specific probe locus-specific identification (LSI) Wolf–Hirschhorn/CEP4 (4p16.3): observation of only one copy of the region 4p16.3.
      3. Multiplex ligation-dependent probe amplification-specific molecular probe detected a 19-Mb deletion of the gene *LETM1* 1.81 Mb from the telomere.
      4. Whole chromosome painting.
3. Management (Battaglia and Carey 1999; Battaglia et al. 1999; Chen 2015)
   1. Multidisciplinary team approach
      1. Early intervention program to improve motor development, cognition, communication, and social skills
      2. Speech, physical, and occupational therapies
      3. Appropriate school placement
   2. Manage feeding difficulties and failure to thrive
      1. Gavage feeding
      2. Gastrostomy
      3. Occasional gastroesophageal fundoplication
   3. Anticonvulsants including bromide therapy (Shimizu et al. 2014) for seizure control
   4. Orthopedic care for skeletal abnormalities
      1. Clubfoot
      2. Scoliosis
      3. Kyphosis
   5. Care for possible immunodeficiency

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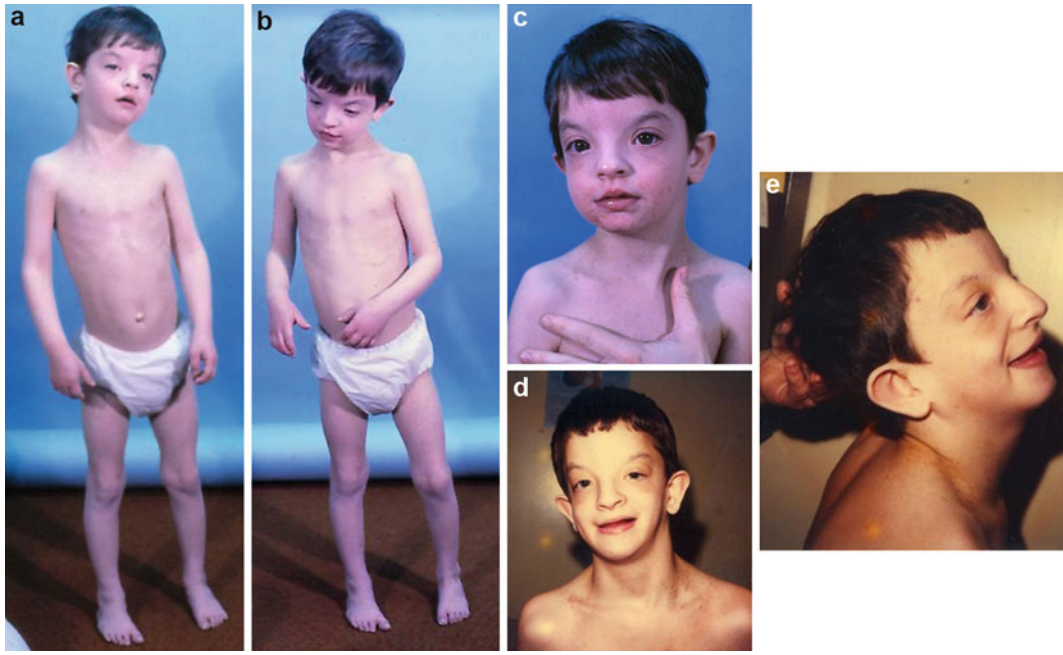

Fig. 1 (**a**–**e**) A patient with Wolf–Hirschhorn syndrome at different ages showing characteristic facial features consisting of prominent glabella, hypertelorism, beaked nose, and frontal bossing, collectively described as "Greek warrior helmet" facies

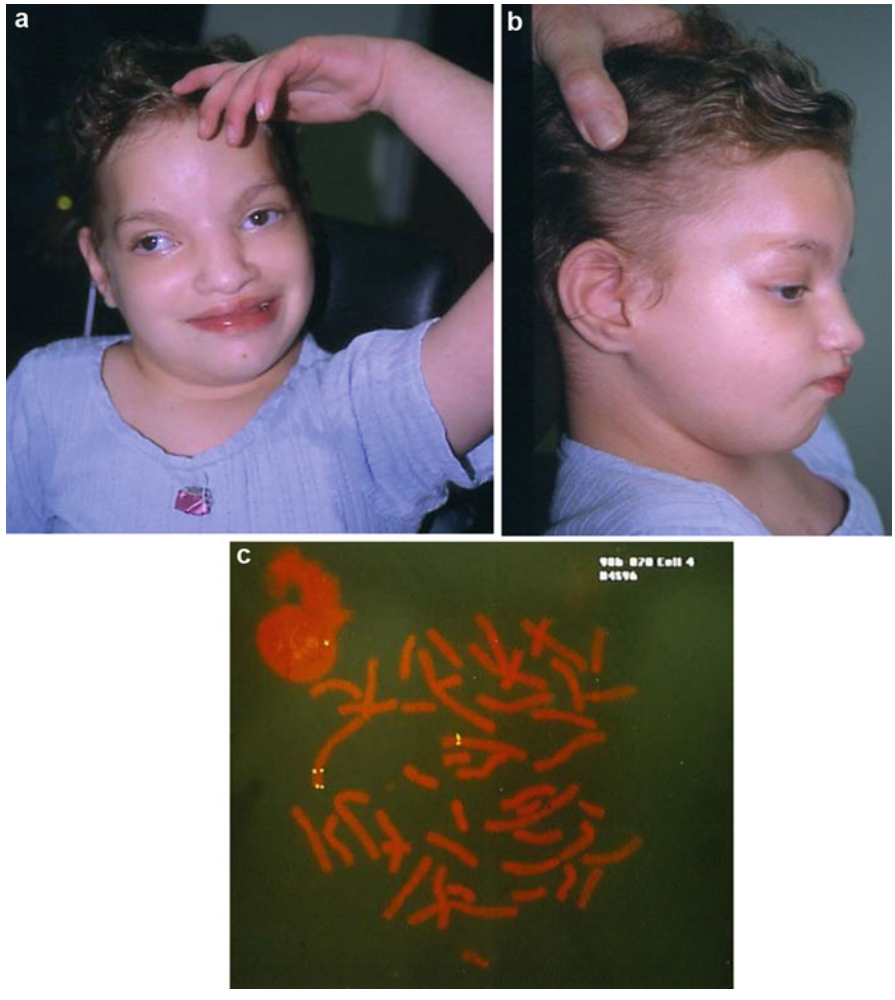

Fig. 2 (**a**–**c**) A girl with WHS showing characteristic face and deletion of WHS locus (FISH)

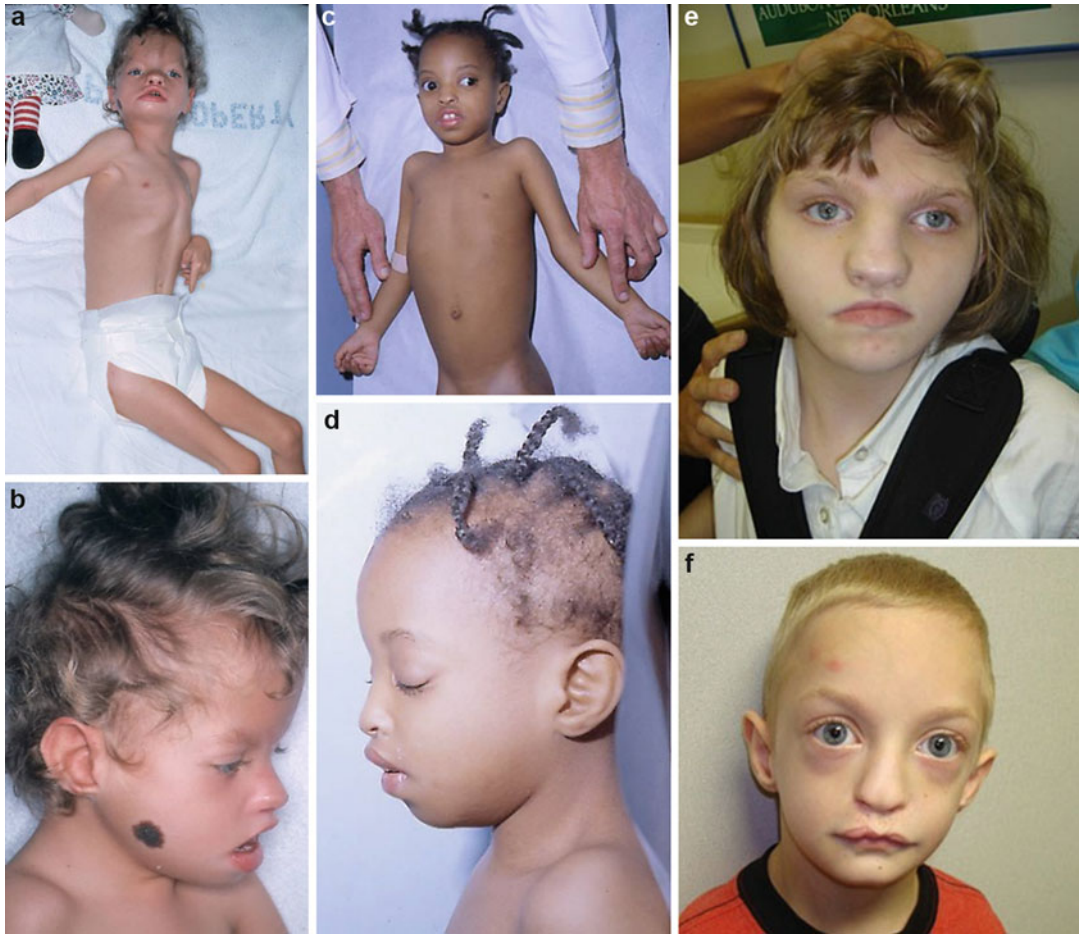

Fig. 3 (**a**–**f**) Four children with WHS showing characteristic facial features of the syndrome

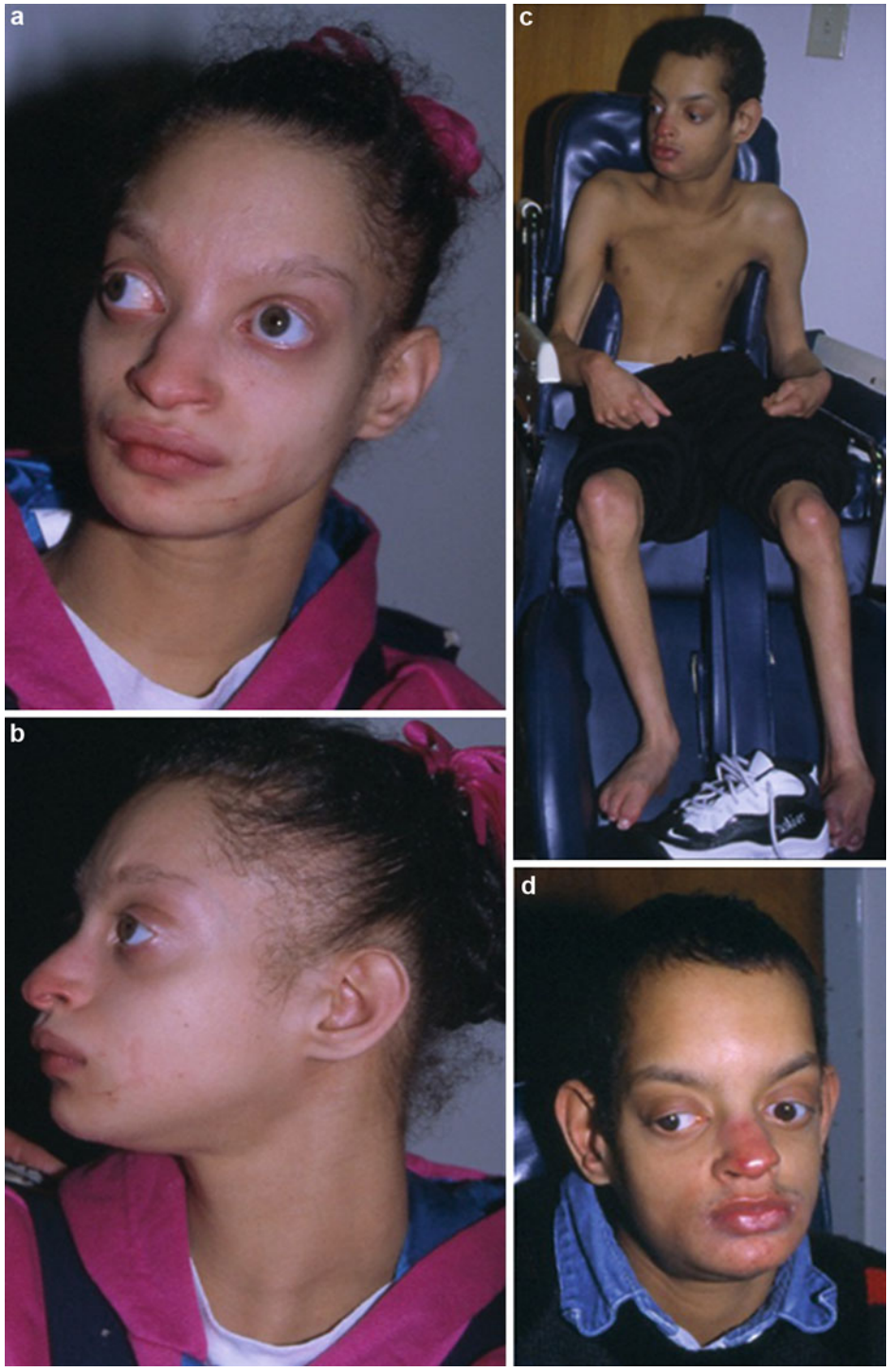

Fig. 4 (**a**–**d**) Two siblings with WHS showing characteristic features of the syndrome

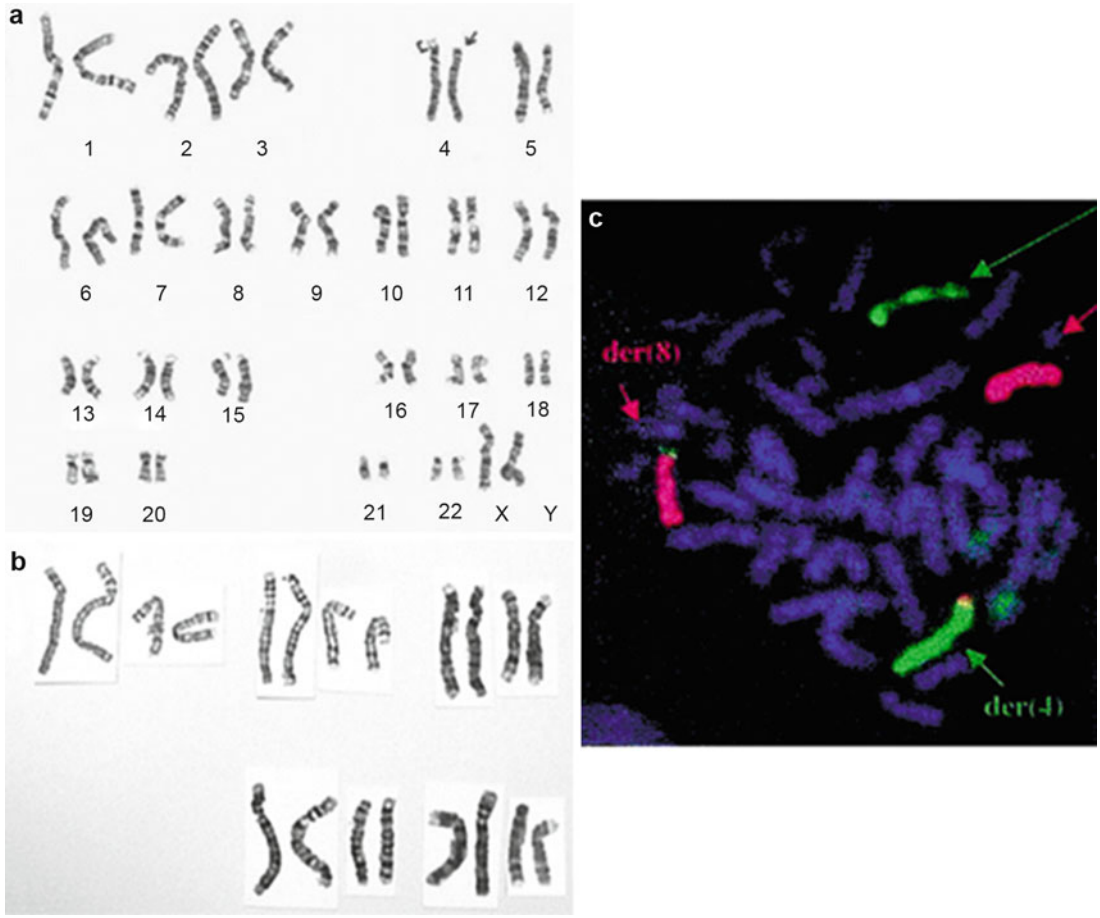

Fig. 5 (**a**–**c**) Karyotype of the sister showing deletion of 4p, derived from the mother with balanced translocation (4p;8p) (partial karyotypes). FISH analysis with whole chromosome paint specific for chromosome 4 (wcp4/SpectrumGreen) and chromosome 8 (wcp8/SpectrumOrange) demonstrated a t(4;8) in all metaphases analyzed. These results confirmed a reciprocal translocation between chromosome 4 and chromosome 8 in the mother

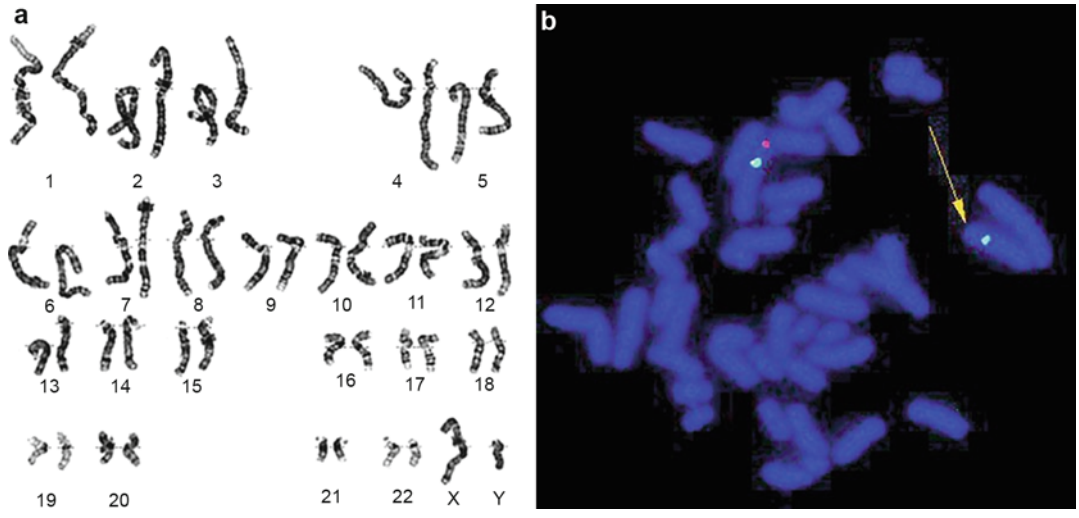

Fig. 6 (**a**, **b**) Karyotype and FISH of another patient with Wolf–Hirschhorn syndrome (4p)

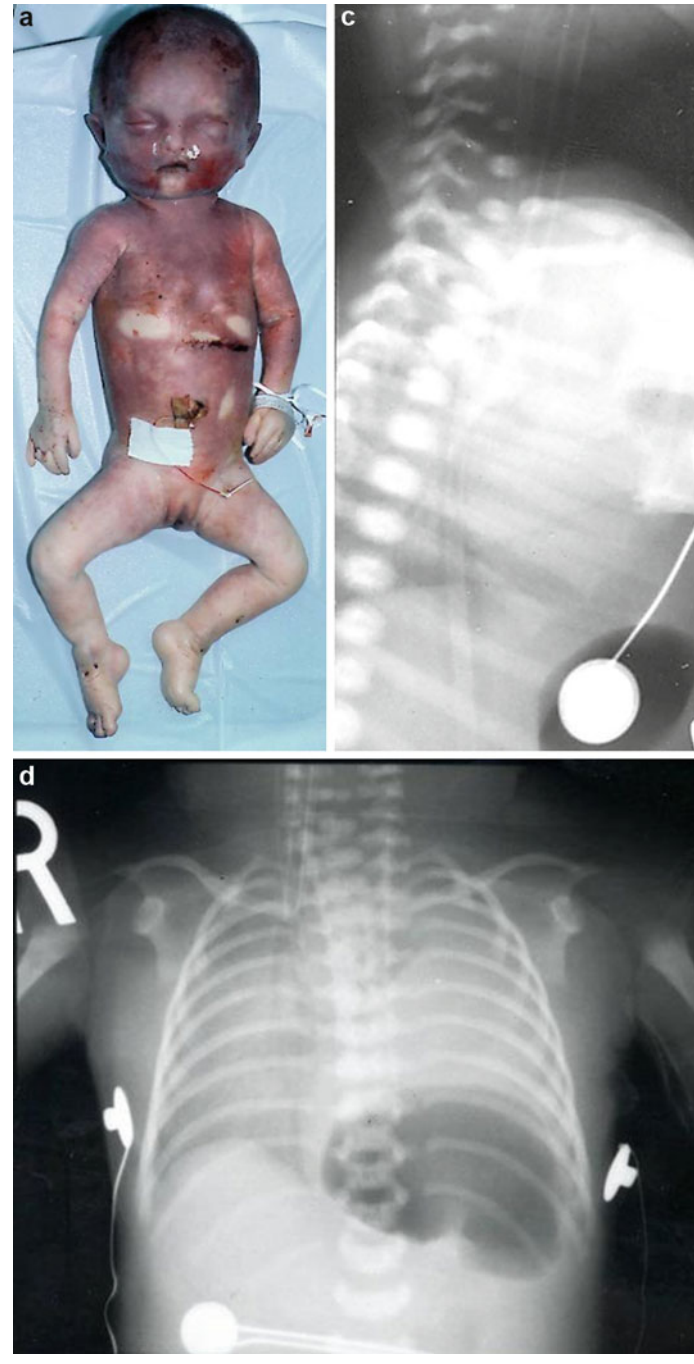

Fig. 7 (**a**–**c**) A fetus with WHS showing broad triangular-shaped nasal root and the flat facial profile resembling "Greek warrior helmet." The radiographs show hypoplasia of the cervical vertebral bodies

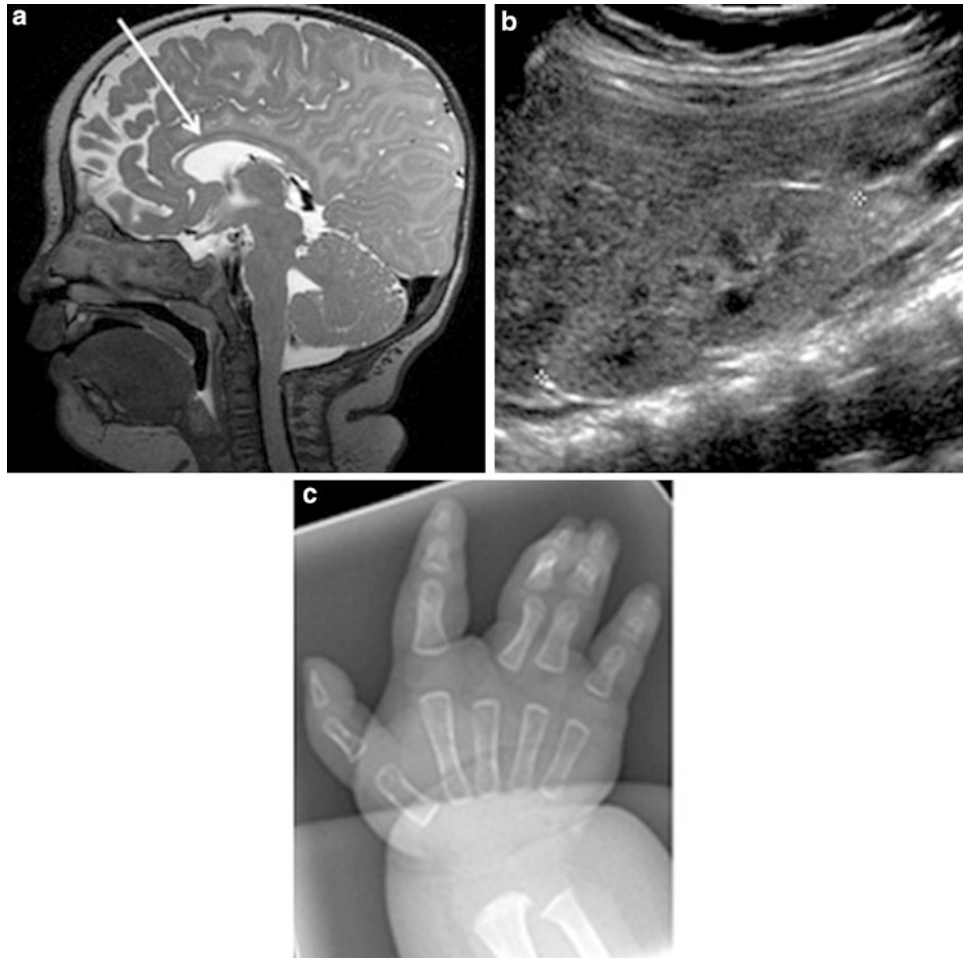

Fig. 8 (**a**–**c**) The 2-year-old female was diagnosed to have Wolf–Hirschhorn syndrome based on chromosome 4p deletion noted on amniocentesis. Clinical features are characterized by secundum atrial septal defect with pulmonary stenosis, global developmental delay, seizure disorder, tethered cord status post repair at 1 year of age, neurogenic bladder, vesicoureteral reflux, chronic kidney disease secondary to renal dysplasia, gastroesophageal reflux status post repair Nissen fundoplication, cortical visual impairment, right hand syndactyly, chronic lung disease, and precocious puberty. Immunoglobulin study revealed very low IgG (185), normal IgA (38), and low IgM (13). MRI of the brain at 6 month of age (**a**) demonstrated global reduction in cerebral white matter volume and severe diffuse thinning of the corpus callosum (*arrow*) and prominence of the lateral and third ventricles. These features have been reported in patients with Wolf–Hirschhorn syndrome. Renal ultrasound at 1 year 3 months of age (**b**) demonstrated increased echogenicity of the renal parenchyma with decrease in corticomedullary differentiation. Findings are suggestive of renal disease with dysplastic change. Right hand radiography at 1 year 7 months of age (**c**) showed soft tissue fusion of the third and fourth digits with mildly dysmorphic phalanges along the third digit and retarded bone age. The left hand was normal (not shown) (Courtesy of Dr. Guo)

X-Linked Agammaglobulinemia

Contents

X-linked agammaglobulinemia (XLA) was first described by Bruton in 1952 (Bruton 1952). It is a prototypical humoral immunodeficiency characterized by early onset of bacterial infections, profound hypogammaglobulinemia, and marked decrease of the peripheral B-lymphocyte population. Associated infections, particularly bacterial meningitis and pneumonia, are often life threatening.

Synonyms and Related Disorders

Agammaglobulinemia tyrosine kinase; B-cell progenitor kinase; Bruton-type agammaglobulinemia; Immunodeficiency 1

Genetics/Basic Defects

1. An X-linked recessive disorder (Sideras and Smith 1995).
2. The responsible gene for XLA (named as Bruton's tyrosine kinase, *BTK*) (Vihinen et al. 1999), mapped on Xq21.3-Xq22, is mainly involved in early B-cell maturation through its function in pre-B-cell receptor signaling pathway, and its absence causes an arrest in B-cell development.
3. Xq22.1 contiguous gene deletion syndrome of X-linked agammaglobulinemia associated with Mohr-Tranebjærg syndrome (MTS) (Shaker et al. 2016):
   1. Microarray identified a 111-kb deletion of genetic material from chromosome region Xq22.1, resulting in the absence of the *BTK*, *TIMM8A*, and *TAF7L* genes.
   2. These genes are respectively responsible for agammaglobulinemia, MTS (deafness-dystonia-optic atrophy syndrome), and spermatogenesis.
4. Mutations in the *BTK* gene cause XLA: 90–95% of males with presumed XLA have mutations in Btk (Conley et al. 1998). The other patients are likely to have defects in other genes.
5. Point mutations were the most common mutations detected, accounting for 68% of all mutations. Deletions and insertions were also seen in a few cases (Singh et al. 2016).
6. The defect in differentiation of pre-B cells into B cells is not absolute in patients with XLA (Conley 1985). The immature phenotype of the B cells additionally suggests that there may be a block in the maturation of B

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cells at more than one stage of differentiation in this disorder.

7. Genetic analysis of patients with defects in early B-cell development: Polymorphic variants in the components of the pre-B cell and B-cell receptor complex, particularly micro heavy chain and lambda5, may contribute to the severity of XLA (Conley et al. 2005).
8. The whole-exome sequencing revealed a somatic mutation in *MLL2* (a histone methyltransferase) in the sample from the onset of B-cell precursor acute lymphoblastic leukemia (BCP-ALL). This study suggests that the alterations of *BTK* and *MLL2* synergistically function as leukemogenesis (Hoshino et al. 2015).
9. Genotype phenotype correlation:
    1. Polymorphic variants in Tec (a cytoplasmic tyrosine kinase that might substitute for BTK) were not correlated with phenotypic markers; however, the specific mutation in Btk did influence disease severity. Mutations that conceivably allow the production of some Btk, amino acid substitutions or splice defects that occur at conserved but not invariant sites in the splice consensus sequence were associated with older age at diagnosis, a higher percentage of B cells in the peripheral circulation and higher concentrations of plasma IgM (Broides et al. 2006).
    2. Globally, a genotype-phenotype correlation is observed, but individual discrepancies between the severity of the mutation and the clinical and analytic phenotype suggest that other loci or ambient factors significantly influence the disease presentation and evolution (López-Granados et al. 2005).
    3. Severe genotypes do not necessarily lead to severe phenotypes. Moreover, a considerable number of patients with mild phenotype showed a severe mutation with a tendency toward C substitution in the polymorphic site on TEC intron 1 (Teimourian et al. 2008).
10. Female XLA can result from heterozygous *BTK* gene abnormality and extreme nonrandom inactivation of X chromosome on which normal *BTK* gene is located (Takada et al. 2004).

Clinical Features

1. Presenting manifestations
    1. Infections in affected boys after the decline of passively transferred maternal antibodies: the major presenting feature
        1. Most frequently respiratory tract and gastrointestinal tract infections (91%), often protracted and recurrent, presenting as otitis media, pneumonitis, and diarrhea.
        2. Other common infections:
            1. Conjunctivitis
            2. Sinusitis
            3. Skin infection
        3. *S. pneumoniae* and *H. influenzae*: the most common organisms found prior to diagnosis and may continue to cause sinusitis and otitis after diagnosis and the initiation of gamma globulin therapy.
        4. Monoarticular or oligoarticular arthritis (20%) affecting large joints: the most common being knees, shoulders, ankles, wrists, and elbows.
        5. Central nervous system infections (16%): meningitis/encephalitis.
        6. Septicemia (10%) excluding bacterial meningitis and associated bacteremia.
        7. Virtually, all patients had infections at more than one anatomic site and on more than one occasion.
    2. Autoimmune or inflammatory disease: a significant proportion of patients with XLA have symptoms that are consistent with a diagnosis of arthritis, inflammatory bowel disease or other inflammatory condition (Hernandez-Trujillo et al. 2014).
    3. Neutropenia (10%): always occur in association with infection, and in all cases resolved after treatment with antibiotics and γ-globulin.
    4. Failure to thrive: a relatively infrequent occurrence.

5. Fever of unknown origin.
6. Complications of immunizations such as paralytic poliomyelitis following live virus vaccine and vaccinia gangrenosum following smallpox vaccination.

2. Age at onset of symptoms
   1. By age 4 months (25%)
   2. By age 8 months (50%)
   3. By age 12 months (75%)
   4. By age 18 months (90%)
3. Chronic complications
   1. Chronic pulmonary disease (46%): the most frequent long-term complication of XLA
      1. Obstructive pulmonary disease (half of cases)
      2. Combined obstructive and restrictive disease (half of cases)
   2. Sensory neurologic disorders
      1. Hearing loss (32%) as a consequence of chronic otitis media and meningoencephalitis
      2. Delayed acquisition of speech (14%)
      3. Learning disorders (15%)
      4. Significant motor dysfunction as a consequence of encephalitis
         1. Hemiparesis
         2. Ataxia
         3. Diplegia
         4. Quadriplegia
4. Miscellaneous illnesses
   1. Dermatomyositis-like syndrome occurred in association with arthritis and with meningitis/encephalitis
   2. Viral infections
      1. Disseminated enterovirus infection
      2. Disseminated adenovirus infection
   3. Hematologic abnormalities: uncommon in treated patients
      1. Chronic Coombs' positive hemolytic anemia
      2. Transient neutropenia and transient thrombocytopenia in conjunction with infection: resolved when the infection resolved
      3. Insulin-dependent diabetes mellitus
5. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia (Conley and Howard 2002)
   1. The majority of patients with XLA were recognized to have immunodeficiency during or shortly after their first hospitalization for infection.
   2. Most of the patients had a history of recurrent otitis at the time of diagnosis, which when combined with the physical finding of markedly decreased or absent tonsils and cervical lymph nodes, could have alerted physicians to the diagnosis of XLA.
6. Complications of γ-globulin therapy
   1. Rash
   2. Fever
   3. Apparent anaphylactic-like symptoms
   4. Acrodynia secondary to γ-globulin preparations containing mercury as a preservative
7. Causes of death
   1. The two major causes of death (Lederman and Winkelstein 1985)
      1. Chronic pulmonary disease with resultant cardiac failure
      2. Disseminated viral infections which characteristically caused a dermatomyositis-like syndrome, hepatitis, pneumonitis, and meningoencephalitis
   2. Cardiorespiratory failure (38%): consequence of chronic pulmonary disease and cor pulmonale
   3. Severe viral infections (50%)
   4. Fulminant necrotizing hepatitis
   5. Aspiration as a consequence of poliomyelitis-related neurologic impairment
   6. Systemic staphylococcal infections

Diagnostic Investigations

1. Clinical clues to the diagnosis of XLA:
   1. Chronic or recurrent nature of infections.
   2. Infections at more than one anatomic location.
   3. Family history of immunodeficiency.
   4. An important clinical clue: absent or barely detectable tonsils and cervical lymph nodes.

5. About 60% of individuals with XLA are recognized as having immunodeficiency when they develop a severe, life-threatening infection such as pneumonia, empyema, meningitis, sepsis, cellulitis, or septic arthritis (Zhu et al. 2015).

2. Clinical laboratory findings in affected individuals
    1. Concentration of serum immunoglobulins:
        1. The serum IgG concentration: typically less than 200 mg/dL
        2. The serum concentrations of IgM and IgA: typically less than 20 mg/dL (Although decreased serum concentration of IgG and IgA can be seen in children with a constitutional delay in immunoglobulin production, low serum IgM concentration is almost always associated with immunodeficiency.)
    2. Antibody titers to vaccine antigens: Affected individuals fail to make antibodies to vaccine antigens like tetanus, *H. influenzae*, or *S. pneumoniae*.
    3. Lymphocyte cell surface markers: markedly reduced numbers of B lymphocytes (CD 19 + cells) in the peripheral circulation (<2% in almost all patients): the most distinctive laboratory finding.
    4. Bruton's tyrosine kinase protein (measured by flow cytometry) is absent in most of the patients.
    5. Severe neutropenia: seen in about 10–25% of individuals at the time of diagnosis, usually in association with pseudomonas or staphylococcal sepsis. Neutropenia is generally not seen after the initiation of gamma globulin therapy (Farrar et al. 1996).
3. The diagnosis of XLA (Ochs and Smith 1996) is based on:
    1. The presence of lymphoid hypoplasia
    2. Markedly reduced serum levels of all 3 major classes of immunoglobulins
    3. Failure to make antibody to antigenic stimulation
    4. Almost complete absence of B lymphocytes in the peripheral blood
4. Molecular genetic testing
    1. Mutations in *BTK*: detectable by sequence analysis in approximately 90% of males with early-onset infections, hypogammaglobulinemia, and absent B cells.
    2. Duplications or deletions in *BTK* gene: detectable by duplication/deletion analysis in 10% of affected males.
    3. Molecular genetic testing of the *BTK* gene is the most reliable way to identify female carriers of XLA.
    4. Single-stranded conformation polymorphism (SSCP) analysis for mutation screening in the BTK (Bruton's tyrosine kinase) gene: molecular genetic testing by SSCP analysis provides an accurate tool for the definitive diagnosis of XLA and the discrimination of borderline cases, such as certain hypogammaglobulinemia or common variable immunodeficiency patients with overlapping clinical features (Holinski-Feder et al. 1998).
5. Diagnosis considered established only in those individuals who have a mutation in the *BTK* gene or who have a maternal uncle or cousin with absent B cells
6. Carrier detection in typical and atypical X-linked agammaglobulinemia (Conley and Puck 1988)
    1. Combining the production of somatic cell hybrids that selectively retain the active X chromosome with the use of X-linked restriction fragment length polymorphisms permits the distinction of the two X chromosomes.
    2. Three obligate carriers of typical XLA and four women whose sons might be considered to have atypical or sporadic XLA were studied.
    3. B cell hybrids from all seven women demonstrated exclusive use a single X as the active X.
    4. In addition, B cell hybrids from four of eight women at 25% or 50% risk of being carriers exhibited nonrandom X chromosome inactivation, indicating that these women were also carriers of X-linked forms of hypogammaglobulinemia.

5. These results illustrate a technique that can be used both to help define XLA and to provide carrier detection for all women at risk of being carriers of this disorder.

7. Application of carrier testing to genetic counseling for X-linked agammaglobulinemia (Allen et al. 1994):
   1. Female carriers of XLA, although asymptomatic, have a characteristic B cell lineage-specific skewing of the pattern of X inactivation. Skewing apparently results from defective growth and maturation of B cell precursors bearing a mutant active X chromosome.
   2. Primary carrier analysis to examine patterns of X inactivation in CD19+ peripheral blood cells (B lymphocytes) was conducted using quantitative PCR at the androgen-receptor locus. Obligate carriers of XLA demonstrated >95% skewing of X inactivation in peripheral blood CD19+ cells but not in CD19 cells.
8. Clinical and mutational characteristics of X-linked agammaglobulinemia and carrier identification by flow cytometric assessment combined with genetic analysis (Kanegane et al. 2001):
   1. Flow cytometric assessment revealed the deficient BTK expression status in 78 families (93 patients), and mutations in BTK were identified in 76 of 78 families with presumed XLA.
   2. Of the patients with normal BTK expression, two showed missense mutations in which the normal amount of altered BTK transcript would cause the XLA phenotype.
   3. As many as 30% of these patients with XLA were clinically or genetically recognized beyond 5 years of age.
   4. Higher concentrations (>300 mg/dL) of serum IgG were evident in the cases diagnosed among adults, seemingly preventing severe infections.
   5. Fifty-seven of 70 mothers of patients with BTK deficiency were diagnosed as obligate carriers on the basis of a bimodal BTK expression pattern.
   6. Nine of the remaining 13 mothers showing nonmosaic BTK expression had no mutations in 2 alleles; surprisingly, the other 4 mothers had the mutated alleles.

Genetic Counseling

1. Recurrence risk
   1. Obligatory carriers: Mothers who have an affected son and one other affected relative in the maternal line (e.g., brother, uncle, nephew)
   2. Negative family history in 50% of affected males: two possibilities exist regarding his mother's carrier status and carrier risks of extended family members
      1. The mother is a carrier of a disease-causing mutation (80–85% of cases).
      2. The mother is not a carrier and the affected male has a de novo disease-causing mutation (15–20% of cases).
   3. Patient's sib
      1. When the mother is a carrier
         1. A 50% chance of transmitting the *BTK* mutation by the mother in each pregnancy.
         2. Male sibs who inherit the mutation will be affected.
         3. Female sibs who inherit the mutation will be carriers.
      2. When the mother's carrier status is unknown and if the proband is the only affected individual in the family, the mother has an approximately 80% chance of being a carrier.
         1. Male sibs have a 40% chance of being affected.
         2. Female sibs have a 40% chance of being carriers.
      3. When the mother is not a carrier (no evidence of her son's BTK disease-causing mutation present in DNA extracted from her leukocytes) and if the affected son represents a single case in the family, the male sibs are still at

increased risk (<5%) of being affected because of the possibility of the presence of germ line mosaicism.

4. Patient's offspring
    1. No sons will inherit the mutant allele and therefore will not be affected.
    2. All daughters will inherit the mutant allele and will be carriers.

2. Molecular analysis of the *BTK* gene is a favorable tool for the diagnosis of XLA and for accurate carrier determination, which is essential for subsequent genetic consulting (Qin et al. 2013; Zheng et al. 2014)
3. Prenatal diagnosis: available to pregnancies of women who are carriers
    1. The usual procedure: to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about 10–12 weeks of gestation or by amniocentesis usually performed at about 15–18 weeks of gestation.
    2. If the fetal karyotype is 46,XY and if the disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known disease-causing mutation.
    3. Preimplantation genetic diagnosis (PGD) (Smith and Berglöf 2016): available for families in which the disease-causing mutation has been identified in an affected family member. However, the reliability of PGD for XLA has not yet been proven.
4. Management
    1. Gamma globulin replacement (weekly subcutaneous injection or intravenous infusion every 2–4 weeks) and aggressive use of antibiotics:
        1. Improve the outlook for affected patients: a remarkable improvement in the health and well-being after therapy is started.
        2. Early intravenous immunoglobulin replacement therapy achieving residual IgG levels >500 mg/dL is effective in preventing severe acute bacterial infections and pulmonary insufficiency. More intensive therapy may be required to fully prevent the onset of bronchiectasis, chronic sinusitis, and nonbacterial infections, particularly enteroviral infections, in all cases (Quartier et al. 1999).
        3. Decrease in systemic infections such as sepsis and meningitis/ meningoencephalitis (Plebani et al. 2002).
        4. Acute, life-threatening infections: rare in patients with XLA who are receiving intravenous gamma globulin.
        5. Chronic lung disease and enteroviral infections still develop in some patients.
        6. Shulman disease (eosinophilic fasciitis) in X-linked agammaglobulinemia (Pituch-Noworolska et al. 2016)
            1. The patient was diagnosed with XLA in the first year of life, followed by regular substitution of immunoglobulins.
            2. The symptoms of pain, edema of muscles of the right shank with skin edema and discoloration after mild injury were noted in a 13-year-old boy.
            3. Shulman disease was diagnosed after 6 months of symptoms, based on histopathology of muscle and skin biopsy.
            4. Before the diagnosis, nonsteroid anti-inflammatory drugs (NSAID) were used with a transient effect.
            5. After the diagnosis, therapy included steroids, immunoglobulins in a high dose and immunosuppression, with improvement of clinical symptoms.
    2. Use of infliximab, a chimeric antitumor necrosis factor alpha monoclonal antibody, in X-linked agammaglobulinemia associated enteropathy (Davey et al. 2014). The use of infliximab in X-linked agammaglobulinemia associated enteropathy.
    3. Use of ibrutinib (Imbruvica) (Ponader and Burger 2014):
        1. The highly encouraging clinical results led to breakthrough therapy designation for ibrutinib by the US Food and Drug

Administration for patients with CLL (chronic lymphocytic leukemia), MCL (mantle-cell lymphoma), and Waldenströom macroglobulinemia, and the recent US Food and Drug Administration approval of ibrutinib (Imbruvica) for previously treated patients with MCL (in November 2013) and CLL (in February 2014).

2. With these exciting new developments, BTK has become a role model for translational research, in which basic research defined the genetic and molecular basis of XLA.
3. These developments allowed for innovative development of BTK inhibitors that already have an impact on the lives of many patients suffering from B-cell malignancies.

4. Inactivated polio vaccine rather than live oral polio vaccine is given to children with XLA and their sibs.
5. Report a series of 6 XLA patients with bronchiectasis who underwent lung transplantation: Short-term outcomes were excellent; however, long-term outcomes were disappointing with a high incidence of pulmonary sepsis and chronic lung allograft dysfunction (Barnes et al. 2015).
6. Molecular genetic testing of at-risk male relatives as soon after birth as possible to ensure that gamma globulin replacement therapy is initiated in affected individuals.
7. Adults with XLA: become productive members of society and excel in many areas despite the disease impacts on the daily lives (Winkelstein et al. 2008).
8. Splice-correction strategies for treatment of X-linked agammaglobulinemia (Bestas et al. 2015):
    1. As for many other genetic diseases, gene therapy represents a future option for XLA.
    2. The transient need of BTK in B cells, which differentiate into long-lived protective plasma cells, makes splice correction therapy particularly feasible for XLA.

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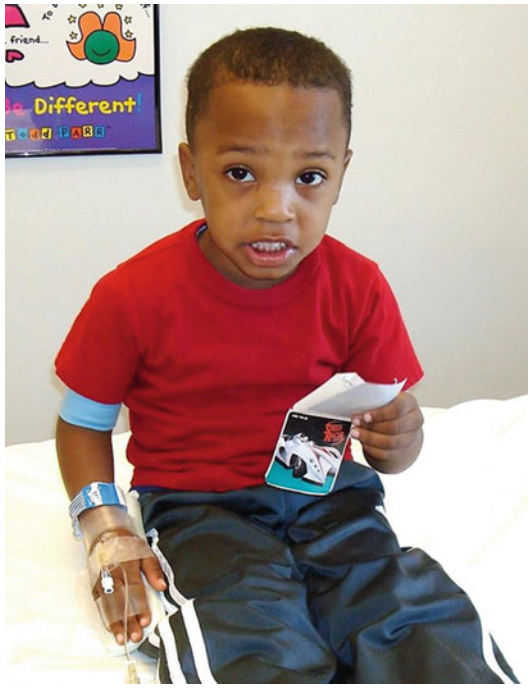

Fig. 1 A 5-year-old boy was evaluated for immune deficiency because of recurrent respiratory tract infections (two pneumonias since late infancy) and one episode of meningitis. Recent immunoglobulin levels revealed IGA of <5 mg/dL (22–159), IGG of 115 mg/dL (141–1,135), and IGM of 11 mg/dL (47–200). Flow cytometry (immune deficiency panel) showed CD3, 92.9% (3,498); CD4, 43% (1,645); CD8, 46% (1,747); CD4/CD8, 1:1.1; CD19, 0.1% (4); and CD16 + CD56+, 6.2% (233). These findings are consistent of B-cell defect with normal T cell subsets and normal NK cells. Bruton's tyrosine kinase mutation analysis revealed a novel mutation in the splice site of exon 6 (g.58919 G > C). Previously, a mutation at this splice site (g.58919) G > A has been reported in the BTKBASE. The impact on protein structure and function for this mutation, assessed using a splice site prediction software, would be the same as that reported for g.58919 G > A. The patient currently receives intravenous immunoglobulin (610 mg/kg) and is responding well

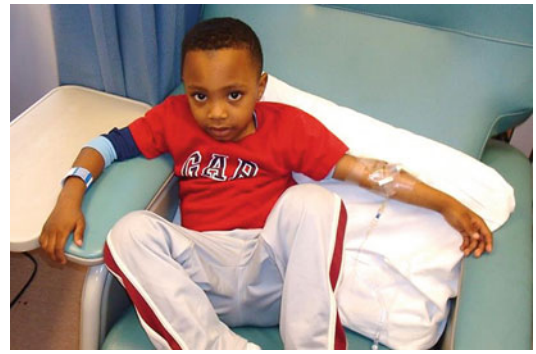

Fig. 2 A 3-year-old male, a brother of the above patient, was also evaluated for immune deficiency because of recurrent upper respiratory infections in the first 2–3 months of life, three pneumonias in later infancy, and a pneumococcus meningitis recently. Recent immunoglobulin levels were IGA of <5 mg/dL, IGG of 184 mg/dL, and IGM of 10 mg/dL. Flow cytometry (immune deficiency panel) revealed CD3, 8 % (1,979); CD4, 55 % (1,365); CD8, 27 % (679); CD4/CD8 ratio, 2:1; CD19+, 1.4 % (34); and CD16+ CD56+, 11 % (270). The patient currently receives intravenous infusion of immunoglobulin (680 mg/kg) and responds well

X-Linked Ichthyosis

Contents

X-linked ichthyosis is a relatively common genetic disorder of keratinization. It is the second most common type of ichthyosis after vulgaris. The incidence is estimated to be between 1 in 2,000 and 1 in 6,000 male live births.

Synonyms and Related Disorders

Placental steroid sulfatase deficiency; Steroid sulfatase deficiency

Genetics/Basic Defects

1. Inheritance
    1. X-linked recessive.
    2. Usually affects males only.
    3. Transmitted by carrier females (about 1 in 2,000 women are carriers of steroid sulfatase (STS) enzyme deficiency).
    4. Most apparently, sporadic cases appear to be inherited based on biochemical analysis (as their mothers showed low values of STS enzyme activity) (Cuevas-Covarrubias et al. 1999).
    5. Reports of a few affected female patients (Mevorah et al. 1981; Murtaza et al. 2014).
2. Etiology (Janniger and Schwartz 2011)
    1. Caused by a deficiency of STS enzyme (Crawfurd 1982)
    2. The *STS* gene
        1. Mapped on the distal part of the short arm of the X chromosome (Xp22.3).
        2. Close to the pseudoautosomal region.
        3. Unlike most X chromosome genes, the *STS* gene escapes the X-inactivation process.
3. Molecular defects
    1. Deletion of the entire steroid sulfatase (*STS*) gene: the most common molecular defect in X-linked ichthyosis (XLI) patients (observed in 90% of patients) (Shapiro et al. 1989).
    2. Partial deletion or point mutation (observed in 10% of patients).
    3. The deletion of *STS* gene may occasionally extend to involve neighboring genes (interstitial and terminal deletions of Xp22.3), resulting in a contiguous gene defect and may be associated with the following conditions. Depending on the length of the

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deletion, these disorders occur independently from each other or in combination as a contiguous gene syndrome (Paige et al. 1994; Aviram-Goldring et al. 2000).
    1. Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)
    2. X-linked chondrodysplasia punctata
    3. Short stature
    4. Mental retardation (Gohlke et al. 2000)
    5. Ocular albinism
    6. Ichthyosis
4. Segregation analysis of paternal transmission of the affected X chromosome (Toral-Lopez et al. 2008): *STS* gene deletion may occur in male meiosis as a result of:
    1. An intrachromosomal event
    2. Recombination between S232 sequences on the same DNA molecule
    3. During the process of DNA replication

Clinical Features

1. Cutaneous manifestation (Hernandez-Martin et al. 1999; Jasmi and Al-Khenaizan 2002)
    1. Generalized scaling of the skin (ichthyosiform hyperkeratosis)
        1. Early onset: usually at birth or within 4 months of life
        2. Large, dark-brown polygonal scales
            1. Usually symmetrically distributed
            2. More prominent on the trunk and the extensor aspects of the limbs
            3. Usually the flexures less affected
        3. Face usually free from scales, except in the preauricular areas, giving the classic "unwashed appearance," which is considered by many to be pathognomonic
        4. Sparing palms and soles in most cases
    2. Normal nails and hair
    3. Seasonal influence
        1. Improve during the summer
        2. Worsen during dry, cold weather
2. Extracutaneous manifestations
    1. Corneal opacities
        1. The most common extracutaneous features
        2. Secondary to deposits of cholesterol sulfate crystals
        3. Asymptomatic (not affecting the visual acuity)
        4. Occurring in the posterior capsule of Descemet's membrane or the corneal stroma (Aviram-Goldring et al. 2000)
        5. More frequent during the 2nd and 3rd decades of life
        6. Observed in 10–50% of affected males and carrier females
    2. Cryptorchidism (Traupe and Happle 1986)
        1. Occurring in 10–20% of patients (versus the incidence of cryptorchidism in the normal population of 1%)
        2. Possible mechanisms
            1. A deficit in the STS enzyme
            2. A genetic disturbance located on the short arm of chromosome X close to the *STS* gene
    3. Patients at an increased risk of testicular cancer development
    4. CNS manifestations
        1. Epileptic seizures
        2. Reactive psychological disorders
    5. Clinical manifestations as a part of the contiguous gene syndrome expression
        1. Kallmann syndrome
        2. Short stature
        3. Mental retardation
        4. X-linked chondrodysplasia punctata
    6. Other rare manifestations
        1. Pyloric hypertrophy
        2. Congenital abdominal wall defect
        3. Acute lymphoblastic leukemia
3. Steroid sulfatase deficiency during pregnancy in carrier females
    1. Leads to an overall decrease in the levels of estrogen
    2. Causes poor cervical dilatation and prolonged labor
    3. Frequently necessitates a caesarean section

Diagnostic Investigations

1. Direct biochemical demonstration of STS deficiency (undetectable levels of STS activity) from the following tissue (Bradshaw and Carr 1986; Hernandez-Martin et al. 1999; Jasmi and Al-Khenaizan 2002):
    1. Placenta
    2. Skin fibroblasts
    3. Leukocytes
    4. Keratinocytes
2. Demonstration of an increase in substrates of STS
    1. Dihydroepiandrosterone sulfate (DHEAS)
    2. Cholesterol sulfate
3. Electrophoresis: rapid migration of serum cholesterol sulfate (negatively charged and carried by low-density lipoprotein (LDL) particles) toward the positive pole during electrophoresis
4. Molecular genetic diagnosis yielding reliable results in most affected patients
    1. Detection of complete deletion of the STS gene in most patients
        1. Fluorescence in situ hybridization (FISH)
        2. Southern blotting (Bonifas and Epstein 1990)
        3. Multiplex polymerase chain reaction (PCR) (Nomura et al. 1995)
    2. Partial deletion by FISH: may provide a false-negative FISH result
    3. A very small number of cases carrying point mutations instead of deletions at the *STS* gene: undetectable by Southern blot or PCR
    4. Phenotype spectrum of X-linked ichthyosis identified by chromosome microarray diagnosis: STS deletions may cause a milder skin phenotype than the typical presentation of X-linked ichthyosis (Hand et al. 2015)
    5. Carrier detection
        1. STS enzyme assay (Cuevas-Covarrubias et al. 1995)
        2. FISH technique especially useful in carrier detection since the enzymatic assay often provides inconclusive results
        3. Somatic and germinal mosaicism for the steroid sulfatase gene deletion in a steroid sulfatase carrier (Cuevas-Covarrubias et al. 2002)

Genetic Counseling

1. Recurrence risk (Ivich 2015)
    1. Patient's sib (given that the mother is a carrier)
        1. Fifty percent of male sibs affected
        2. Fifty percent of female sibs carriers
    2. Patient's offspring
        1. Affected male patients
            1. Male offspring normal
            2. All female offspring carriers
        2. Affected female patients (heterozygous)
            1. Fifty percent of male offspring affected
            2. Fifty percent of female offspring carriers
        3. Affected female patients (homozygous)
            1. All male offspring affected
            2. All female offspring carriers
2. Prenatal diagnosis
    1. Maternal plasma demonstrating low or undetectable unconjugated estriol levels in routine maternal serum screening, which is associated with the following conditions (Braunstein et al. 1976; Ahmed et al. 1998; Zalel et al. 1996; Kashork et al. 2002):
        1. Placental steroid sulfatase deficiency (Lykkesfeldt et al. 1984)
        2. Fetal death
        3. Miscarriages
        4. Anencephaly
        5. Fetal adrenal hypoplasia
        6. High-dose corticosteroid therapy
        7. Aneuploidies
            1. Down syndrome
            2. Triploidy
        8. Smith-Lemli-Opitz syndrome in rare cases

2. Maternal urine (Glass et al. 1998) and plasma (Keren et al. 1995) profile of affected fetuses indicating a primary placental sulfatase deficiency (low estriol levels) (Basler et al. 1992)
3. Amniocentesis (Aviram-Goldring et al. 2000)
    1. Elevated sulfated steroids in the amniotic fluid
    2. FISH to detect deletion in one copy of X chromosome at region Xp22.3 using steroid sulfatase probe (Lebo et al. 1993; Watanabe et al. 2003)
4. Skin biopsy through fetoscopy to measure sulfated steroid

3. Management (Hernandez-Martin et al. 1999)
    1. Most patients have disease limited to the skin.
    2. Spontaneous improvement in most cases with age and during summer months and hardly require any treatment.
    3. Attempt to diminish the abnormal cohesion of corneocytes by facilitating their separation in the milder forms.
        1. Topical keratolytics
        2. Emollients
        3. Hydrating agents
    4. Retinoids for potential treatment in severely affected patients.
    5. Liarozole, a imidazole derivative which inhibits cytochrome P450 to increase the level of endogenous retinoid acid by blocking its P450-dependent catabolism.
    6. Examination of male patients to detect cryptorchidism which has an increased risk of testicular cancer.

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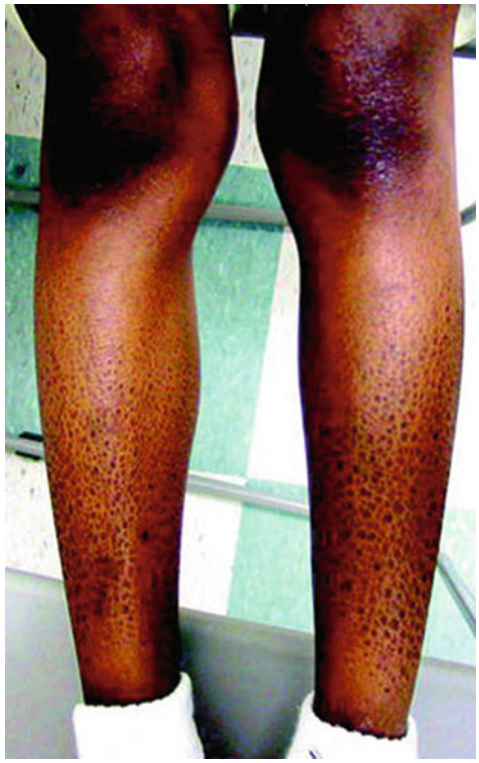

Fig. 1 A sporadic case of X-linked ichthyosis showing thick, large, polygonal, *dark-brown* scales involving the extensor

Fig. 2 X-linked ichthyosis affecting three boys in a family

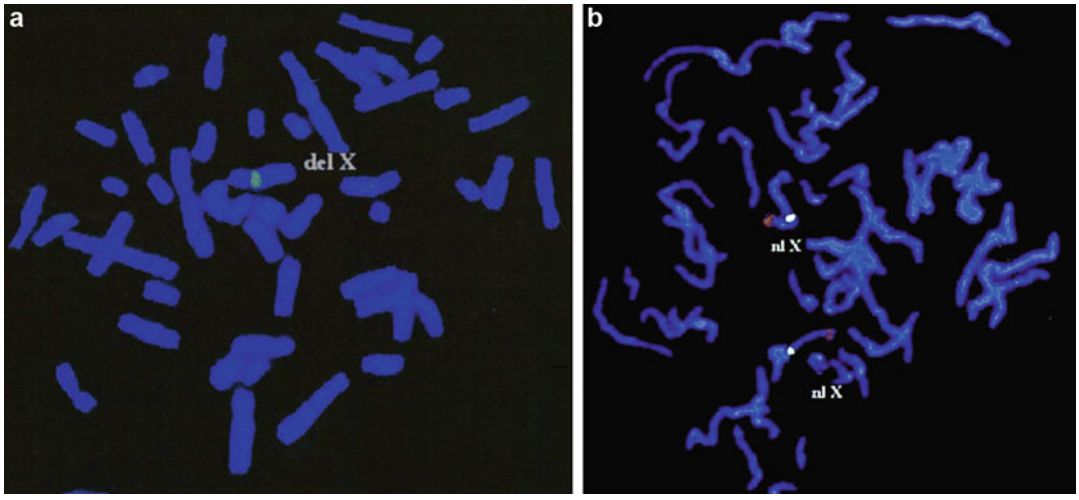

Fig. 3 (**a**, **b**) Abnormal FISH analysis showed a deletion in the steroid sulfatase critical region on the X chromosome [del(X)(p22.3p22.3)(STS-)] in a male fetus (*left photo*). The case was ascertained because of undetectable UE3 from maternal serum screen. The *right photo* (FISH) showed a normal XX control

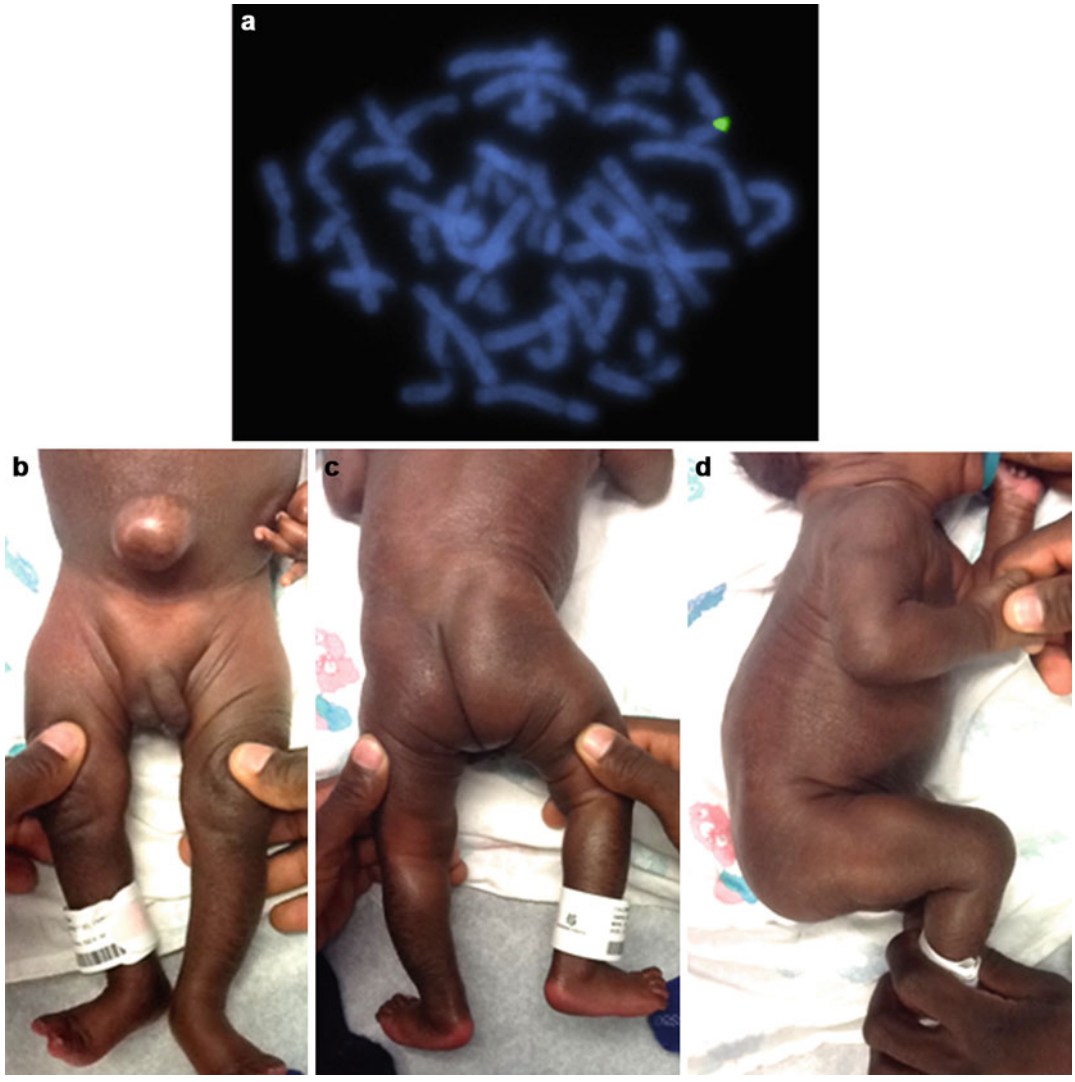

Fig. 4 (**a**–**d**) This 2-month-old premature male infant was evaluated for X-linked ichthyosis. During pregnancy, the mother was noted to have an extremely low maternal serum unconjugated estriol levels (0.1 MOM; 0.9 MOM) which indicated an increased risk for X-linked ichthyosis due to positive family history (maternal grandfather is affected of ichthyosiform hyperkeratosis). The mother was found to be a carrier (46,XX,ish del(X)(p22.3p22.3) (STS-)), a female karyotype with a deletion including the steroid sulfatase gene in the terminal short arm of an X chromosome. Amniocentesis was performed with FISH analysis showing deletion of steroid sulfatase locus, indicative of X-linked ichthyosis of the fetus (**a**). Physical examination of the infant (**b**–**d**) showed generalized dark-brown scaling (polygonal) of the skin (ichthyosiform hyperkeratosis). In addition, the infant has moderate umbilical hernia and bilateral inguinal hernias (**b**).

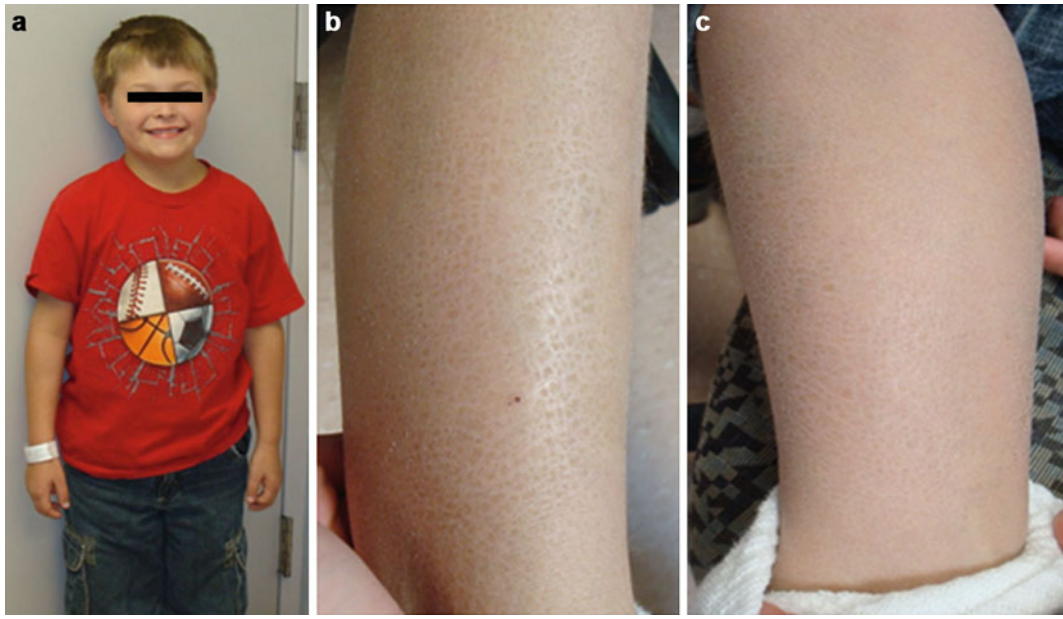

Fig. 5 (**a–c**) This 7-year-old boy was evaluated for X-linked ichthyosis with generalized thick, polygonal, and light-brown scales (ichthyosiform hyperkeratosis). He is tall with height of 130 cm. The chromosome study showed 47,XYY (not shown)

XX Male

Contents

46,XX maleness (XX male syndrome) is a rare disorder occurring in about 1 in 20,000–25,000 newborn males (De la Chapelle 1972; Rajender et al. 2006). Three clinical categories of sex-reversed 46,XX individuals have been identified: (1) XX males with normal external or internal genitalia; (2) XX males with ambiguity, usually detected at birth by external genital ambiguities such as hypospadias, micropenis, or clitoromegaly; and (3) XX true hermaphrodites, who carry internal or external genital ambiguities detected at birth (Valetto et al. 2005). Recently, the term "46,XX testicular DSD (disorder of sex development)" has been proposed for XX male or XX sex reversal (Lee et al. 2006; Hughes et al. 2006; Hughes 2008).

Synonyms and Related Disorders.

46,XX disorder of sex development; 46,XX sex reversal syndrome.

Genetics/Basic Defects

1. Sex differentiation: Please see the chapter on ▶ "XY Female" (Vilain 2009).
2. The *SRY* gene (Valetto et al. 2005).
   1. Located in the short arm of Y chromosome (Yp11.32) near the pseudoautosomal boundary of the Y chromosome.
   2. Encodes the sex-determining region Y protein.
   3. Has many predicted properties of the testis-determining factor (TDF) (Sinclair et al. 1990).
   4. XX transgenic mice carrying the murine *SRY* gene developed as phenotypic male mice (Koopman et al. 1991).
   5. Loss-of-function mutations in the *SRY* gene: can cause a complete sex reversal (genetically male individuals developing as XY females, presenting a streak gonad lacking germ cells) (Jager et al. 1990; Hawkins et al. 1992).
   6. The gene most commonly known to be associated with 46,XX testicular DSD.
      1. Presence of Y chromosome material including *SRY* in some XX individuals: leads to testis determination and the development of a male phenotype.
      2. The majority of XX males carry the *SRY* gene, with the *SRY* gene translocated into the terminus of the X chromosome short arm, as a result of an

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
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XY chromosomal interchange during paternal meiosis, leading to the differentiation of primary gonads into testes (Fechner et al. 1993; Gao et al. 2013).
3. *SRY*-negative individuals resulting from *SRY* gene mutation.

7. Description of three novel 46,XX-SRY-negative patients, two brothers, and an unrelated man with testicular DSD and azoospermia, who carry a microduplication upstream of SOX9. The detailed analyses of these patients and the incorporation of the published datasets have enabled the minimal critical region located ~600 kb upstream of SOX9 to be resolved to an approximately 40 kb element that contains putative enhancers elements and DNA-binding sites for known factors to be involved in early testis formation (Hyon et al. 2015).
8. 46,XX testicular disorder of sex development caused by *SOX9* duplication (Xia et al. 2013).
9. Several genetic mishaps conceive the 46, XX male genotype (Rizvi 2008).
    1. An original 47,XXY configuration with the loss of the Y chromosome early in embryogenesis
    2. A loss-of-function gene mutation on an autosomal chromosome or on the X chromosome that leads to an aberrancy in the testis differentiation pathway
    3. Possibility that 46,XX males actually have a "hidden" cell line with a Y chromosome present ("cryptic mosaicism")
    4. Translocation of the Y chromosome fragment containing the *SRY* gene to the short arm of an X chromosome or an autosome by unequal interchange between homologous regions during paternal meiotic division (Rego et al. 1996)
        1. The affected individual has male sexual characteristics because of the Y fragment, with the testis-determining factor, being located on the autosome or X chromosome, despite the XX sex chromosome pattern.
        2. If the translocation is in a "pseudoautosomal region" proximal to the *SRY* gene, there may be no significant outcome.
        3. Only if the translocation involves the SRY region of the Y chromosome, then the X chromosome will "act" like a Y chromosome in determining the phenotypic gender of the person.

3. Pathogenesis of 46,XX sex reversal syndrome: currently not clear with the following hypotheses (Wang et al. 2009):
    1. Hypothesis of target gene mutation (Liu et al. 2005)
        1. The structural gene that determines human gender may be located in the autosome, which is regulated by the inhibition of X chromosome and the activation of Y chromosome.
        2. 46,XX individuals, due to defects of the inhibition of X chromosome, result in spontaneous activation of the downstream gene in the absence of *SRY* gene, transform into 46,XX males.
    2. Hypothesis of overexpression of *SOX9* gene (SRY box-related gene 9 located in 17q24.3-q25.1): Upregulation of *SOX9* expression caused by chromosomal abnormalities or mediated by other bypass activation (e.g., PGD2) may result in the occurrence of the *SRY*-gene-negative 46, XX male patient.
    3. Hypothesis of Xp-Yp translocation: Abnormal exchange of the ends of X-Y chromosomes (Xp-Yp translocation) occurred during paternal sperm meiosis resulting in X-type sperm containing *SRY* gene, which could lead to 46,XX offspring when combining with eggs.
4. Approximately 85% of individuals with 46, XX testicular DSD (Queipo et al. 2002; Zenteno-Ruiz et al. 2001).
    1. *SRY* positive

2. Phenotypically males with unambiguous male genitalia at birth
3. Not diagnosed until puberty when they fail to proceed normally

5. Remaining 15% of individuals with 46,XX testicular DSD (Zenteno-Ruiz et al. 2001; Kusz et al. 1999).
   1. Genital ambiguity
   2. *SRY* positive in only a minority of cases
6. XX male sex reversal with genital abnormalities associated with a de novo *SOX3* gene duplication (Moalem et al. 2012).
7. Demonstration of altered *SOX3* expression in an individual with XX male sex reversal and suggests that *SOX3* can substitute for *SRY* to initiate male development in humans (Haines et al. 2015).
8. *NR5A1*, previously associated with 46,XY DSD and 46,XX primary ovarian insufficiency, as a novel gene for 46,XX (ovo)testicular DSD (Baetens et al. 2016).
   1. Testicular and ovotesticular DSD may represent different phenotypes resulting from a common cause.
   2. *NR5A1*, a well-established gene for male gonadal development, is also involved in correct female gonadal development, the exact molecular mechanisms of which are still elusive.
   3. Identical NR5A1 missense mutations in two unrelated 46,XX individuals with testicular tissues (Igarashi et al. 2016).
9. 46 XX ovotesticular DSD may present with virilization at puberty and may be accompanied by dysmorphic features (Selver Eklioglu et al. 2015).
10. A proposed classification of causes of 46,XX disorders of sex development (DSD) (Hughes 2008; Öcal et al. 2015).
    1. Disorders of gonadal (ovarian) development
       1. Gonadal dysgenesis
       2. Ovotesticular DSD
       3. Testicular DSD (e.g., *SRY*+, *dup SOX*9, RSP01)
    2. Androgen excess
       1. Fetal
          1. 3β-Hydroxysteroid dehydrogenase 2 (HSD3B2)
          2. 21-Hydroxylase (CYP21A2)
          3. P450 oxidoreductase (POR)
          4. 11β-Hydoxylase (CYP11B1)
          5. Glucocorticoid receptor mutations
       2. Fetoplacental
          1. Aromatase (*CYP19*) deficiency
          2. Oxidoreductase (*POR*) deficiency
       3. Maternal
          1. Maternal virilizing tumors (e.g., luteomas)
          2. Androgenic drugs
    3. Other
       1. Syndromic associations (e.g., cloacal anomalies)
       2. Müllerian agenesis/hypoplasia (e.g., MURCS)
       3. Uterine abnormalities (e.g., MODY5)
       4. Vaginal atresia (e.g., McKusick-Kaufman)
       5. Labial adhesions

Clinical Features

1. Natural history (Vilain 2009)
   1. Approximately 80% of patients
      1. Present after puberty with normal pubic hair and normal penile size, but small testes, gynecomastia, and sterility resulting from azoospermia.
      2. The small testes are usually soft but may become firmer with age.
      3. A minority have cryptorchidism and/or anterior hypospadias (Boucekkine et al. 1994).
      4. Gender role and gender identity are reported as male for the common, unambiguous presentation, but systematic psychosexual assessment has not been performed on a significant number of individuals with 46,XX testicular DSD.
   2. Approximately 20% of patients: ambiguous genitalia noted at birth, typically

penoscrotal hypospadias with or without chordee
3. Untreated patients: similar to typical consequences of testosterone deficiency
    1. Low libido and possible erectile dysfunction
    2. Decrease in secondary sexual characteristics, such as sparse body hair, infrequent need to shave, and reduced muscle mass
    3. Increase in fat mass with lower muscle strength
    4. Increased risk of osteopenia
    5. Increased risk of depression
2. SRY-positive 46,XX males
    1. Present after puberty
        1. Shorter-than-average stature (De la Chapelle 1972)
        2. Gynecomastia
        3. Small testes
        4. Azoospermia
    2. Rarely present with atypical genitalia and are less likely than individuals with *SRY*-negative 46,XX males to have gynecomastia (Ferguson-Smith et al. 1990; Boucekkine et al. 1994; Ergun-Longmire et al. 2005)
3. SRY-negative 46,XX males
    1. Tend to present with ambiguous genitalia at birth, such as penoscrotal hypospadias and cryptorchidism
    2. If untreated, almost always develop gynecomastia around the time of puberty
4. Genotype-phenotype correlations
    1. Presence of *SRY*: often associated with the presence of normal male external genitalia
    2. Absence of *SRY*: more often associated with ambiguous genitalia (Grigorescu-Sido et al. 2005)
    3. Genotype-phenotype correlation: not entirely reliable because a small number of individuals with *SRY*-negative 46,XX males have normal external genitalia (Vilain et al. 1994; Zenteno et al. 1997; Kolon et al. 1998; Vernole et al. 2000; Abusheikha et al. 2001)
5. Long-term outcome: most had male sexual potential and male sex identity as long as testicular tissues were preserved (Kojima et al. 2009)
6. Familial sex reversal (Sarafoglou and Ostrer 2000)
    1. Familial true hermaphroditism and XX maleness
        1. True hermaphroditism is a distinct clinical entity based on the histological findings of the gonads.
        2. True hermaphrodites contain both ovarian and testicular gonadal tissue separately or, more commonly, together as ovotestis.
        3. In contrast, XX males have only testes, and their phenotype varies from normal male to a male with genital ambiguity.
        4. Greater than 80% of the XX males have an *SRY* gene, almost always transmitted as the result of an aberrant Y-to-X chromosomal interchange (Fechner et al. 1993).
        5. Like individuals with Klinefelter syndrome, these males have small testes, but invariably, their stature is significantly shorter.
        6. The majority of the XX males with genital ambiguity, such as micropenis, hypospadias, and cryptorchidism, do not have *SRY* genes (6).
        7. The induction of testicular tissue in this subgroup of XX males underlines the role of genes other than SRY that are involved in sex determination.
    2. Familial 46,XY complete gonadal dysgenesis
        1. Individuals affected with 46,XY complete gonadal dysgenesis lack testicular development and present with streak gonads, well-developed Mullerian structures, absent Wolffian structures, and female phenotype.
        2. Because no other somatic abnormalities are present, they are usually not diagnosed until puberty, when they present

with absence of secondary sexual characteristics and amenorrhea.
3. Genetically, complete 46,XY gonadal dysgenesis is a very heterogeneous disorder with both Y-linked and non-Y-linked forms. Eighty percent of patients with sporadic or familial 46,XY gonadal dysgenesis do not have a mutation or deletion of the *SRY* gene, indicating that other autosomal or X-linked genes have a role in sex determination.
4. Whereas the majority of the cases occur sporadically, there are several reports of pedigrees with familial transmission of the disorder.

3. Familial partial gonadal dysgenesis and embryonic testicular regression syndrome
   1. The term "partial gonadal dysgenesis" has been used to describe individuals who have partial testis determination, dysgenetic gonads, a mix of Mullerian and Wolffian structures, and ambiguous genitalia.
   2. Other terms used to describe this syndrome are "mixed gonadal dysgenesis" or "dysgenetic male pseudohermaphroditism."
   3. It is regarded as part of the clinical spectrum of 46,XY gonadal dysgenesis.
   4. The gonadal histology of patients with 46,XY partial gonadal dysgenesis consists of poorly formed seminiferous tubules in combination with ovarian-like stroma.
   5. Gonads can be dysgenetic in one side and normal testis on the other side or dysgenetic bilaterally.
   6. "Embryonic testicular regression syndrome" is a term used to describe the spectrum of genital anomalies resulting from regression of testis development from 8 to 14 weeks of gestation.
   7. For example, if the regression of the fetal testes occurs between the 8 and 10 weeks of gestation, the individual may have complete absence of gonads, rudimentary Mullerian and/or Wolffian ductal structure, hypoplastic uterus, and female genitalia with or without ambiguity. This condition has been referred as true agonadism or gonadal agenesis.
   8. Regression of the testes after the critical period of male differentiation (around 12–14 weeks) results in anorchia, where the individual has male internal and external genitalia.
   9. Partial testicular regression after the critical period would result to a male phenotype as in anorchia but with small rudimentary testes (Acquafredda et al. 1987).

7. Differential diagnosis
   1. Syndromic XX testicular DSD.
   2. Isolated XX testicular DSD.
   3. Sex chromosome abnormalities.
      1. Klinefelter syndrome
      2. 46,XX/46,XY
      3. 45,X/46,XY
   4. Mosaic duplication of 17q23.1-q24.3 including *SOX9* gene.
   5. 46,XX ovotesticular DSD.
   6. 21-hydroxylase deficiency causing congenital adrenal hyperplasia.
   7. Prenatal exposure of a pregnancy to androgens with an XX karyotype can cause virilization resulting in an infant with ambiguous genitalia that may look similar to those of a male with 46,XX testicular DSD and genital ambiguity.
      1. Externally administered androgens such as danazol
      2. Endogenously produced androgens by the mother

Diagnostic Investigations

1. Routine cytogenetic studies: 46,XX karyotype (Vilain 2009)
2. Endocrine studies
   1. Hypergonadotropic hypogonadism secondary to testicular failure (Pérez-Palacios et al. 1981).

1. Moderately elevated basal serum concentrations of LH and FSH
2. Usually decreased serum testosterone concentration
3. HCG stimulation test
    1. Low to subnormal testosterone response
    2. Little or no elevation of serum testosterone concentration

2. Preservation of hypothalamic-pituitary axis: GnRH stimulation test shows a normal LH and FSH response (not warranted for diagnosis).

3. Testicular biopsies (De la Chapelle 1981)
    1. Decrease in size and number of seminiferous tubules
    2. Peritubular fibrosis
    3. Absence of germ cells
    4. Hyperplasia of Leydig cells
4. Molecular genetic testing
    1. Fluorescence in situ hybridization (FISH) using commercially available FISH probe to locate *SRY* gene on the short arm of one X chromosome
    2. PCR amplification
        1. Used when FISH fails to detect the *SRY* region
        2. More likely to detect a small amount of Y chromosome translocated onto the X chromosome
        3. To detect the Y chromosome material in an individual who is an XX-*SRY*-positive/XX-*SRY*-negative mosaic
    3. Comparative genomic hybridization (CGH) method to identify the small unbalanced chromosome rearrangement implicated in an XX male (Rigola et al. 2002)

Genetic Counseling

1. Recurrence risk (Vilain 2009)
    1. Patient's sib
        1. Sibs of a proband with *SRY* translocation to an X chromosome
            1. Proband with a de novo translocation (in most cases): has a low risk to XX sibs (<1%). No instances of germline mosaicism have been reported, but it remains a possibility.
            2. Proband with familial translocation (father carrying two copies of SRY, one translocated to his X chromosome and one on his Y chromosome): XX sibs will have 46,XX testicular DSD or XX true hermaphroditism; XY sibs will not be affected.
        2. Sibs of a proband with *SRY* translocation to an autosome
            1. Proband with a de novo translocation: risk to sibs not increased.
            2. Proband with familial translocation (father carrying an *SRY* gene translocated onto an autosome): XX sibs of a proband each have a 50% chance of inheriting the translocated *SRY* gene and will have 46,XX testicular DSD or XX true hermaphroditism.
        3. Sibs of a proband with SRY-negative 46, XX testicular DSD: 25% risk
    2. Patient's offspring
        1. Men with SRY-positive 46,XX testicular DSD: infertile
        2. Men with SRY-negative 46,XX testicular DSD: infertile
2. Prenatal diagnosis
    1. Available for pregnancies at risk for SRY-positive 46,XX DSD from fetal cells obtained by amniocentesis or CVS using FISH.
    2. Fetal karyotype discordant with the phenotypic sex observed by ultrasound examination in most cases.
    3. An *SRY*-positive result decreases but does not exclude the likelihood of ambiguous genitalia.
    4. Prenatal diagnosis has been described in several cases (Margarit et al. 1998; Trujillo-Tiebas et al. 2006).
    5. Cell-free fetal DNA (cfDNA) testing: detection of Y chromosome in a 46,XX male with SRY translocation (Benedict et al. 2015).
        1. cffDNA screening in the first trimester indicated presence of Y

chromosome material, consistent with a male fetus.
2. On the ultrasound, a phenotypic male fetus was observed.
3. Results of the amniocentesis, however, revealed 46,XX.
4. A follow-up ultrasound was performed to reassess fetal anatomy following the results of the amniocentesis, which again confirmed nonambiguous male genitalia in the fetus.
5. A fluorescence in situ hybridization probe for the *SRY* gene and X chromosome centromeric control probe DXZ1 were used to analyze metaphase cells. Results indicated that the *SRY* region was present on the distal short arm of one of the X chromosomes [46,XX.ish der(X)t(X;Y)(p22.3;p11.3)(SRY+,DXZ1+)].
6. In summary, a fetus with a 46,XX karyotype with an SRY translocation and normal male genitalia on ultrasound was accurately detected as being male on cffDNA testing. The finding presents an exciting and novel capability of cfDNA technology, but at the same time highlights the limitations of using this new technology as a complementary tool in prenatal care.

3. Management
   1. Testosterone replacement therapy: low-dose testosterone therapy: initiate after age 14 years
      1. Testosterone enanthate injection: preferred
      2. Transdermal patches and gels
   2. Reduction mammoplasty for gynecomastia for:
      1. Failure of regression of gynecomastia after testosterone replacement therapy
      2. Presence of gynecomastia causing psychological distress
   3. Male-to-female transsexual operation for an XX male patient who is eager to live as a female (Kurita et al. 2006)
      1. Resection of the penis
      2. Repositioning of the urethra
      3. Vaginal construction
   4. Orchiopexy
   5. Calcium, exercise, vitamin D, biphosphonates, or calcitonin for osteopenia
   6. Psychological support

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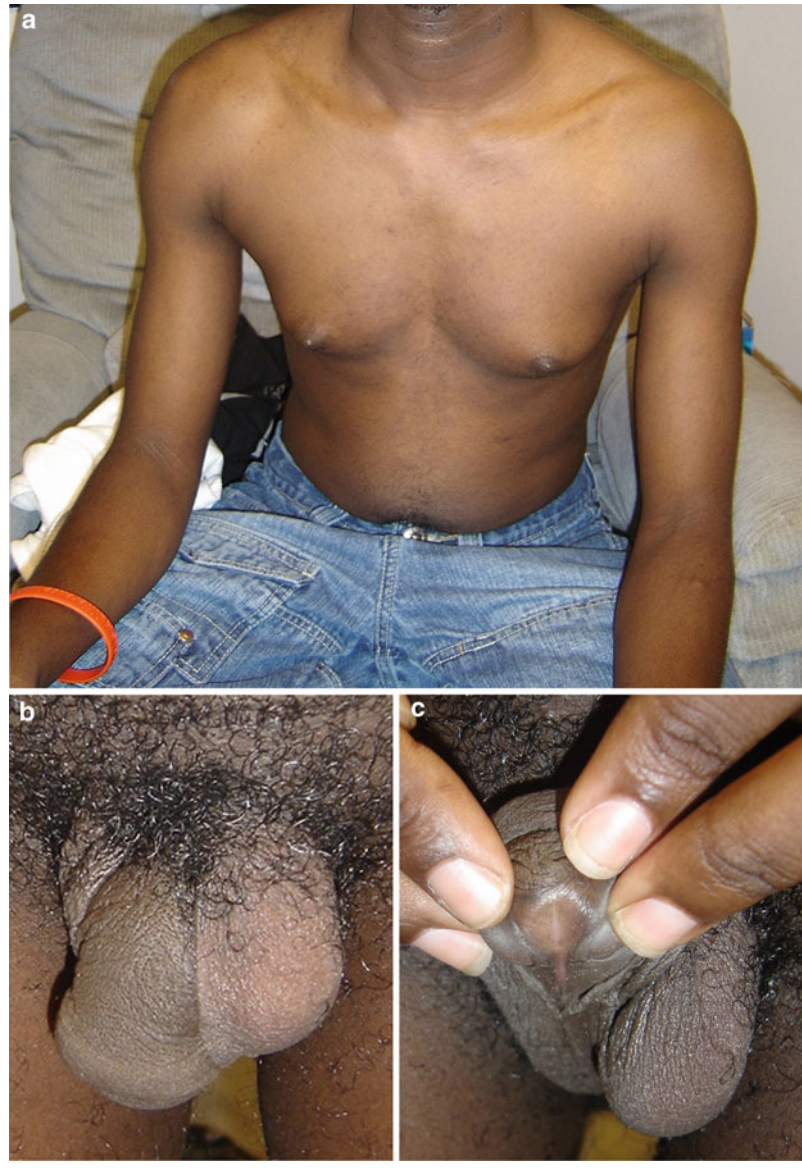

Fig. 1 (**a**–**c**) A 19-year-old phenotypically male patient has been evaluated for slightly high-pitched voice, gynecomastia (**a**), and cryptorchidism on the right, a small atrophic testis on the left (**b**, **c**), and penile hypospadias (**c**). Chromosome study revealed 46,XX

XXX Syndrome

Contents

Females with a 47,XXX karyotype were first described by Jacobs (1979). The incidence of 47,XXX among female newborns is approximately 1 in 1,000 live births (Pennington et al. 1980). It is the most common female chromosomal abnormality. As some individuals are only mildly affected or asymptomatic, it is estimated that only 10% of individuals with trisomy X are actually diagnosed (Tartaglia et al. 2010).

Synonyms and Related Disorders

47,XXX; Trisomy X syndrome

Genetics/Basic Defects

1. Etiology: An extra chromosome X is responsible for 47,XXX.
2. Mechanism of the origin for the 47,XXX condition (Hassold et al. 1990; May et al. 1990).
    1. Almost all 47,XXX result from maternal nondisjunction.
    2. Typically at meiosis I.
    3. The risk of trisomy X increases with advanced maternal age and errors at maternal meiosis I, but not maternal meiosis II.
    4. Postzygotic nondisjunction occurs in approximately 20% of cases.
3. The phenotype in trisomy X is hypothesized to result from overexpression of genes that escape X-inactivation, but genotype-phenotype relationships remain to be defined (Tartaglia et al. 2010).
4. 47,XXX male.
    1. Complex mosaicism in a 53-year-old Japanese male with 46,XX/47,XXX/48,XXXX may be due to the age-related increase in mitotic nondisjunction which is prone to occur in rapidly dividing lymphocytes and to the presence of two randomly inactivated X chromosomes which may behave asynchronously during mitosis.
    2. Clinical features (bilateral hypoplastic scrotal testes, normally formed small penis, relatively poor pubic hair development (tanner stage 3), gynecomastia, age-appropriated male height, and mental retardation) of this male would primarily be explained by the genetic information on the SRY (+) der (X) chromosome and his advanced age (Ogata et al. 2001).

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_251

Clinical Features

1. No specific phenotype exists in 47,XXX females (Chudley et al. 1990).
2. A higher incidence of minor anomalies.
    1. Epicanthal folds
    2. Upslanting palpebral fissures
    3. Ear abnormalities
    4. Clinodactyly
3. Growth and development (Linden et al. 1988; Otter et al. 2010).
    1. Birth weights tend to be slightly lower than the general population.
    2. The physical phenotype shows earlier growth and longer legs.
    3. Taller in older children.
    4. Relative microcephaly.
    5. Hypotonia.
    6. At risk for mild speech/language and motor delays and learning disabilities.
    7. The behavioral phenotype often shows auditory processing disorders, disorders in language development, and problems in forming stable interpersonal relationships.
    8. Psychiatric disorders seem to be more common in triple X syndrome.
    9. Quality of life seems to increase after leaving school.
    10. Intelligence.
        1. Normal range
        2. Lower intelligence quotients (10–15 points) in comparison to unaffected sibs
4. Brain structure and behavioral characteristics in 47,XXX syndrome (Lenroot et al. 2014).
    1. The most common psychiatric disorders present in trisomy X girls included:
        1. Anxiety disorders (40%)
        2. Attention-deficit disorder (17%)
        3. Depressive disorders (11%)
    2. The most strongly affected brain regions are consistent with phenotypic characteristics such as:
        1. Language delay
        2. Poor executive function
        3. Heightened anxiety
5. Expanding the phenotypes of triple X syndrome (Wigby et al. 2016)
    1. Common physical features include hypertelorism, epicanthal folds, clinodactyly, and hypotonia.
    2. Medical problems included dental disorders (44.4%), seizure disorders (16.2%), and genitourinary malformations (12.2%).
6. Gonadal structures and function.
    1. Heterosexual
    2. Normal secondary sexual characteristics
    3. Normal menstruation
    4. Fertility usually normal
    5. Late menarche
    6. Occasional amenorrhea
    7. Premature ovarian failure
    8. Sterility with streak gonads
7. Congenital anomalies reported in a very small number of patients (Barr et al. 1969; Bağci et al. 2010).
    1. Urogenital tract abnormalities
    2. Brain abnormalities including encephalocele and seizures
    3. Skeletal abnormalities
    4. Congenital heart defects
    5. Intestinal atresia
    6. Craniofacial abnormalities
8. Adaptation status: variable (Harmon et al. 1998).
    1. At risk for intellectual and psychological problems
    2. 47,XXX women during adolescence and young adulthood
        1. Less well adapted
        2. With more stress
        3. With work, leisure, and relationship problems
        4. With a lower IQ
        5. With more psychopathology when contrasted with the comparison group
    3. Most 47,XXX women
        1. Self-sufficient
        2. Functioning reasonably well
9. 45,X/47,XXX mosaicism and short stature (Everest et al. 2015).
    1. Phenotypes tend to be milder.

2. The height may be quite short in a way that is out of proportion to the relative mildness of the remainder of the phenotype.

10. De novo Xp terminal deletion in a triple X female with recurrent spontaneous abortions (Malla et al. 2014).
    1. Xp terminal deletion of the extra copy of X chromosome was the only possible cause of recurrent spontaneous abortions.
    2. As the female had two normal copies of X chromosome, no syndromic facies or dysmorphism was observed.
11. Differential diagnosis prior to definitive karyotype results includes (Tartaglia et al. 2010):
    1. Fragile X (please see the chapter on "Fragile X Syndrome")
    2. Tetrasomy X
    3. Pentasomy X (please see the chapter on "XXXXX Syndrome")
    4. Turner syndrome mosaicism (please see the chapter on "Turner Syndrome")

Diagnostic Investigations

1. Chromosome analysis.
2. Triple X syndrome and puberty: focus on the hypothalamus-hypophysis-gonad axis (Stagi et al. 2016).
    1. Triple X syndrome patients showed premature activation of the GnRH pulse generator, even without puberty signs.
    2. Both basal and peak LH and FSH are more elevated than in control subjects, whereas E2 and inhibin levels and ovarian volume are reduced, which may contribute to a reduced gonadal function.
3. Triple X syndrome should also be suspected in patients with short stature, elevated estradiol and low level of IGF-1, even with normal result of arginine provocation test (Li et al. 2012).
4. Psychological and psychiatric evaluation when needed.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased
    2. Patient's offspring (Dewhurst 1978)
        1. An increased risk of a cytogenetically abnormal child but the extent of the risk cannot yet be determined.
        2. Majority of offspring normal.
2. Prenatal diagnosis
    1. By fetal karyotyping from amniocytes or CVS, followed by detailed ultrasonographic examinations of multiple organ systems to screen for possible associated congenital malformations (Bağci et al. 2010).
    2. The frequency of the diagnosis of the 47, XXX karyotype by genetic amniocentesis is estimated to be 1/1000, the same incidence as in the newborn population (Linden et al. 1988).
    3. A rare case of massive congenital bilateral chylothorax in a hydropic fetus with true mosaicism 46,XX/47,XXX (Cremonini et al. 2014).
3. Management
    1. Infancy/toddler: assess milestones
    2. Childhood
        1. Assess school performance
        2. Provide intervention if needed
            1. Speech/language therapy
            2. Physical/occupational therapy
            3. Educational remediation
    3. Adolescence: usually no intervention needed
    4. Adulthood: annual physical examination

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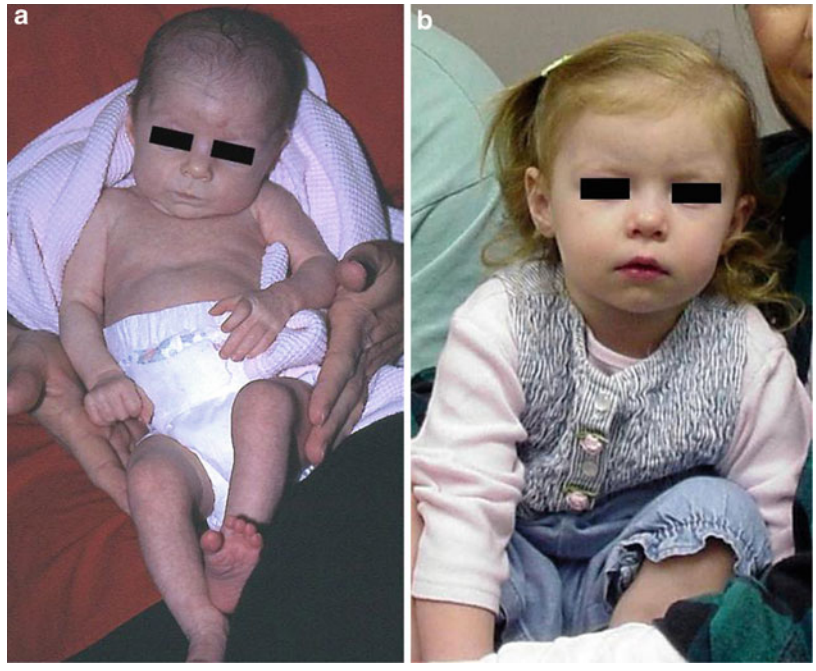

Fig. 1 (**a**, **b**) A girl with 47, XXX at different ages showing normal phenotype

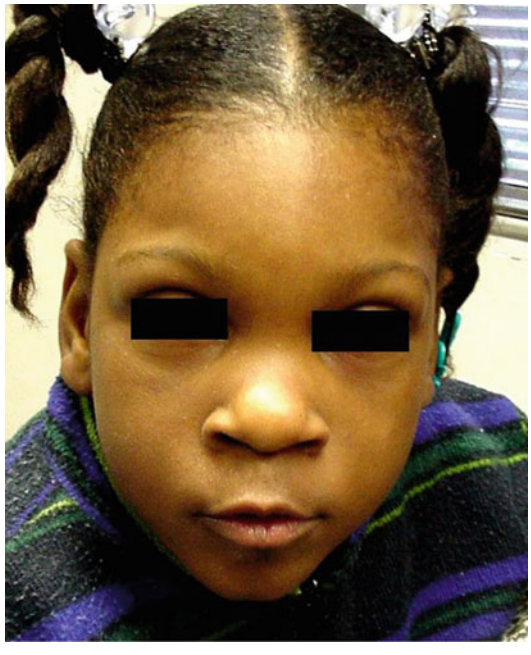

Fig. 2 A girl with 47,XXX showing normal phenotype

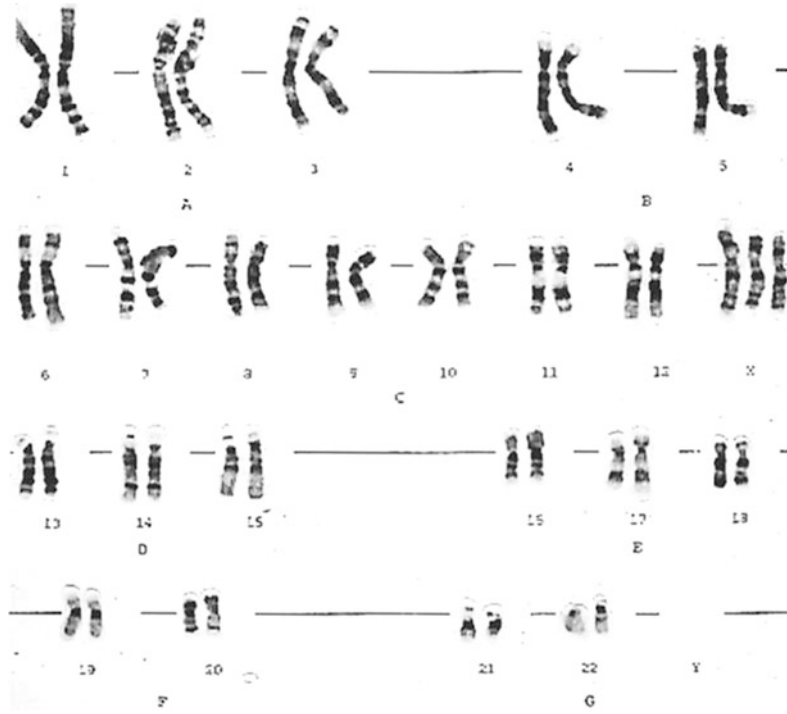

Fig. 3 47,XXX karyotype

XXXXX Syndrome

Contents

49,XXXXX (pentasomy X), a rare sex chromosome aneuploidy, was first described by Kesaree and Woolley (1963). The birth prevalence of pentasomy X is estimated to be one in 85,000 females (Martini et al. 1993).

Synonyms and Related Disorders

49,XXXXX syndrome; Penta X; Pentasomy X syndrome

Genetics/Basic Defects

1. Etiology: Three extra X chromosomes are responsible for the pentasomy X syndrome (Brody et al. 1967; Archidiacono et al. 1979).
2. Parental origin of the extra chromosomes: All four X chromosomes in 49, X polysomies were maternal in origin (Leal et al. 1994; Cho et al. 2004).
3. Occurrence of a 49,XXXXX complement: secondary to sequential nondisjunctions in meiosis I and meiosis II in the mother (Kassai et al. 1991; Martini et al. 1993).
    1. Involves the survival of both X chromosomes in a single oocyte through both meiotic divisions (Deng et al. 1991)
        1. Once between homologous X chromosomes at the first meiosis
        2. Twice between sister chromatids in both X chromosomes in the secondary oocytes at the second meiosis
    2. Followed by the fertilization by a sperm contributing the fifth chromosome X
4. Formation of four Barr bodies.
    1. Lyon hypothesis
        1. Inactivation of all X chromosomes but one
        2. Accounts for the viability of the X chromosome aneuploidies
    2. Inactivation of four X chromosomes resulting in four Barr bodies
5. Four presumably inactive X chromosomes were late replicating but not in a strictly synchronous fashion (Monheit et al. 1980).
6. X chromosome inactivation in a 49,XXXXX pentasomy (Moraes et al. 2009): 12% of X chromosomes with the M1 haplotype, 43.5% of X chromosomes with the M2 haplotype, and 100% of the paternal X chromosome (with the P haplotype) were likely to be functionally active in the proband's cells, a finding

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_252

indicating that disruption of X inactivation was associated with her severe phenotype.

7. Effect of supernumerary X chromosomes: a direct relationship between the number of supernumerary X chromosomes and phenotypic abnormalities and mental retardation, with each additional chromosome increasing the severity (Linden et al. 1995).
    1. Affects somatic development most significantly
        1. Skeletal abnormalities
        2. Cardiovascular abnormalities
    2. Delays sexual development
    3. Affects cognitive development
        1. Severe mental retardation
        2. Language delay (both expressive and receptive language)
        3. Behavioral problems

Clinical Features

1. Growth and development
    1. Prenatal growth retardation
    2. Small birth weight
    3. Low postnatal weight
    4. Failure to thrive
    5. Hypotonia
    6. Short stature
    7. Delayed psychomotor retardation
    8. Mental retardation
2. Craniofacial features
    1. Microcephaly
    2. Flattened occiput
    3. Epicanthus
    4. Upslanting palpebral fissures
    5. Ocular hypertelorism
    6. Uncoordinated eye movements
    7. Flat broad nose
    8. Cleft palate
    9. Low-set ears
    10. Malformed teeth
3. Skeletal abnormalities
    1. Short neck
    2. Lax joints
    3. Multiple dislocations (Dryer et al. 1979)
        1. Shoulders
        2. Elbows
        3. Hips
    4. Radioulnar synostosis
    5. Spinal abnormalities
    6. Thenar atrophy (Demirhan et al. 2015)
    7. Clinodactyly of the fifth fingers
    8. Lower leg abnormalities
        1. Genu valgum
        2. Talipes
        3. Metatarsus varus
    9. Delayed bone age
4. Congenital heart defects
    1. Ventricular septal defect
    2. Patent ductus arteriosus
5. Abnormal lobulation of the lungs
6. Renal hypodysplasia (Toussi et al. 1980)
7. Sexual development
    1. Delayed puberty
    2. Incomplete secondary sexual development
    3. Small uterus
    4. Hypoplastic/absent ovaries
        1. Composed mainly of stroma and atrophic follicles
        2. Absence of ova
        3. Unilateral absence of an ovary (Toussi et al. 1980)
    5. Reduced fertility
8. Normal external genitalia
9. Dermatoglyphics
    1. Finger-dermal-ridge hypoplasia and a low total ridge count, consistent with the inverse proportion between the number of X chromosomes and the total ridge count (exceptions exist)
    2. Transverse palmar creases
10. 48,XXXX/49,XXXXX mosaicism (Cirillo Silengo et al. 1979)
    1. The physical findings are similar to those of the cases with a penta-X chromosome and are also similar to the signs of the more common 49,XXXXY syndrome of males (Sergovich et al. 1971).
    2. In both instances, the dysmorphic features are less impressive than the mental retardation and the skeletal malformations.
    3. A newborn girl with a life-threatening laryngomalacia and extreme hypotonia (Schoubben et al. 2011).

11. 47,XXX/48,XXXX/49,XXXXX mosaicism (Wood et al. 2011)
    1. Primary amenorrhea
    2. Physical features
        1. Epicanthal folds
        2. Long philtrum
        3. High-arched palate
        4. Facial asymmetry
        5. Short webbed neck
        6. Low posterior hairline
        7. Mild scoliosis
        8. Cubitus valgus
        9. Clinodactyly
        10. Osteoporosis
        11. Premature ovarian failure
        12. Mental retardation

Diagnostic Investigations

1. Chromosome analysis
    1. 49,XXXXX karyotype in peripheral blood lymphocytes and skin fibroblasts (Funderburk et al. 1981).
    2. Fluorescence in situ hybridization (FISH), using DNA probe for α-satellite sequence in chromosome X (DXZ1), reveals five signals representing the presence of XXXXX.
2. Radiography
    1. Dislocations of the shoulder (with hypoplasia of the glenoid process) (Dryer et al. 1979), elbows, and/or hips
    2. Radioulnar synostosis
    3. Clinodactyly

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased
    2. Patient's offspring: not reported due to severe mental retardation
2. Prenatal diagnosis
    1. Ultrasonography.
        1. Cystic hygroma (Sepulveda et al. 1999)
        2. Transient hydrops fetalis (Aytac et al. 2012)
        3. Bilateral radioulnar synostosis
        4. Dandy-Walker malformation (Myles et al. 1995)
        5. X pentasomy in an intracytoplasmic sperm injection pregnancy detected by nuchal translucency testing (Cheng et al. 2008)
    2. Amniocentesis and CVS.
        1. Chromosome analysis
        2. FISH (Myles et al. 1995) using DNA probe (DXZ1) applied to uncultured amniocytes
    3. The need to include a noninvasive prenatal test (NIPT), which expands clinical coverage to include the X and Y chromosomes in routine prenatal diagnosis as molecular noninvasive tool, and three-dimensional ultrasound to detect any helpful indicative echographic prognostic signs should be evaluated (Samango-Sprouse et al. 2013; Pirollo et al. 2015).
3. Management
    1. Physical/occupational therapy
    2. Speech therapy

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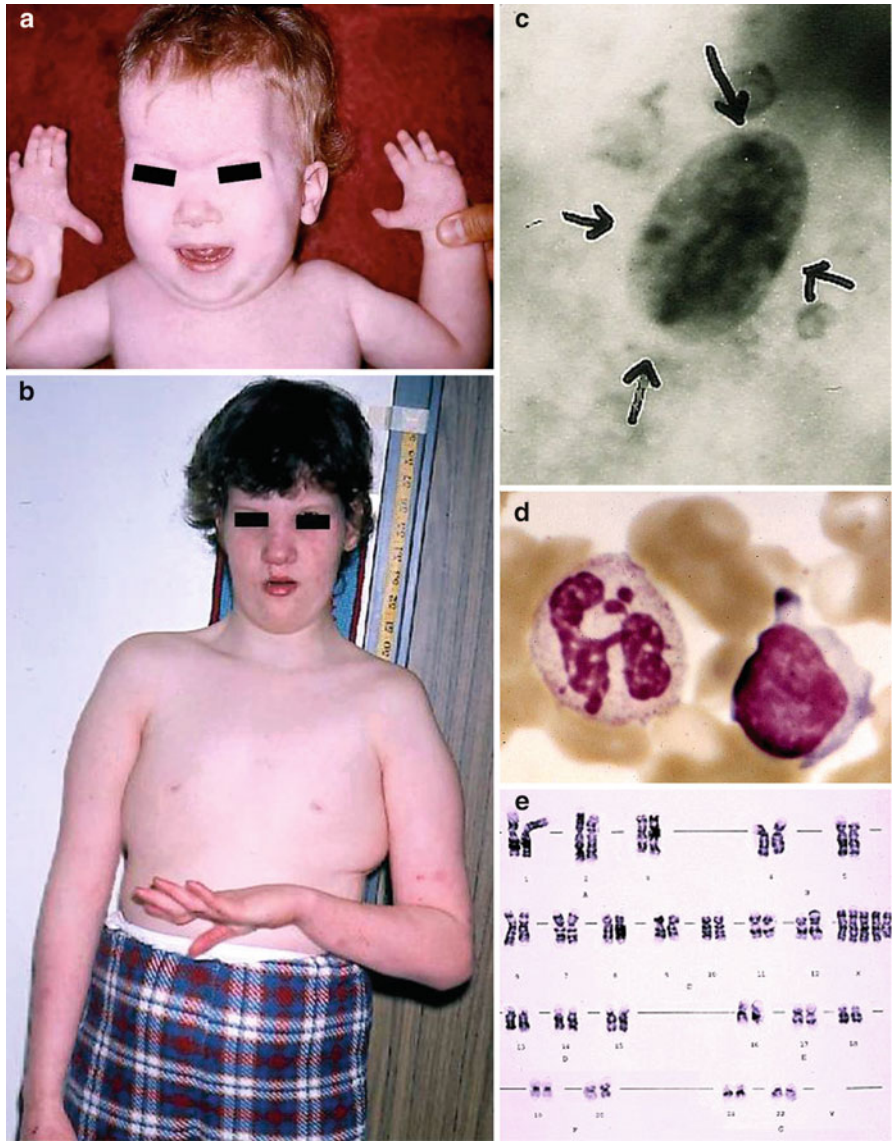

Fig. 1 (**a**–**e**) The first reported case of 49,XXXXX (Kesaree and Woolley 1963) at infancy (**a**) and adulthood (**b**) with four Barr bodies (*arrows*) (**c**), two drumsticks in a polymorphonuclear leukocyte (**d**), and a karyotype of 49, XXXXX (**e**)

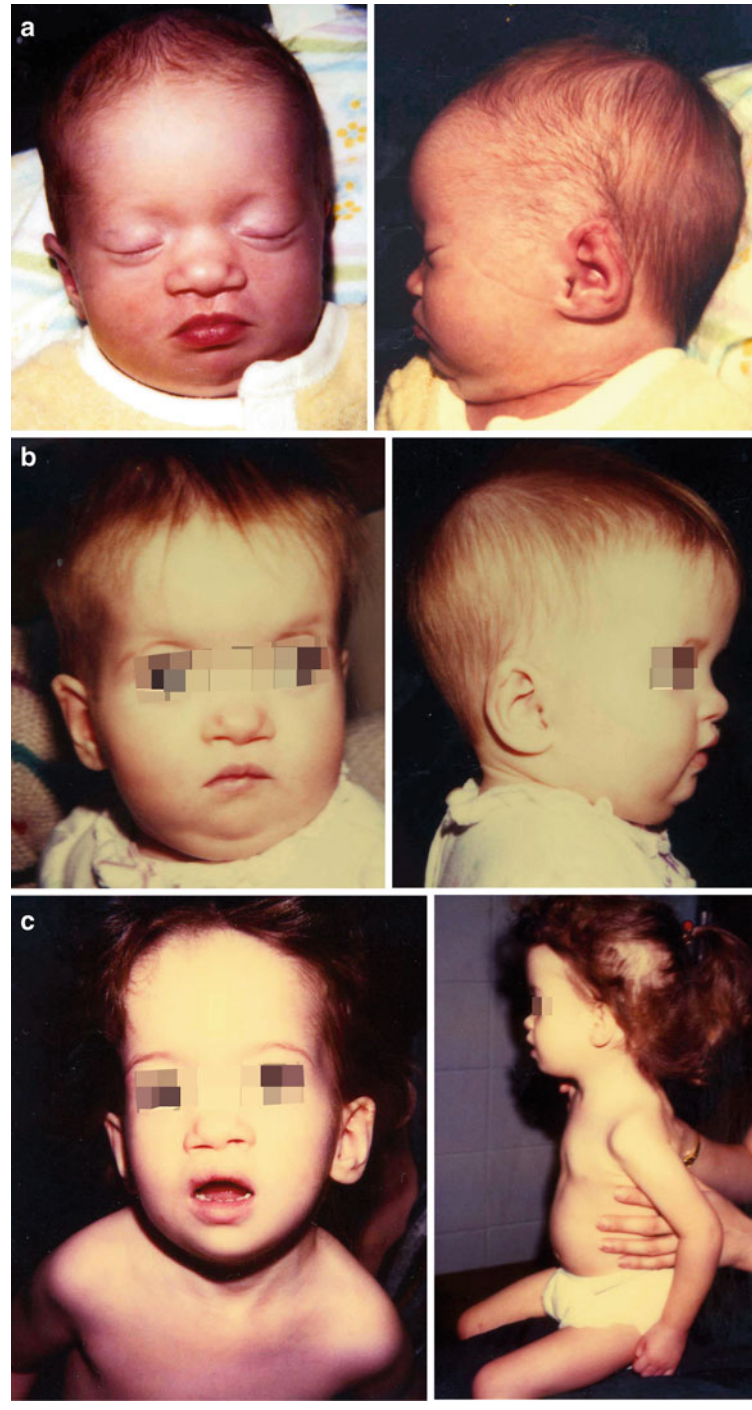

Fig. 2 (**a**–**f**) A girl with 49, XXXXX syndrome at birth (**a, b**), 6 months (**c, d**), and 2 years and 4 months (**e, f**)

XXXXY Syndrome

Contents

49,XXXXY syndrome was first described by Fraccaro and Lindsten in 1960. The incidence is estimated to be approximately 1 in 85,000 newborn males (Pallister 1982).

Synonyms and Related Disorders

48,XXXY/49,XXXXY mosaicism; 49,XXXXY syndrome

Genetics/Basic Defects

1. Etiology: three extra X chromosomes are responsible for the 49,XXXXY syndrome.
2. Mechanism.
    1. All four X chromosomes are of maternal in origin.
    2. Resulting from successive nondisjunctions in maternal meiosis I and II, fertilized by a normal Y sperm (Deng et al. 1991; Villamar et al. 1989; Chen et al. 2000; Etemadi et al. 2015).
    3. Inactivation of three out of four X chromosomes results in three Barr bodies (Lyon hypothesis).
3. Effect of supernumerary X chromosomes: a direct relationship between the number of supernumerary X chromosomes and phenotypic abnormalities and mental retardation, with each additional chromosome increasing the severity.
    1. Somatic development most significantly affected
        1. Skeletal abnormalities
        2. Cardiovascular abnormalities
    2. Gonadal development in males: particularly susceptible to extra genetic material
        1. Addition of a single X chromosome to a 46,XY karyotype resulting in seminiferous tubal dysgenesis rendering infertile such males with Klinefelter syndrome.
        2. Additional extra X chromosomes in polysomy X males such as 48,XXXY and 49,XXXXY can result in not only infertility but also hypoplastic and malformed genitalia.
    3. Affects cognitive development
        1. Severe mental retardation
        2. Language delay (both expressive and receptive language)
        3. Behavioral problems

H. Chen (ed.), *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_253

Clinical Features

1. A distinct phenotype (Peet et al. 1998).
2. "Classic triad" (Peet et al. 1998).
    1. Mental retardation
    2. Radioulnar synostosis
    3. Hypogonadism
3. Growth and development.
    1. Growth retardation
    2. Severe speech impairment
    3. Varying degree of mental retardation
4. Craniofacial features.
    1. Microcephaly
    2. A full, round face
    3. Ocular hypertelorism
    4. Upslanted palpebral fissures
    5. Epicanthus
    6. Broad nasal bridge
    7. Micrognathia
    8. Prognathism
    9. High-arched or cleft palate
    10. Irregular teeth implantation
    11. Malformed ears
5. Ocular abnormalities: The dural ectasia may have facilitated access of cerebrospinal fluid through anomalous optic nerves, resulting in neurosensory (macular) detachment (Hajrasouliha et al. 2016).
6. Webbed and short neck.
7. Congenital heart defects (Karsh 1975).
    1. Patent ductus arteriosus
    2. Atrial septal defect
    3. Pulmonic stenosis
    4. Tetralogy of Fallot
8. Musculoskeletal abnormalities (Sprouse et al. 2013).
    1. An increased incidence of;
        1. Hypotonia
        2. Clubfoot
        3. Avascular necrosis of the femoral head
        4. Radioulnar synostosis (Kidszun et al. 2012)
        5. Pes planus
    2. Short stature
    3. Proximal tibiofibular synostosis (Nishimura et al. 2008)
    4. Vertebral anomalies
    5. Clinodactyly of the fifth fingers
    6. Coxa valga
    7. Genu valgum
9. Genital abnormalities.
    1. Hypoplastic male genitalia.
    2. Micropenis.
    3. Hypospadias.
    4. Small testes.
    5. Hypogonadism.
    6. Infertility.
    7. Cryptorchidism: very common and absence of Leydig's cells may differentiate the XXXXY chromosome anomaly from polysomic variants of Klinefelter's syndrome (Zaleski et al. 1966).
    8. Leydig cell tumor (Maqdasy et al. 2015).
10. Renal abnormalities: hydronephrosis caused by intravesical ureterocele (Kojima et al. 1999).
11. A high incidence of both atopy and antibody deficiency in boys with 49,XXXXY (Keller et al. 2013).
12. Dermatoglyphics.
    1. Decrease in total finger ridge count
    2. Transverse palmar creases
13. Psychological/behavioral features (Curfs et al. 1990; Lomelino and Reiss 1991).
    1. Language development: severely retarded with a remarkable discrepancy between language expression and comprehension
    2. Emotional disturbances with low frustration level
    3. Adaptive function higher than cognitive function
    4. Timid and shy
    5. Strong reaction to minor changes
14. The phenotypic presentation of the boys with 49,XXXXY (Gropman et al. 2010).
    1. Shares some characteristics with 47, XXY
    2. Other unique and distinctive features
        1. Previously unappreciated intact nonverbal skills are evident in conjunction with moderate to severe developmental dyspraxia.
        2. Variability in clinical and cognitive functioning may reflect skewed X inactivation, mosaicism, or other factors that warrant further investigation.

15. 48,XXXY/49,XXXXY mosaicism (Milani et al. 2015).
    1. Report of the first case of a craniocervical junction (CVJ) malformation associated with 48,XXXY/49,XXXXY syndrome.
    2. The mosaicism can lead to a milder neuroradiological phenotype.
    3. Mosaicism could also have an effect on two different embryogenetic components of CVJ (the central pillar and the surrounding rings) leading to different and coexisting dysmorphic aspects (platybasia and hyperhypoplastic occipital condyles).
    4. Skeletal abnormalities are not exclusively related to the limbs, but also to the axial structures (such as the cervical spine) and could give neurological signs.
    5. Considering all the reported abnormalities and the possible relevant clinical impact of some findings, the neuroradiological assessment (MRI and CT) seems potentially useful in the diagnostic approach to patients with 48,XXXY and 49,XXXXY syndrome.

Diagnostic Investigations

1. Chromosome analysis showing 49,XXXXY.
2. Radiography (Houston 1967).
    1. Elbows
        1. Proximal radioulnar dysostosis
        2. Radioulnar dislocation without synostosis
        3. Elongated upper radius
        4. Wide, club-shaped proximal ulna
    2. Wrists and hands
        1. Elongated distal ulna
        2. “Pseudoepiphyses”
        3. Clinodactyly of the fifth fingers
        4. Brachymesophalangia V
        5. Retarded bone age
        6. Corner defect in capitate
        7. Poor modeling of the fifth metacarpals
    3. Pelvis and hips
        1. Coxa valga
        2. Narrow iliac wings
    4. Knees
        1. Shallow intercondylar fossa
        2. Genu valgum
    5. Ankles and feet
        1. Gap between the first and second toes
        2. Short wide distal phalanx of the great toes
    6. Skull
        1. Sclerotic cranial sutures
        2. Thick cranial vault
        3. Ocular hypertelorism
        4. J-shaped sella
        5. Prognathism
    7. Spine
        1. Scoliosis
        2. Thoracic kyphosis
        3. Square vertebral bodies
    8. Sternum
        1. Thick
        2. Abnormal segmentation
3. Echocardiography for congenital heart defects.
4. EEG for seizure activity (Galasso et al. 2003).
5. MRI of the brain (Hoffman et al. 2008).
    1. Varying degree of brain volume loss.
    2. Abnormalities in white matter.
    3. Enlargement in the occipital horn of the left hemisphere (Galasso et al. 2003).
    4. Cerebral white matter changes in children are generally considered suggestive of an underlying metabolic defect. Our findings and the review of the literature also strongly suggest that chromosomal abnormalities, and in particular 49,XXXXY syndrome, should also be considered (Tabarki et al. 2012).
6. A pediatric magnetic resonance imaging study: Brain morphological abnormalities in 49, XXXXY syndrome (Blumenthal et al. 2013).
    1. Total brain size was significantly smaller and rates of brain abnormalities such as colpocephaly, plagiocephaly, periventricular cysts, and minor craniofacial abnormalities were significantly increased.
    2. White matter lesions were identified in 50% of subjects, supporting the inclusion of 49, XXXXY in the differential diagnosis of small multifocal white matter lesions.

3. Further evidence of abnormal development of white matter was provided by the smaller cross sectional area of the corpus callosum.
4. These results suggest that increased dosage of genes on the X chromosome has adverse effects on white matter development.

7. Frontal aslant tract abnormality on diffusion tensor imaging in an aphasic patient with 49, XXXXY syndrome: A poorly developed frontal aslant tract may underlie the expressive language deficits and provide some insight into the role of X chromosome in modulating the development of language tracts (Dhakar et al. 2016).
8. Histology of testicular biopsies: dysgenesis of testicular germ cells and tubules leading to fibrosis.
9. Fetal pathology (Rehder et al. 1986).
    1. Facial aspect featuring fetal Down's syndrome
    2. Hypogenitalism and hypogonadism with excessive reduction of germ cells
    3. Skeletal abnormalities that may be interpreted as early changes, preceding phalangeal shortening V and radioulnar synostosis.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased
    2. Patient's offspring: no offspring due to infertility of the condition
2. Prenatal diagnosis
    1. Ultrasonography (Chen et al. 2000; Schluth et al. 2002)
        1. Intrauterine growth retardation
        2. Hydrops fetalis
        3. Cystic hygroma (Sepulveda et al. 1999): the commonest finding (Peitsidis et al. 2009)
        4. Polyhydramnios
        5. Clubfoot
        6. Micropenis
    2. Amniocentesis and CVS
        1. Chromosome analysis
        2. FISH using DNA probe (DXZ1) applied to uncultured amniocytes
3. Management
    1. Early intervention and stimulation programs
        1. Speech/language therapy
        2. Physical/occupational therapy
    2. Testosterone replacement therapy
        1. Continuous treatment with testosterone can have a beneficial effect on neurobehavioral phenotype and psychosocial adaptation in patients with sex chromosome aneuploidy (Galasso et al. 2003).
        2. After 12 months of treatment, normalization of testosterone levels was observed. There was also an increase in pubic hair growth, testicular volume and penis size, weight loss, homeostatic model assessment index reduction, and the normalization of vitamin D values. Moreover, the patient showed greater interaction with the social environment and context (Mazzilli et al. 2016).

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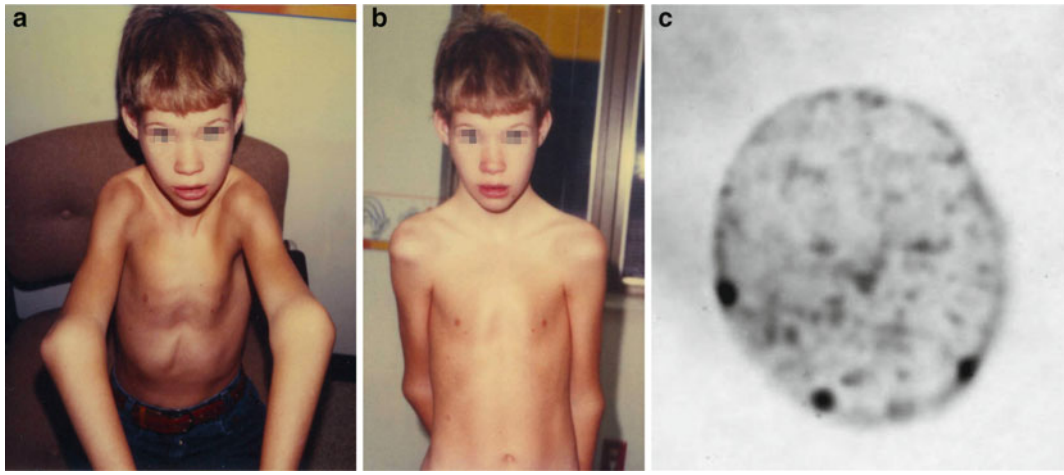

Fig. 1 (**a**–**c**) An older boy with 49,XXXXY showing bilateral dislocation of the elbows, radioulnar synostosis (**a**, **b**), and three Barr bodies (buccal smear) (**c**)

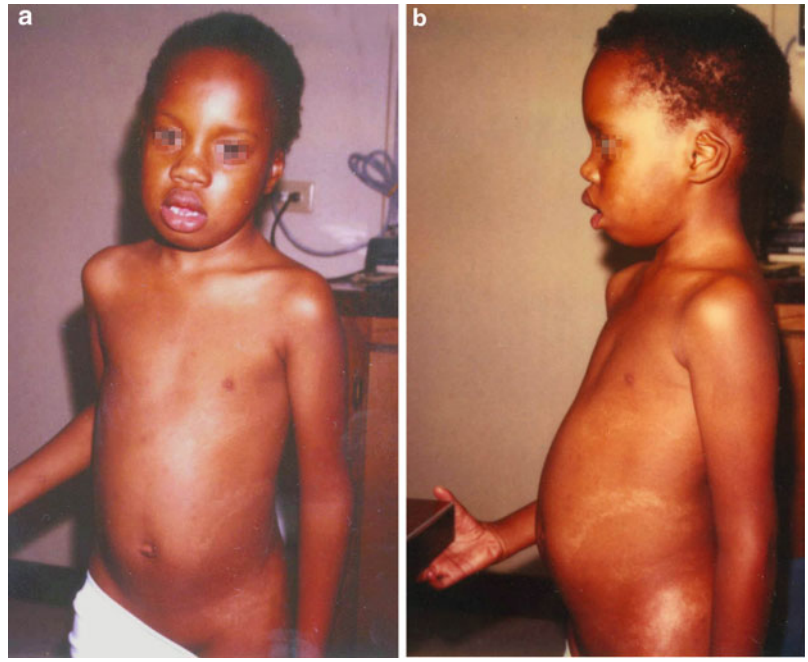

Fig. 2 (**a**, **b**) A younger boy with 49,XXXXY showing a full, round face (**a**, **b**). He also has incontinentia pigmenti achromians (**b**)

XY Female

Contents

XY females are completely sex-reversed individuals who are phenotypically females with 46,XY karyotype, failure to develop secondary sex characteristics, amenorrhea, and "streak gonads."

Synonyms and Related Disorders

46,XY female with complete gonadal dysgenesis; 46,XY female with partial gonadal dysgenesis; 46,XY disorder of sex development; 46,XY sex reversal syndrome; Androgen Insensitivity Syndrome; Embryonic testicular regression syndrome

Genetics/Basic Defects

1. Inheritance: genetic heterogeneity (Simpson et al. 1981; Sarafoglou and Ostrer 2000).
    1. Familial 46,XY complete gonadal dysgenesis.
        1. Genetically, complete 46,XY gonadal dysgenesis is a very heterogeneous disorder with both Y-linked and non-Y-linked forms.
        2. Eighty percent of patients with sporadic or familial 46,XY gonadal dysgenesis do not have a mutation or deletion of the SRY gene, indicating that other autosomal or X-linked genes have a role in sex determination.
        3. Whereas the majority of the cases occur sporadically, there are several reports of pedigrees with familial transmission of the disorder.
        4. One would not expect a Y-linked form of familial 46,XY dysgenesis, because affected 46,XY individuals are usually sterile females and, thus, unable to pass on the mutant gene. Yet, one third of the described SRY mutations are inherited. In all three pedigrees, the fathers carried the transmitted mutation without being mosaic for wild-type SRY and mutant SRY alleles.
        5. Less puzzling are the familial cases of 46,XY gonadal dysgenesis for which the father has mosaicism for an SRY mutation.
        6. Familial 46,XY sex reversal can be paternally inherited (Bhagavath et al. 2014).
            1. This is the first report of a familial 46, XY sex reversal in three siblings

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caused by paternally inherited deletion in the region upstream of SOX9.
2. Our report further confirms that a 67 kb region upstream of SOX9 gene is critical for the development of testis from the indeterminate gonad.
3. Small deletions confined around this region can result in sex reversal without campomelic or acampomelic dysplasia and could predispose to gonadoblastoma.

7. Evidence for an X-specific gene involved in sex determination was first postulated after the identification of a family with three phenotypic 46,XY females in three different sibships related via the maternal line. Later, another pedigree demonstrated five phenotypic 46, XY females in three different sibships and with a similar mode of transmission of the disorder.
8. An autosomal recessive mode of inheritance has been postulated as another mechanism for 46,XY sex reversal because of the rate of affected individuals are ~28.6% in one pedigree or by virtue of the association of 46,XY gonadal dysgenesis with other syndromic features.

2. Familial partial gonadal dysgenesis and embryonic testicular regression syndrome.
   1. The term "partial gonadal dysgenesis" has been used to describe individuals who have partial testis determination, dysgenetic gonads, a mix of Mullerian and Wolffian structures, and ambiguous genitalia. Other terms used to describe this syndrome are "mixed gonadal dysgenesis" or "dysgenetic male pseudohermaphroditism." It is regarded as part of the clinical spectrum of 46,XY gonadal dysgenesis. The gonadal histology of patients with 46,XY partial gonadal dysgenesis consists of poorly formed seminiferous tubules in combination with ovarian-like stroma. Gonads can be dysgenetic in one side and normal testis on the other side or dysgenetic bilaterally.
   2. "Embryonic testicular regression syndrome" is a term used to describe the spectrum of genital anomalies resulting from regression of testis development from 8 to 14 weeks of gestation.
      1. If the regression of the fetal testes occurs between the 8 and 10 weeks of gestation, the individual may have complete absence of gonads, rudimentary Mullerian and/or Wolffian ductal structure, hypoplastic uterus, and female genitalia with/or without ambiguity. This condition has been referred as true agonadism or gonadal agenesis.
      2. Regression of the testes after the critical period of male differentiation (around 12–14 weeks) results in anorchia, where the individual has male internal and external genitalia.
      3. Partial testicular regression after the critical period would result to a male phenotype as in anorchia but with small rudimentary testes.
   3. The etiology of either of the above syndromes is very heterogeneous.
      1. Some of the subjects with 46,XY partial gonadal dysgenesis seem to have autosomal abnormalities.
      2. Sporadic cases of partial gonadal dysgenesis have been described with mutations of the WT1 genes and deletions of 9p and 10q chromosomes.
      3. Only two SRY mutations, a de novo deletion 3′ to the SRY-ORF and a missense mutation 5′ to SRY-ORF, have been found in two subjects with sporadic partial gonadal dysgenesis.
      4. The causes of the vast majority of cases of partial gonadal dysgenesis or embryonic testicular regression are unknown.
      5. Analysis of families with several affected individuals with either 46,

XY partial gonadal dysgenesis or embryonic testicular regression syndrome implicate X-linked, autosomal recessive, or autosomal dominant inheritance.

3. The mechanism of familial sex reversal seems to be due to SRY mutations, mutations in autosomal or X-linked genes, and gonadal mosaicism or chimerism for a Y chromosome-bearing cell line.
    1. As has been shown for SRY and for other sex-determining genes, such as *SOX9*, *WT1 SF-1* (Siklar et al. 2014), and *XH2*, there is phenotypic variability associated with different mutations.
    2. Novel mutation of the sex-determining region on the Y chromosome in a 46,XY female patient with monolateral dysgerminoma (Battaglia et al. 2013).
    3. A 46,XY female DSD patient with bilateral gonadoblastoma, a novel *SRY* missense mutation combined with a *WT1* KTS splice-site mutation (Hersmus et al. 2012).
    4. As a guide for identifying new genes, presence of syndromic features may be suggestive of mutation in a known gene.
    5. Preliminary linkage studies demonstrate that other genes, the identities of which have not yet been established, are likely to play a role.

2. Sexual differentiation (Michala and Creighton 2010): Genetic sex is determined at conception, when the ovum is fertilized by an X or Y chromosome containing spermatozoon (Ahmed and Hughes 2002).
    1. Testicular development
        1. The presence of the Y chromosome directs testicular development, through a switch gene present on its short arm, called the *SRY* gene (Sinclair et al. 1990).
        2. This, along with other testes-determining factors (TDFs), will guide the differentiation of the undifferentiated gonad into testicular tissue (Cameron and Sinclair 1997).
        3. Further genital differentiation is promoted by hormones that are produced by testicular tissue and that will lead to virilization.
        4. Sertoli cells produce anti-Müllerian hormone (AMH), which triggers the regression of Müllerian structures while Leydig cells secrete testosterone, which promotes the development of Wolffian structures into the vas deferens, seminal vesicles, and epididymis (Rey and Picard 1998).
        5. Testosterone is further converted into dihydrotestosterone (DHT), a potent androgen, in the periphery, leading to the virilization of the external genitalia (Zhu et al. 1998).
    2. Ovarian development
        1. Ovarian tissue develops in the absence of TDFs and in the face of the antitesticular action of the genes *DAX1* (Swain et al. 1996), *Rspo1*, and *WNT4.*
        2. Ovaries do not produce hormones during fetal life and the development of female genitalia is independent of hormone production.
        3. The fetus is recognizable as male or female at 12 weeks, and this can be identified ultrasonographically from the second trimester of pregnancy onwards (Odeh et al. 2009).

3. *SRY* gene and its mouse homologue, *Sry* (Goodfellow and Lovell-Badge 1993; Schäffler et al. 2000).
    1. The sex-determining region on the Y chromosome
        1. Mapped to the short arm of the Y chromosome.
        2. Encodes for a testis-determining factor (TDF).
        3. Candidate gene narrowed down to a 35-kb interval on the Y chromosome adjacent to the pseudoautosomal boundary which contains a Y chromosomal-specific sequence, named SRY (sex-determining region Y gene).
        4. Demonstration that female mice transgenic for Sry developed into

sex-reversed males (Koopman et al. 1991) despite an XX karyotype provided the confirmation of SRY being the TDF that directs the undifferentiated gonad into a testis (Berta et al. 1990).

2. Deletions or mutations occurring in the *SRY*
    1. Result in failure of testis development
    2. Sex differentiation along the female pathway

4. Mechanism of male to female sex reversal (abnormalities of XY sex determination).
    1. SRVX, a sex reversing locus in Xp21.2-> p22.11 (Arn et al. 1994).
        1. SRVX is inferred a part of a pathway of sex-determining genes that includes SRY and SRA1, the latter recently assigned to chromosome 17q.
        2. If mutation of SRA1 or SRVX can reverse the sex of the XY fetus, this would explain why mutation within SRY is found only sporadically in women with XY gonadal dysgenesis.
    2. The region Xp21.3-p22.11 is critical for sex determination (Harley and Goodfellow 1994).
        1. If the presence of two active copies of the Xp distal region correlates with impaired testis formation, a gene normally subject to X inactivation is involved in sex determination.
        2. The association of sex determination, X-inactivation, and gene dosage is seductive.
    3. Mutations in the SRY gene resulting in XY females with gonadal dysgenesis (vs. translocation of this gene sequence to X chromosome giving rise to XX males) (Hawkins 1995).
        1. Several genes are involved in the process of sex differentiation, including *SRY*, *RSPO1*, *SOX9*, *NR5A1*, *WT1*, *NR0B1*, and *WNT4* (Helszer et al. 2013b).
        2. Increasing variety of unique mutations within SRY gene reported in patients with gonadal dysgenesis/XY reversal (Jäger et al. 1990). These patients are, in general, normal 46,XY females with complete gonadal dysgenesis (Hawkins et al. 1992b).
    3. *SRY* gene mutations noted in 15–20% of cases with complete gonadal dysgenesis (Graves et al. 1999).
        1. Most mutations are located in the High Mobility Group (HMG) box.
        2. XY sex reversal associated with a deletion 5′ to the SRY "HMG box" in the testis-determining region (McElreavey et al. 1992).
        3. Loss of sequences 3′ to the testis-determining gene, SRY, including the Y pseudoautosomal boundary associated with partial testicular determination (McElreavey et al. 1996).
        4. De novo mutations affect only one individual in a family in the majority of cases.
        5. Phenotypic variability is associated with different mutations.
    4. About one third of the *SRY* mutations reported are inherited.
        1. No apparent explanation available to explain why an inherited SRY mutation which results in sex reversal in the offspring is associated with a normal male phenotype in the father and sometime in brothers and uncles.
        2. Paternal mosaicism for the mutant *SRY* provides an explanation for the other familial cases of XY gonadal dysgenesis.
    5. Eighty percent of patients with sporadic or familial 46,XY gonadal dysgenesis lack a mutation or deletion of the SRY gene, indicating that other autosomal or X-linked genes have a role in sex determination.
    6. Familial mutation in the testis-determining gene SRY shared by an XY female and her normal father: The allelic variant of SRY transmitted in this family and shared by both a phenotypic female (proband) and a phenotypic male (proband's father) emphasizes the

importance of modifier genes in the sex determination pathway (Jordan et al. 2002).

4. *Sox9*.
    1. Another gene (*SOX9*) involved in sex determination identified by positional cloning of a chromosomal breakpoint has been identified in the XY female with campomelic dysplasia (Kwok et al. 1995), a condition in which three quarters of XY patients show genital and gonadal malformations.
    2. Belongs to a family of SRY-box-related (SOX) genes which encode proteins with at least 60% amino acid homology to the HMG box of the SRY protein.
5. *Atrx*.
    1. The gene responsible for the ATR-X syndrome causes α-thalassemia, severe mental retardation, and multiple congenital anomalies which may include 46,XY gonadal dysgenesis and undermasculinization.
    2. The C-terminal region of the protein has been lost in most cases where there has been gonadal dysgenesis associated with ATR-X syndrome.
6. Deletions of variable portions of the short arm of chromosome 9 (*DMRT-1* identified as a candidate gene) result in partial or complete gonadal dysgenesis in XY females (Calvari et al. 2000).
7. XY sex reversal and gonadal dysgenesis due to 9p24 monosomy (McDonald et al. 1997).
    1. The observation that all seven patients with sex reversal share a deletion of the distal short arm of chromosome 9 is consistent with the hypothesis that the region 9p24 contains a gene or genes necessary for male sex determination.
    2. This present case narrows the chromosome interval containing a critical sex determination gene to the relatively small region 9p24.
8. Sex-reversing Xp duplication (Xp21) (Bardoni et al. 1994).
5. Classification of 46,XY disorders of sex development (DSD) (Hughes 2008; Mendonca et al. 2009).
    1. 46,XY DSD due to gonadal (testicular) development
        1. Gonadal agenesis
        2. Complete or partial gonadal dysgenesis (e.g., *SRY*, *SOX9*, *SF1*, WT1, DHH)
        3. Ovotesticular DSD
        4. Embryonic testis regression syndrome
        5. Gonadal dysgenesis associated with syndromic phenotype
    2. Disorders of androgen syndromes
        1. Disorders of androgen synthesis
            1. LH receptor mutations
            2. Smith-Lemli-Opitz syndrome
            3. Steroidogenic acute regulatory protein mutations
            4. Cholesterol side-chain cleavage (*CYP11A1*)
            5. 3β-hydoxysteroid dehydrogenase 2 (*HSD3B2*)
            6. 17α-hydroxylase/17,20-lyase (*CYP17*)
            7. P450 oxidoreductase (*POR*)
            8. 17β-hydoxysteroid dehydrogenase (*HSD17B3*)
            9. 5α-reductase 2 (*SRD5A2*)
        2. Disorders of androgen action
            1. Androgen insensitivity syndrome
            2. Drugs and environmental modulators
    3. Others
        1. Syndromic associations of male genital development (e.g., cloacal anomalies, Robinow, Aarskog, hand-foot-genital, popliteal pterygium)
        2. Persistent Müllerian duct syndrome
        3. Vanishing testis syndrome
        4. Congenital hypogonadotropic hypogonadism
        5. Cryptorchidism (*INSL3*, *GREAT*)
        6. Environmental influences
        7. Nonclassical forms
            1. Isolated hypospadias (*CXorf6*)
            2. 46,XY gender identity disorders (male to female transsexualism)

Clinical Features

1. Clinical presentation of an XY female (Berkovitz 1992; Michala and Creighton 2010)
    1. Primary amenorrhea with delayed puberty (Swyer syndrome)
        1. 46,XY females (individuals with 46, XY complete gonadal dysgenesis) (Mannaerts et al. 2015).
        2. Diagnosis usually not made until puberty when the patient presents with delayed pubertal development.
        3. Unambiguous female phenotype with completely female external genitalia.
        4. Gonadal dysgenesis (streak gonads).
        5. Well-developed Müllerian structures: Lack of secretion of anti-Müllerian hormone (AMH) results in the normal development of the uterus, fallopian tubes, and vagina.
        6. Absence of testicular development (Vilain et al. 1993).
        7. Absence of Wolffian structures.
        8. Absence of other somatic abnormalities.
        9. Absence of secondary sexual characteristics.
        10. Amenorrhea.
        11. High risk of developing gonadal tumors (Du et al. 2014).
            1. Gonadoblastoma
            2. Dysgerminoma (Morerio et al. 2002)
    2. Androgen insensitivity syndrome (AIS) (Ramprasad et al. 2012) (please see the chapter on "► Androgen Insensitivity Syndrome")
        1. AIS was first described in details by Morris (1953), who provided the descriptive terms – testicular feminization syndrome – for this disorder, which is inherited as X-linked recessive disorder.
        2. The underlying pathology is the inability of the end organs to respond to androgens, either due to lack of androgen cytosol receptor or defect in the receptor.
        3. Genotypically, they are male (XY) but phenotypically and psychologically female (Ahlquist 1994), usually present with primary amenorrhea or infertility with well-developed breast, but absent axillary and pubic hair, normal external genitalia, and short and blind vagina. The upper two thirds of vagina, uterus, and tubes are absent. Gonads (testes) are normally developed but abnormally positioned, either placed in the labia, or inguinal canal or intra-abdominal.
        4. The hormone profile in these individual is typical – high LH, normal to slightly elevated testosterone levels, high estradiol (for men), and normal to elevated FSH.
        5. There is correlation between specific androgen receptor mutation and phenotype corresponding to androgen insensitivity syndrome (Helszer et al. 2013a).
    3. Ambiguous genitalia at birth or virilization at puberty: Possible causes:
        1. Mixed gonadal dysgenesis
        2. 5α-reductase deficiency
        3. 17β-hydroxysteroid dehydrogenase deficiency
        4. Partial androgen insensitivity syndrome
        5. Leydig cell hypoplasia
    4. Inguinal hernia: Possible causes:
        1. Complete androgen insensitivity syndrome (Nair Rema and Bhavana 2012)
        2. 5α-reductase deficiency
        3. 17β-hydroxysteroid dehydrogenase deficiency
        4. Partial androgen insensitivity syndrome
    5. Discordant phenotype to karyotype following prenatal diagnostic testing: can be due to all conditions
    6. Testing following the diagnosis of an affected sibling: can be due to all conditions
2. Differential diagnosis
    1. Individuals with 46,XY partial gonadal dysgenesis (also called 46,XY mixed gonadal dysgenesis or dysgenetic male pseudohermaphroditism) (Barr et al. 1967)

1. Majority of patients present in the newborn period for evaluation of ambiguous genitalia.
2. Partial testicular determination. The extent of masculinization of the external genitalia depends on the extent of testicular differentiation.
3. Dysgenetic gonads.
4. Presence of Müllerian and Wolffian structures.
5. Regarded as the clinical spectrum of 46, XY gonadal dysgenesis.

2. Individuals with 46,XY embryonic testicular regression syndrome (also called true agonadism or gonadal agenesis)
   1. A term used to describe the spectrum of genital anomalies resulting from regression of testis development from 8 to 14 weeks of gestation
   2. Regression of the fetal testes between 8 and 10 weeks of gestation
      1. Complete absence of gonads
      2. Rudimentary Müllerian and/or Wolffian ductal structures
      3. Hypoplastic uterus
      4. Female genitalia with/or without ambiguity
   3. Regression of the testes after the critical period of male differentiation (around 12–14 weeks)
      1. Anorchia
      2. Partial testicular regression resulting in a male phenotype as in anorchia but with small rudimentary testes

Diagnostic Investigations

1. Karyotype analysis
   1. 46,XY in phenotypic females
   2. To exclude 45,X/46,XY and other forms of mosaicism, served to exclude the more common forms of gonadal dysgenesis
2. Molecular analysis for *SRY* gene
   1. Nucleotide substitutions (missense/nonsense) (Hawkins et al. 1992a; Veitia et al. 1997)
   2. Deletions
   3. Insertions
3. Ultrasonography/laparotomy
   1. Complete gonadal dysgenesis
      1. Streak gonads
      2. Presence of Müllerian ducts
      3. Absence of Wolffian ducts
   2. Partial gonadal dysgenesis
      1. Dysgenetic gonads
      2. Presence of Müllerian and Wolffian structures
4. Gonadal histology
   1. Streak gonads
      1. Absence of primordial follicles
      2. Wavy ovarian stroma intermixed with fibrous tissue
   2. Gonadal tumors observed in about 30% of cases
      1. H-Y antigen in 46,XY pure testicular dysgenesis (Nazareth et al. 1979)
      2. Gonadoblastomas: usually benign
      3. Dysgerminoma
      4. Embryonal carcinoma: more life-threatening
5. Biochemical findings
   1. Elevated levels of FSH and LH
   2. Low levels of estradiol
   3. No elevation of androgen levels

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: recurrence risk depending on whether the inheritance is X-linked recessive, male-limited autosomal dominant, or autosomal recessive.
   2. Patient's offspring: The patients are nonreproductive.
   3. To rule out the disease in siblings because of the presence of familial aggregation.
   4. Recurrent 46,XY sex reversal secondary to paternal somatic and germ-line mosaicism for a sex-determining region on Y (SRY) missense mutation (Hines et al. 1997).

2. Prenatal diagnosis: demonstration of the sexual discrepancy between fetal karyotype (XY) and ultrasonographic fetal phenotype (Bretelle et al. 2002)
    1. To exclude sample error and placental mosaicism
    2. Detailed fetal ultrasound examination to check for syndromic gender discrepancy such as:
        1. Campomelic dysplasia (skeletal malformation) (please see the chapter on "Campomelic Dysplasia")
        2. Denys-Drash syndrome
        3. Smith-Lemli-Opitz syndrome (please see the chapter on "Smith–Lemli–Opitz Syndrome")
            1. Microcephaly
            2. Abnormal cholesterol metabolism
        4. Alfi syndrome
            1. Craniostenosis
            2. Trigonocephaly
            3. Multiple congenital anomalies
    3. Prenatal diagnosis possible by SRY analysis for XY gonadal dysgenesis (SRY-negative XY female and SRY-positive XY female)
        1. FISH using SRY probe on metaphase chromosomes
        2. Sequencing of entire coding region
3. Management (Portuondo et al. 1986)
    1. Laparoscopy and gonadal biopsy might be useful in some patients to avoid confusion between XY gonadal dysgenesis and testicular feminization syndrome.
    2. Early diagnosis of XY gonadal dysgenesis is always desirable, and bilateral gonadectomy is indicated to avoid malignancy as soon as the diagnosis is made in patients with a Y chromosome and elevated FSH levels.
    3. Surgical removal of the gonads from patients with testicular feminization should be delayed until the completion of puberty because of the low risk of malignancy.
    4. Initiate cyclic hormonal therapy with estrogen and progesterone at puberty.
    5. Vaginoplasty should be performed in adolescence to prevent the risk of vaginal stenosis.
    6. Successful twin pregnancy after embryo donation to a patient with XY gonadal dysgenesis (Sauer et al. 1989).
    7. Psychological counseling.
        1. Raise as a female.
        2. Information regarding the condition and the karyotype should be provided to the patient and her family.
        3. Increase patient's knowledge about medical and surgical history and karyotype.
        4. Counseling for sexual function.
        5. Achievement of pregnancy in some patients following in vitro fertilization with a donor egg.

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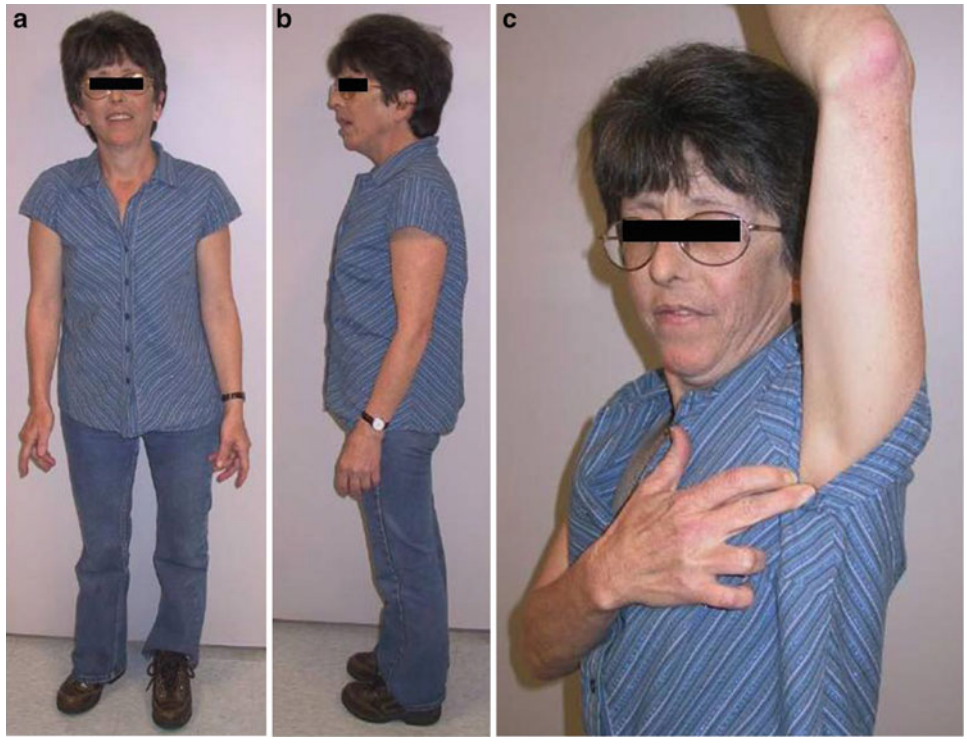

Fig. 1 (**a**–**c**) A patient (**a**, **b**) with 46,XY female with gonadal dysgenesis at 42 years of age. Patient has short stature (4′6″), primary amenorrhea, lack of secondary sex characteristics (absent axillary hair (**c**), poor breast development), but normal female external genitalia. Laparotomy revealed absent Wolffian structures and presence of uterus and streak gonads which were excised

XYY Syndrome

Contents

In 1961, Sandberg et al. (1961) described an XYY man. The incidence is estimated to be approximately 1 in 1,000 live male newborns and more frequent in infertile population (Martin 2008).

Genetics/Basic Defects

1. Caused by an additional Y chromosome in males (Rives et al. 2003).
2. Mechanisms of the extra Y chromosome in 47, XYY males (Robinson and Jacobs 1999).
    1. Paternal nondisjunction at meiosis II after a normal chiasmate meiosis I (84%)
    2. Postzygotic mitotic error or nondisjunction at meiosis II after a nullichiasmate meiosis I (16%)
3. Spermatogenesis.
    1. Normal spermatogenesis in majority of XYY males.
        1. The supernumerary Y chromosome probably lost at the early stage of spermatogenesis
        2. A large proportion of primary spermatocytes containing only one Y chromosome
    2. Altered spermatogenesis in a proportion of XYY males: Persistence of the supernumerary Y chromosome through meiotic prophase increases spermatocyte degeneration.
    3. The abnormal mode of pairing caused by the presence of the extra Y chromosome disturbs achievement of spermatogenesis resulting in severe oligoasthenoteratozoospermia. In contrast, the loss of the supernumerary Y before meiosis allows achievement and normal sperm production (Gabriel-Robez et al. 1996).
    4. Preferential Y-Y pairing and synapsis and abnormal meiotic recombination in a 47, XYY man with nonobstructive azoospermia (Wu et al. 2016).
4. A higher incidence of the XYY complement in the institutions for the retarded, the mentally ill, the criminally insane, and the aggressive offender: controversial and biased.
5. Expression of *NLGN4Y*, a gene that may be involved in synaptic function, is increased in boys with XYY, and the level of expression correlates with overall social responsiveness and autism symptoms (Ross et al. 2015). Thus, further investigation of NLGN4Y as a plausible ASD risk gene in XYY is warranted.

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Clinical Features

1. Earlier observation of the association between the additional Y chromosome and aggressive behavior: considered to be due to selection bias and has since been challenged (Court Brown 1968; Money et al. 1975; Hoffman 1977; Linden et al. 2002).
2. No consistent physical stigmata or medical disorders.
3. Growth and development.
    1. Increased growth velocity during earliest childhood
    2. Tall stature
    3. Oral features: larger tooth size (macrodontia), dental agenesis, taurodontism (Scheidt et al. 2015)
    4. At risk for mild speech/language and motor delays and learning disabilities
4. Intelligence.
    1. Normal range
    2. IQ: 10–15 points lower than siblings
5. Behavioral profile.
    1. Childhood temper tantrums
    2. No increased incidence of aggression
    3. Heterosexual
    4. Autism spectrum disorders (Margari et al. 2014)
6. Normal reproduction.
7. Normal adult adaptation.
8. Physical phenotypic features were similar in boys diagnosed prenatally vs. postnatally. Prenatal diagnosis was associated with higher cognitive function and less likelihood of an ASD diagnosis (Bardsley et al. 2013).
9. Many men with 47,XYY karyotype are fertile in spite of their sex chromosome abnormalities.
10. Nonmosaic 47,XYY syndrome presenting with male infertility (El-Dahtory and Elsheikha 2009; Abdel-Razic et al. 2012).
11. Combination of XYY and XXYY syndromes associated with cognitive, affective dysfunction and renal malrotation (Resim et al. 2015).
12. Diagnosis and mortality in 47,XYY persons: a registry study (Stochholm et al. 2010).
    1. A significant delay to diagnosis
    2. Reduced life expectancy
    3. An increased total and cause-specific mortality

Diagnostic Investigations

1. Chromosome analysis to detect 47,XYY.
2. Psychological and psychiatric evaluations when needed.
3. Studies of sperm karyotypes or FISH analysis of sperm: The majority of sperm are chromosomally normal in 47,XYY men (Martin et al. 2001).
4. EEG (Tomiero et al. 2011).
    1. Normal background activity and sleep organization
    2. Particular local spikes and sharp waves localized mostly over the vertex and/or central-temporal regions which increased during sleep
5. Genetic variations associated with XYY syndrome result in increased brain matter volumes, a finding putatively related to the increased frequency of ASDs in individuals with this condition. In addition, frontotemporal grey and white matter reductions in XYY syndrome provide a likely neuroanatomical correlate for observed language impairments (Bryant et al. 2012).
6. 47,XXY (Klinefelter syndrome) and 47,XYY (Abramsky and Chapple 1997).
    1. Most males born with these chromosome patterns will go through life without being karyotyped.
    2. The commonest indication for a 47,XYY male to be karyotyped will be developmental delay and/or behavior problems.
    3. The commonest indication for a Klinefelter male to be karyotyped will be hypogonadism and/or infertility.

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased.

2. Patient's offspring: Patient generally has chromosomally normal children, despite the high theoretical risk of aneuploidy.

2. Prenatal diagnosis
   1. Ultrasonography: a hypoplastic nasal bone and a large facial angle might be important sonographic phenotypes of male fetuses with 45,X/47,XYY mosaicism (Lin et al. 2015).
   2. Fetal karyotyping from amniocytes or CVS.
3. Management (Bender et al. 1984; Linden et al. 2002)
   1. The extra Y chromosome represents a risk factor for motor and language development, but the environment remains a primary force in shaping the child's development.
   2. The increased frequency of prenatal detection of 47,XYY by amniocentesis necessitates the importance of making accurate information about the developmental prognosis of these individuals.
   3. Infancy and toddler: assess developmental milestones.
   4. Childhood: assess school performance and provide intervention if needed.
   5. Adolescence: no intervention needed.
   6. Adulthood: annual physical examination.
   7. Positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY (Samango-Sprouse et al. 2015).

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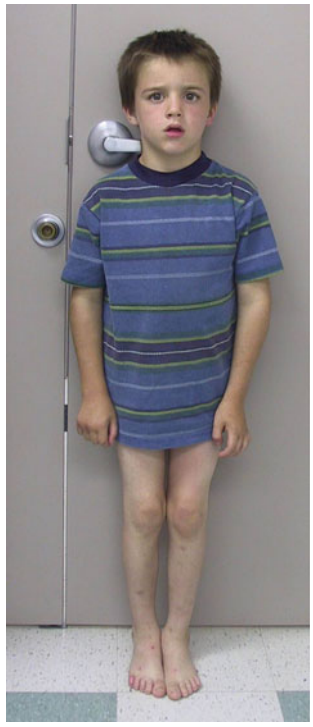

Fig. 1 A 7-year-old boy with 47,XYY syndrome showing normal phenotype

Fig. 2 A 13-year-old boy with XYY syndrome showing normal phenotype. He also has systemic carnitine deficiency and received Carnitor treatment

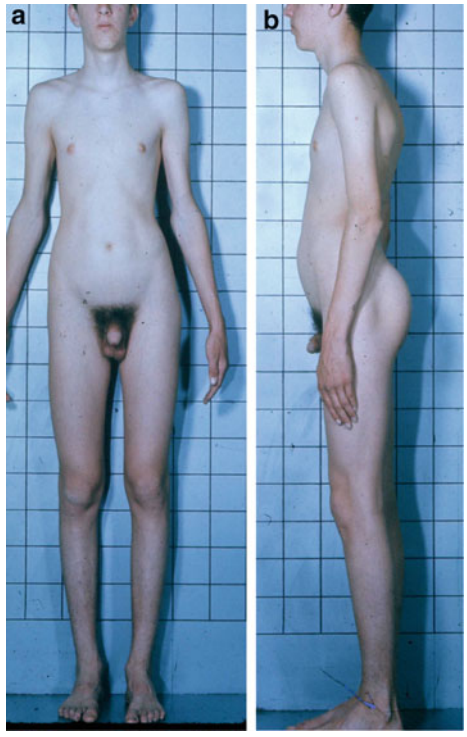

Fig. 3 (**a**, **b**) An adult with 47,XYY syndrome showing tall stature

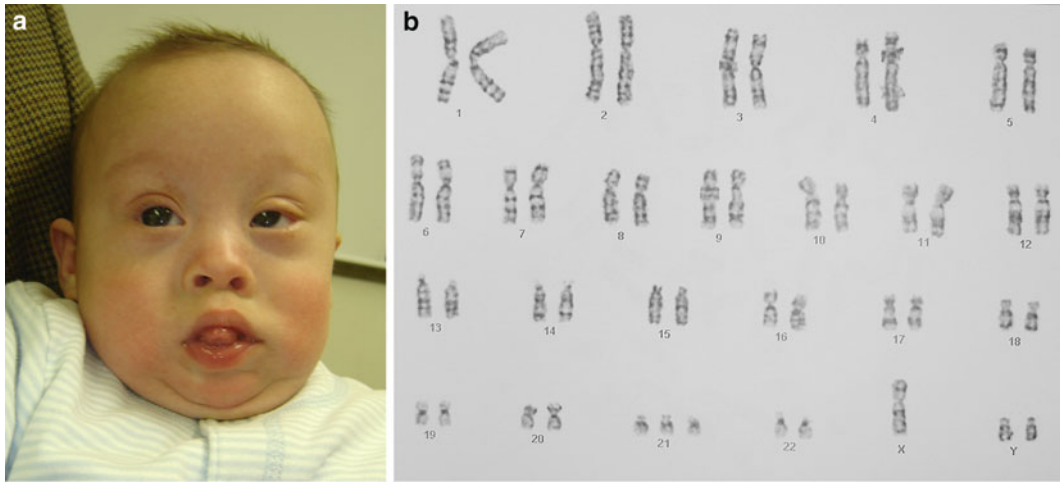

Fig. 4 (**a**, **b**) An infant (**a**) with XYY and trisomy 21 (48,XYY,+21) (**b**)